Aldrichimica Acta

Volume 12, Number 1, 1979

Boranes for Organic Reductions. **See Page 3.**
Trialkylborohydrides in Organometallic Syntheses. **See Page 13.**

chemists helping chemists in research & industry
aldrich chemical co.

Aldrichimica Acta

Volume 12, Number 1, 1979
A publication of ALDRICH CHEMICAL COMPANY, INC.

Main Sales Office:
940 West Saint Paul Ave.
Milwaukee, Wisconsin 53233
Telephone: (414) 273-3850
Order Desk: (800) 558-9160 Toll-free
TWX: (910) 262-3052
Telex: 26 843

East Coast Service and Distribution Center:
159 Forrest Street
Metuchen, New Jersey 08840
Telephone: (201) 549-6300
TWX: (710) 998-0575

In Canada:
Aldrich Chemical Co. (Canada), Ltd.
1500 Stanley Street, Suite 405
Montreal, Quebec H3A 1R3
Telephone: (514) 845-9289
Eastern & Atlantic: (800) 361-6141 Toll-free
TWX: (610) 421-4608

In Great Britain:
Aldrich Chemical Company, Ltd.
The Old Brickyard, New Road
Gillingham, Dorset
SP8 4JL, England
Telephone: 074-76 2211
Telex: (851) 417238

In West Germany/Continental Europe:
EGA-Chemie KG
7924 Steinheim am Albuch
West Germany
Telephone: (07329) 6011
Telex: (841) 714838

In Belgium/Continental Europe:
Aldrich-Europe
B-2340 Beerse
Belgium
Telephone: 014/611431
Telex: (846) 32540

In Japan:
Aldrich Japan
c/o Tokyo Danchi Sohko Kanrito
4-1, 3-chome, Heiwajima, Ohta-ku
Tokyo, Japan
Telephone: 768-0555
TWX: (781) 222-3756

About Our Cover:

When our chemist-collector first saw this interesting study (oil on paper, mounted on wood, 14-$^1/_4$ x 15-$^1/_2$ inches), it was attributed to Jacob Jordaens, a Flemish contemporary of Rubens. Our chemist doubts this attribution, and even doubts that it is by an artist from Northern Europe. Rather, he thinks it is Bolognese, *ca.* 1600, by Annibale Caracci or an artist closely associated with him.

To us, this work seemed particularly fitting for the cover of the Acta which bears a summary of the work of Professor Herbert C. Brown and shows Aldrich's contribution to teaching the art and the science of hydroboration. For obviously, here is a young and dedicated teacher explaining an intriguing problem to his alert student. One of Professor Brown's great strengths is his ability as a teacher. As one of his associates put it, "Professor Brown inspires confidence in his students that they can solve problems systematically." We can almost hear Professor Brown say, "It's very simple," and proceed with a clear explanation. His counselling is best on an individual basis — teacher to student — just as depicted in our painting.

This is also how we envisioned our role when we created Aldrich-Boranes. The brilliance of Professor Brown's work in hydroboration had been recognized for many years, but the application of the process was not widespread. It was considered dangerous, and many of the requisite reagents and specialized equipment were not readily available. Aldrich takes pride in its role as teacher and supplier of the tools of the hydroboration technique. And we do our best to treat each of our customers on an individual basis. We are chemists helping chemists.

Are you interested in our Acta Covers? *Selections from the Bader Collection*, with 30 duotone reproductions, many of previous Acta covers, and an introduction by Professor Wolfgang Stechow is available to all chemist art-lovers.

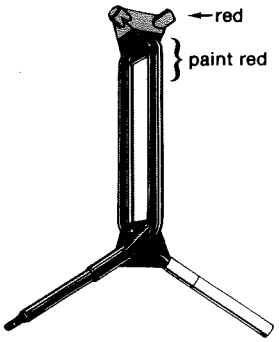
Also, many paintings reproduced on our Acta covers were shown at the Milwaukee Art Center in an exhibition, "The Bible Through Dutch Eyes," arranged by Dr. Bader in 1976. The fully illustrated catalog with 66 black-and-white and 4 full-color reproductions contains many art historical and Biblical comments.

Many of the early issues of the *Aldrichimica Acta* have become very rare. Please do not throw your issues away. In time, we believe that complete sets will become valuable, and — if you do not want to keep them — there probably are chemists near you who would be interested.

Lab Notes

For years I used the Fieser Molecular Models now supplied by you. I feel they are probably the best models for class demonstration. However, there is one feature that I have had to change to meet my needs: no carbonyl.

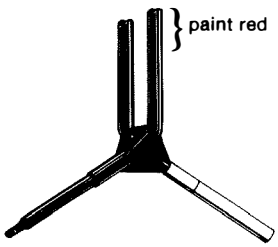
I make a carbonyl by breaking apart a C=C at a "joint" then gluing on the red oxygen piece. I remove the aluminum bonding tube and cut off the long, red bonding projection. This piece is dissolved



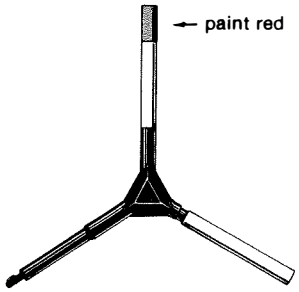
in methylene chloride to paint over some of the black of my new carbonyl to enhance the red color on that end.

James W. Hill
Professor of Chemistry
Panhandle State University
Goodwell, OK 73939

Editor's Note: Various modifications of the Fieser molecular models to give other functional groups are discussed by Prof. Fieser in *J. Chem Educ.*, **42**, 408 (1965). Prof. Fieser recommended cutting a double bond into two to produce two carbonyl groups.

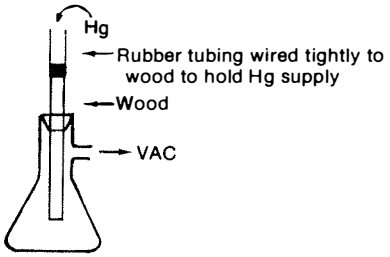


A carbonyl model may also be contructed by following Fieser's directions for a carbonium ion. The resulting planar structure resembles a Dreiding carbonyl model if one arm is painted red.



Frequently a laboratory worker wishes to clean some mercury for purposes such as filling manometers, McLeod gauges, etc. Although a preliminary cleaning may be achieved by allowing the mercury to trickle through a pin hole in a piece of filter paper shaped into a cone, this method is often time-consuming and does not remove all impurities.

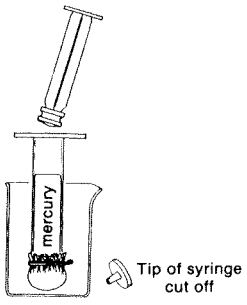
A preferable technique with respect to both speed and cleanliness is to draw the mercury through the pores of a piece of wood (a 6-in. section of a broomstick works well) using an arrangement similar to that shown in the diagram.



The mercury cleaned in this manner can be used for all purposes except those requiring the purity achieved with triple distillation.

Arden P. Zipp
Chairman & Professor
Chemistry Department
State University of New York
College at Cortland
Cortland, New York 13045

Mercury may be cleaned and dried by forcing it through a piece of chamois. Cut off the end of a 10- or 20-cc plastic hypodermic syringe and slightly flare the end of the barrel. Firmly tie a small piece of chamois over the barrel, using Nichrome or Chromel wire. Remove the plunger, pour in the mercury, replace the plunger and force the mercury slowly through the chamois. Hold the syringe near the bottom of a small beaker, as extremely fine jets of mercury squirt in all directions. The residue can be shaken out of the syringe. This device is inexpensive, very effective, and will last for years.

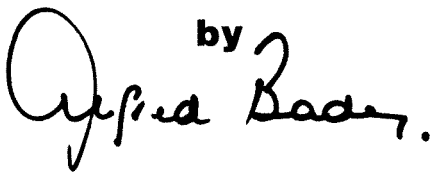


William D. Murray
Environmental Engineer
AMP Inc.
Harrisburg, PA 17105

Any interesting shortcut or laboratory hint you'd like to share with ACTA readers? Send it to Aldrich (attn: Lab Notes) and if we publish it, you will receive a handsome red and white ceramic Aldrich coffee mug as well as a copy of **Selections from the Bader Collection** *(see "About Our Cover"). We reserve the right to retain all entries for consideration for future publication.*

"Please Bother Us!"

by



Dr. Dieter M. Kramsch of the Boston University School of Medicine called me recently to ask whether we could lower our price substantially for 5-methyl-2-thiophenecarboxylic acid in large quantities. Dr. Kramsch and his associates have found[1] that this acid prevents hardening of the arteries in rabbits. They now want to study this effect in monkeys and, of course, need larger amounts. We had been making small quantities only, but our preparation could be scaled up. Naturally, we wanted to help, particularly in an application that might become so important. Hence we quoted much lower prices for kilo quantities, received the order and filled it rapidly.

It was no bother at all, just a pleasure to be able to help.

1) C.T. Chan, H. Wells, and D.M. Kramsch, *Circulation Res.*, **43**, 115 (1978).

Boranes For Organic Reductions - A Forty-Year Odyssey[1]

Herbert C. Brown
and S. Krishnamurthy
Richard B. Wetherill Laboratory
Purdue University
West Lafayette, Indiana 47907

I. INTRODUCTION

In 1939 there appeared a publication in the March issue of the *Journal of the American Chemical Society*, "Hydrides of Boron. XI. The Reaction of Diborane with Organic Compounds Containing a Carbonyl Group," by H.C. Brown, H.I. Schlesinger, and A.B. Burg.[2] This is the first report of the application of a hydride for the reduction of organic functional groups.

Forty years have elapsed since this original report. This observation initiated rapid progress in the development of new boron hydride reducing agents and in the exploration of their scope and applications in organic synthesis. These developments have revolutionized the procedures for the regio-, stereo-, and chemoselective reduction of various organic functional groups.[3,4] It appears appropriate at this time to summarize the progress of these forty years in the application of borane and borohydride reducing agents.

Before the discovery of hydrides as reducing agents for the reduction of organic functional groups, there were available a number of nonhydridic reduction procedures to achieve such transformations. Thus, the reduction of aldehydes to the corresponding alcohols was achieved by a variety of metal-acid (zinc dust + acetic acid, sodium amalgam + acetic acid, iron + acetic acid, etc.) procedures (eq. 1).[5]

$$CH_3(CH_2)_5CHO \xrightarrow[6hr,\ 100°]{Fe,\ HOAc} CH_3(CH_2)_5CH_2OH \quad 80\% \qquad \text{(eq. 1)}$$

The corresponding reduction of ketone to alcohol was achieved by sodium in ethanol or zinc-sodium hydroxide in ethanol.[6,7]

The discovery of the Meerwein-Ponndorf-Verley reduction introduced a more general, improved procedure for the reduction of aldehydes and ketones to the corresponding carbinols.[8-12] Similarly, the Bouveault-Blanc method enabled the reduction of carboxylic acid esters to the corresponding alcohols.[13]

The nonhydridic reduction procedures for the reduction of carbonyl groups often required elevated temperatures and long reaction times and resulted in low yields of the desired products. However, the discovery of boron hydride reducing agents has dramatically changed the situation, not only for the reduction of carbonyl groups, but for reduction of a wide variety of other organic functional groups.

II. THE DISCOVERY OF BORON HYDRIDES AS REDUCING AGENTS. HISTORICAL DEVELOPMENTS

In 1936 there was considerable discussion about the structure of borane-carbonyl, then recently synthesized by Professor H.I. Schlesinger and Dr. A.B. Burg at the University of Chicago (eq. 2).[14]

$$\tfrac{1}{2}(BH_3)_2 + CO \rightleftharpoons H_3B:CO \qquad \text{(eq. 2)}$$

It was suggested that the senior author, then a new graduate student at the University of Chicago, undertake a study of the reaction of diborane with aldehydes and ketones in the hope that the results would contribute to the better understanding of the structure of borane-carbonyl. Soon it was discovered that aldehydes and ketones react rapidly with diborane at 0° (or even at -78°); hydrolysis of the resulting dialkoxyborane yielded the corresponding alcohol (eqs. 3 and 4).[2]

$$2\,R_2CO + \tfrac{1}{2}(BH_3)_2 \longrightarrow (R_2CHO)_2BH \qquad \text{(eq. 3)}$$

$$(R_2CHO)_2BH + 3\,H_2O \longrightarrow 2\,R_2CHOH + H_2 + B(OH)_3 \qquad \text{(eq. 4)}$$

However, interest in this new development among organic chemists was minimal because diborane was a chemical rarity, available only in milligram quantities through complex preparative procedures.[15-17]

The situation was soon altered by pressures of World War II. The National Defense Agency was interested in new volatile uranium compounds with as low molecular weights as possible. Uranium(IV) borohydride appeared to be a suitable candidate in meeting these requirements. Accordingly, it was decided to undertake the preparation of uranium borohydride from aluminum borohydride.[18-20] Indeed, this was successful and the chemical proved to be volatile (eq. 5).[21]

$$UF_4 + 2\,Al(BH_4)_3 \longrightarrow U(BH_4)_4\uparrow + 2\,AlF_2(BH_4)\downarrow \quad \text{(eq. 5)}$$

This development led to the need for considerable quantities of uranium borohydride for large-scale testing.

The development of practical procedures for the synthesis of diborane (ingredient in the synthesis of aluminum borohydride) was stimulated by this requirement. Indeed, such routes to diborane[22] and lithium borohydride[23] were developed from lithium hydride and boron trifluoride. These intermediates could be readily utilized for the synthesis of uranium borohydride (eqs. 6-9).[24]

$$6\,LiH + 8\,BF_3:OEt_2 \xrightarrow{Et_2O} (BH_3)_2\uparrow + 6\,LiBF_4 \quad \text{(eq. 6)}$$

$$LiH + \tfrac{1}{2}\,(BH_3)_2 \xrightarrow{Et_2O} LiBH_4 \quad \text{(eq. 7)}$$

$$AlCl_3 + 3\,LiBH_4 \xrightarrow{\Delta} Al(BH_4)_3\uparrow + 3\,LiCl \quad \text{(eq. 8)}$$

$$UF_4 + 2\,Al(BH_4)_3 \longrightarrow U(BH_4)_4\uparrow + 2\,AlF_2(BH_4)\downarrow \quad \text{(eq. 9)}$$

Unfortunately, lithium hydride was in very short supply and could not be spared for the synthesis of uranium borohydride on a commercial scale. The supply of sodium hydride was ample.

Although sodium hydride could not be utilized in the same way, a new sodium hydride derivative, sodium trimethoxyborohydride,[25] solved the problem and achieved the desired transformations (eqs. 10-13).[22,23]

$$NaH + B(OCH_3)_3 \longrightarrow NaBH(OCH_3)_3 \quad \text{(eq. 10)}$$

$$6\,NaBH(OCH_3)_3 + 8\,BF_3:OEt_2 \longrightarrow (BH_3)_2\uparrow + 6\,B(OCH_3)_3\uparrow + 6\,NaBF_4 + 8\,Et_2O \quad \text{(eq. 11)}$$

$$NaBH(OCH_3)_3 + \tfrac{1}{2}\,(BH_3)_2 \longrightarrow NaBH_4 + B(OCH_3)_3 \quad \text{(eq. 12)}$$

$$AlCl_3 + 3\,NaBH_4 \longrightarrow Al(BH_4)_3\uparrow + 3\,NaCl \quad \text{(eq. 13)}$$

At this point (1943), the Signal Corps became interested in the new compound, sodium borohydride (eq. 12), for the field generation of hydrogen. Further research under their sponsorship led to an improved method for the synthesis of sodium borohydride, the basis of the present U.S. industrial process for this chemical (eq. 14).[26]

$$4\,NaH + B(OCH_3)_3 \xrightarrow{250^\circ} NaBH_4 + 3\,NaOCH_3 \quad \text{(eq. 14)}$$

The reaction provides a mixture of two solids, sodium borohydride and sodium methoxide. Acetone was among the solvents tested for the separation of these two components. With acetone, a vigorous reaction was observed. Hydrolysis of the reaction mixture indicated the absence of any active hydrogen and the presence of four moles of isopropyl alcohol per mole of sodium borohydride. In this way it was discovered that sodium borohydride was a valuable new reagent for the hydrogenation of organic molecules (eq. 15).

$$NaBH_4 + 4\,(CH_3)_2C{=}O \longrightarrow NaB[OCH(CH_3)_2]_4 \xrightarrow{H_2O} NaB(OH)_4 + 4\,(CH_3)_2CHOH \quad \text{(eq. 15)}$$

The alkali metal hydride route was later successfully extended to the synthesis of lithium aluminum hydride (eqs. 16-18).[27]

$$4\,LiH + AlCl_3 \xrightarrow{Et_2O} LiAlH_4 + 3\,LiCl \quad \text{(eq. 16)}$$

$$3\,LiAlH_4 + AlCl_3 \longrightarrow 4\,AlH_3 + 3\,LiCl \quad \text{(eq. 17)}$$

$$4\,AlH_3 + 4\,LiH \longrightarrow 4\,LiAlH_4 \quad \text{(eq. 18)}$$

III. MODIFICATION OF BOROHYDRIDES

The discovery of sodium borohydride[23] in 1942 and of lithium aluminum hydride[27] in 1945 brought about a revolutionary change in procedures for the reduction of functional groups in organic molecules.[4,28] Indeed, numerous major applications have appeared for both the reagents and more are still appearing. Lithium aluminum hydride is an exceptionally powerful reducing agent capable of reducing almost all organic functional groups.[29] Sodium borohydride is an exceptionally mild reducing agent, which readily reduces only aldehydes, ketones, and acid chlorides (Table I). The mildness of sodium borohydride limits its applicability to selective reductions involving relatively reactive groups. Consequently, it appeared desirable to develop various boron hydride reagents with markedly different reactivities towards various organic functional groups, reagents possessing a high degree of selectivity. Accordingly, we undertook a program of research on "Selective Reductions" to explore these possibilities. The reducing characteristics of the parent hydride, sodium borohydride, could be modified by various means, such as varying the cation in the complex hydride, introduction of substituents (alkyl or alkoxy) in the complex ion that would exert marked steric and electronic influences upon the reactivity of the parent ion, etc. Yet another approach would be the development of acidic reducing agents such as borane and its substituted derivatives (alkylboranes, alkoxyboranes, haloboranes, etc.). In the following section we shall discuss the evolution of various new boron hydrides as selective reducing agents and their utility in organic synthetic transformations.

IV. EVOLUTION OF VARIOUS BORON HYDRIDE REAGENTS AND THEIR APPLICABILITY

1. Sodium borohydride

Sodium borohydride is a very mild reducing agent, insoluble in ethyl ether, only slightly soluble in tetrahydrofuran, but readily soluble in diglyme and triglyme.[30] In hydroxylic solvents, it reduces aldehydes and ketones rapidly at 25°, but is essentially inert to the other organic functional groups. The reductions can be carried out in aqueous solutions (basic), ethanol, or 2-propanol (eq. 19).

$$4\,R_2CO + NaBH_4 \longrightarrow Na[B(OCHR_2)_4] \xrightarrow{H_2O} NaB(OH)_4 + 4\,R_2CHOH \quad \text{(eq. 19)}$$

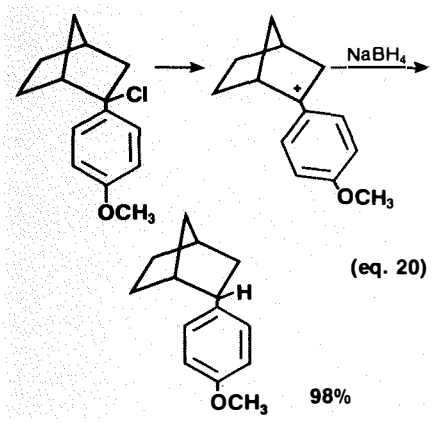
In aqueous solvents, sodium borohydride reacts with ionizable alkyl halides to

Table I. Comparison of sodium borohydride with lithium aluminum hydride

	$NaBH_4$ in EtOH	$LiAlH_4$ in THF
Aldehyde	+	+
Ketone	+	+
Acid chloride	R	+
Lactone	—	+
Epoxide	—	+
Ester	—	+
Acid	—	+
Acid salt	—	+
tert-Amide	—	+
Nitrile	—	+
Nitro	—	+
Olefin	—	—

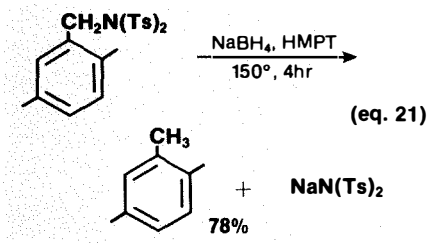
(+) = Rapid reaction
(—) = Insignificant reaction
R = Reaction with solvent

give the corresponding hydrocarbons, proceeding through the intermediacy of carbonium ions (eq. 20).[31]



(eq. 20)

Recently, sodium borohydride has been successfully employed for the reductive deamination of primary amines through their sulfonimide derivatives (eq. 21).[32]



(eq. 21)

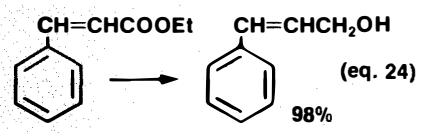
2. Lithium Borohydride

Preliminary exploratory studies on the reduction characteristics of lithium and sodium borohydrides indicated a marked difference in their reactivity.[33,34] Lithium borohydride is a more powerful reducing agent. The reagent can be synthesized conveniently *in situ* by the addition of an equivalent quantity of lithium halide to a solution of sodium borohydride in diglyme or monoglyme (reflux, eq. 22).

$$NaBH_4 + LiBr \longrightarrow LiBH_4 + NaBr\downarrow \quad \text{(eq. 22)}$$

Lithium borohydride reduces a number of representative esters to the corresponding carbinols quantitatively in 1-3 hr at 100° in diglyme.[35] Under these conditions, sodium borohydride alone brings only slight reduction of such esters (eqs. 23 and 24).

$$CH_3(CH_2)_{16}COOEt \xrightarrow[\text{diglyme, } 100°]{NaBH_4\text{-}LiBr} CH_3(CH_2)_{16}CH_2OH \quad 98\% \quad \text{(eq. 23)}$$

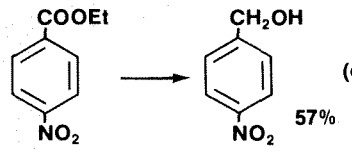


(eq. 24)

3. Borohydrides Containing Polyvalent Metal Ions

Ions of higher ionic potential would be expected to be even more effective. Thus, magnesium borohydride synthesized by the addition of an equivalent amount of solid magnesium chloride to a diglyme solution of sodium borohydride, brings about the facile reduction of esters (eqs. 25 and 26).[35]

$$CH_3(CH_2)_{16}COOEt \xrightarrow[\text{diglyme, } 100°]{NaBH_4\text{-}MgCl_2} CH_3(CH_2)_{16}CH_2OH \quad 74\% \quad \text{(eq. 25)}$$



(eq. 26)

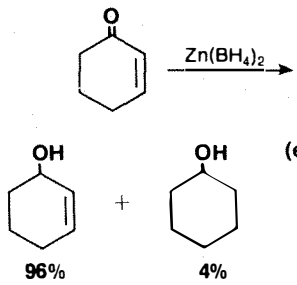
Kollonitsch and coworkers have achieved rapid reduction of esters by sodium borohydride in the presence of magnesium, calcium, barium and strontium salts.[36,37]

Aluminum borohydride is synthesized by the addition of one equivalent of aluminum chloride to three equivalents of sodium borohydride solution in diglyme. The reaction mixture remains clear; no precipitation of sodium chloride is observed, indicating an equilibrium[38] which must favor the reverse reaction (eq. 27).

$$AlCl_3 + 3\ NaBH_4 \rightleftharpoons Al(BH_4)_3 + 3\ NaCl \quad \text{(eq. 27)}$$

Nevertheless, the resulting solutions exhibit markedly enhanced reducing power approaching that of lithium aluminum hydride itself, capable of reducing lactone, epoxide, carboxylic acid, *tert*-amide, nitrile, etc. The mixture is capable of hydroborating olefins to the corresponding organoboranes.[38a]

Zinc borohydride, synthesized from zinc chloride and sodium borohydride in ethyl ether, is useful for the selective reduction of α,β-unsaturated aldehydes and ketones to the corresponding allylic alcohols (eq. 28).[39]



(eq. 28)

4. Sodium and Potassium Triisopropoxyborohydrides

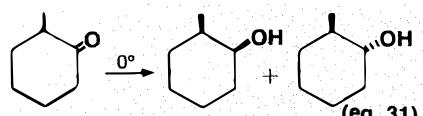
Sodium and potassium triisopropoxyborohydrides are synthesized from triisopropyl borate and sodium or potassium hydride (eqs. 29 and 30).[40,41]

$$NaH + (i\text{-}PrO)_3B \xrightarrow[170hr]{THF,\ 67°} Na(i\text{-}PrO)_3BH \quad \text{(eq. 29)}$$

$$KH + (i\text{-}PrO)_3B \xrightarrow[1hr]{THF,\ 25°} K(i\text{-}PrO)_3BH \quad \text{(eq. 30)}$$

Fortunately, unlike the less hindered derivatives[40] (such as sodium trimethoxyborohydride), triisopropoxyborohydride solutions in THF are quite stable and do not undergo disproportionation.

Potassium triisopropoxyborohydride in tetrahydrofuran behaves as an exceptionally mild reducing agent similar to sodium borohydride and lithium tri-*tert*-butoxyaluminohydride.[42] It reduces only aldehydes and ketones, being essentially inert to almost all other organic functional groups. In contrast to the other two mild reagents, the new reagent has the ability to introduce major steric control into the reduction of cyclic ketones (eq. 31).



(eq. 31)

$NaBH_4$	31%	69%
$Li(t\text{-}BuO)_3AlH$	27%	73%
$K(i\text{-}PrO)_3BH$	92%	8%

5. Alkali Metal Trialkylborohydrides[43]

In recent years, a number of alkali metal trialkylborohydrides have emerged as highly attractive reducing agents capable of achieving stereo- and regioselective synthetic transformations, unequalled by any other reagent currently available. These reagents are soluble in a variety of organic solvents (ethyl ether, tetrahydrofuran, diglyme, benzene, pentane, etc.) and are stable indefinitely when stored under nitrogen.

i) *Lithium Triethylborohydride (Super-Hydride®)*

Lithium hydride reacts rapidly and quantitatively with triethylborane in refluxing tetrahydrofuran to give lithium triethylborohydride in quantitative yield. The corresponding deuterium derivative is synthesized from lithium deuteride (eqs. 32 and 33).[44]

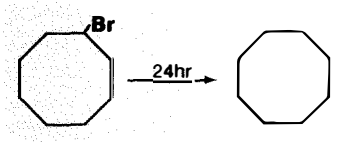
$$LiH + Et_3B \xrightarrow[0.25hr]{THF,\ 65°} LiEt_3BH \quad 100\% \quad \text{(eq. 32)}$$

$$LiD + Et_3B \xrightarrow[1hr]{THF,\ 65°} LiEt_3BD \quad 100\% \quad \text{(eq. 33)}$$

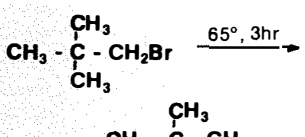
Lithium triethylborohydride (Super-Hydride) is an extraordinarily powerful reducing agent, far more powerful than lithium aluminum hydride and lithium borohydride.[45] Lithium triethylborohydride is the most powerful nucleophile available to organic chemists, considerably more powerful than nucleophiles such as thiophenoxide.

The reagent is exceptionally useful for the facile reductive dehalogenation of alkyl halides. The reaction involves a clean inversion at the reaction site (S_N2, eqs. 34-37).[45]

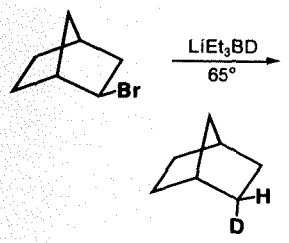
$$CH_3(CH_2)_6CH_2Br \xrightarrow[25°,\ 2min]{LiEt_3BH} CH_3(CH_2)_6CH_3 \quad \text{(eq. 34)}$$



(eq. 35)

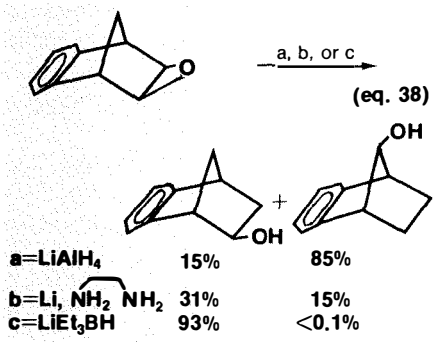


(eq. 36)



(eq. 37)

Lithium triethylborohydride reduces **epoxides** rapidly with remarkable regio- **and** stereospecificity to give the Markov**nikov** alcohol. The advantage is especially evident for the reduction of labile bicyclic epoxides (eq. 38).[46]

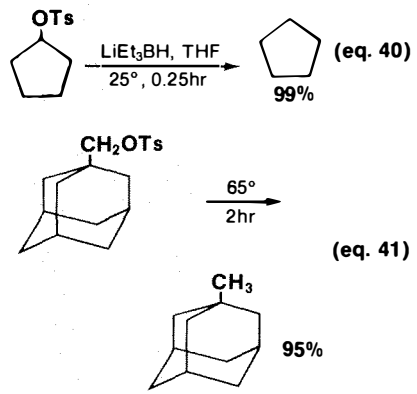


(eq. 38)

Super-Hydride reduces quaternary ammonium salts rapidly and cleanly to the corresponding amines in quantitative yield. The reagent is remarkable in discriminating between methyl and ethyl groups (eq. 39).[47]

$$PhN(C_2H_5)(CH_3)_2I \xrightarrow[25°,\ 0.75hr]{LiEt_3BH,\ THF} \underset{96\%}{PhN(C_2H_5)CH_3} + \underset{4\%}{PhN(CH_3)_2} \quad \text{(eq. 39)}$$

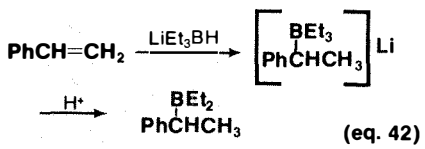
Super-Hydride provides an advantageous procedure for the deoxygenation of acyclic, cyclic and hindered alcohols through the reduction of their *p*-toluenesulfonate esters (eqs. 40 and 41).[48,49]



(eq. 40)

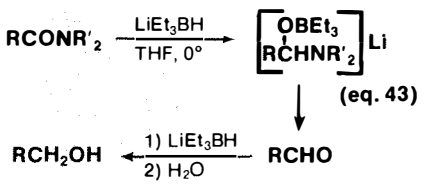
(eq. 41)

Lithium triethylborohydride adds to substituted styrenes providing a convenient entry into Markovnikov trialkylboranes (eq. 42).[50]



(eq. 42)

Reduction of tertiary amides with lithium triethylborohydride proceeds with carbon-nitrogen fission producing the corresponding alcohol (eq. 43).[51]



(eq. 43)

ii) *Lithium and Potassium Tri-sec-butylborohydrides (L- and K-Selectrides®)*

A number of methods have been developed for the quantitative synthesis of alkali metal trialkylborohydrides carrying hindered alkyl substituents (eqs. 44-47).[41,44,52-55]

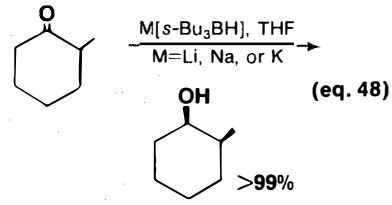
$$s\text{-}Bu_3B + NaH \xrightarrow[3hr]{THF,\ 65°} Na[s\text{-}Bu_3BH] \quad \text{(eq. 44)}$$

$$s\text{-}Bu_3B + KH \xrightarrow[0.25hr]{THF,\ 25°} K[s\text{-}Bu_3BH] \quad \text{(eq. 45)}$$

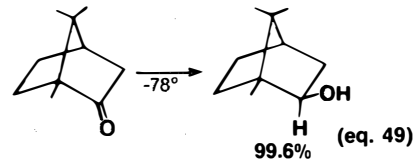
$$s\text{-}Bu_3B + LiAlH(OMe)_3 \xrightarrow[0.25hr]{THF,\ 25°} Li[s\text{-}Bu_3BH] + [Al(OMe)_3]\downarrow \quad \text{(eq. 46)}$$

$$s\text{-}Bu_3B + t\text{-}BuLi \xrightarrow[-78°]{THF} Li[s\text{-}Bu_3BH] + \quad \text{(eq. 47)}$$

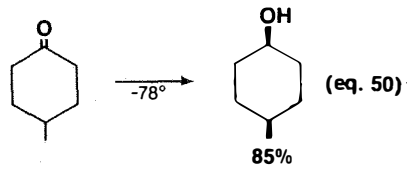
Aldehydes and ketones are reduced by alkali metal trialkylborohydrides rapidly and quantitatively to the corresponding alcohols even at -78°. One of the remarkable features of hindered trialkylborohydrides is their unusual ability to introduce major steric control into the reduction of cyclic ketones (eqs. 48-50).[56,57]



(eq. 48)

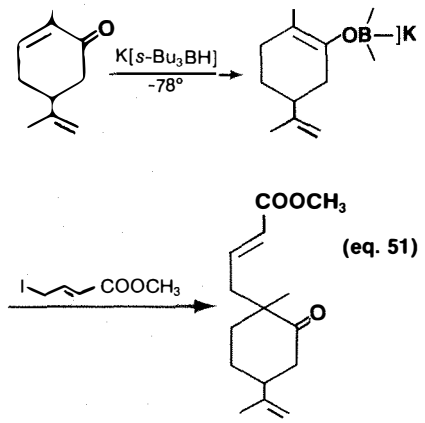


(eq. 49)



(eq. 50)

L- and K-Selectrides reduce α,β-enones and α,β-enoates in a conjugate fashion (1,4-reduction). This provides a convenient method for the generation of enolates which are trapped with a variety of electrophiles (eq. 51).[58,59]



(eq. 51)

iii) *Lithium and Potassium Trisiamylborohydrides (LS- and KS-Selectrides™)*

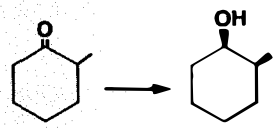
It was desirable to achieve the synthesis of a reagent that would reduce even 3- and 4-alkylcyclohexanones to the corresponding alcohols in a stereoselectivity of 99% or better. Recently, we have synthesized two highly hindered trialkylborohydrides — lithium tris(*trans*-2-methylcyclopentyl)-borohydride and lithium trisiamylborohydride — both of them containing secondary alkyl groups substituted by β-methyl (eq. 52).[60]

$$Sia_3B + t\text{-}BuLi \xrightarrow[-78°]{THF} LiSia_3BH \quad \text{100\%} \quad \text{(eq. 52)}$$

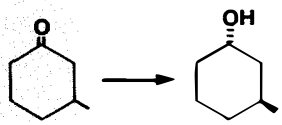
$$Sia \equiv (CH_3)_2CHCH(CH_3)-$$

The reagents can also be prepared by using lithium trimethoxyaluminohydride as the hydride source.[55]

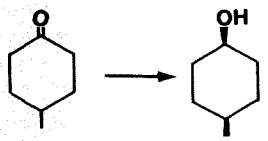
Lithium trisiamylborohydride reduces cyclic ketones with super stereoselectivity. Thus, 2-, 3-, and 4-alkylcyclohexanones are all reduced with lithium trisiamylborohydride at -78°C in ≥99% stereoselectivity (eqs. 53-55).



99.7% (eq. 53)



99.6% (eq. 54)

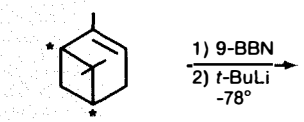


99.0% (eq. 55)

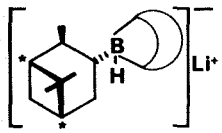
The corresponding potassium derivative synthesized recently by a catalytic process is equally effective.[61]

iv) *Lithium B-Isopinocampheyl-9-borabicyclo[3.3.1]nonyl Hydride. An Asymmetric Reducing Agent*[62]

A trialkylborohydride containing an asymmetric alkyl group, lithium *B*-isopinocampheyl-9-borabicyclo[3.3.1]nonyl hydride, has been synthesized (eq. 56).

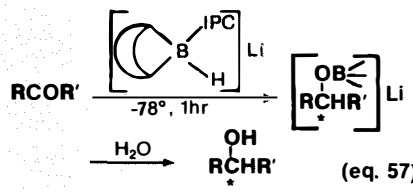


(1*R*, 5*R*) (+) (eq. 56)



100%

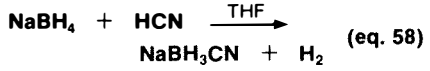
The reagent, prepared from (+)-α-pinene, rapidly and quantitatively reduces a wide variety of ketones to the corresponding alcohols. The alcohols produced are optically active (3-36% *e.e.*) and are consistently enriched in the *R* enantiomer (eq. 57).



(eq. 57)

6. Sodium Cyanoborohydride

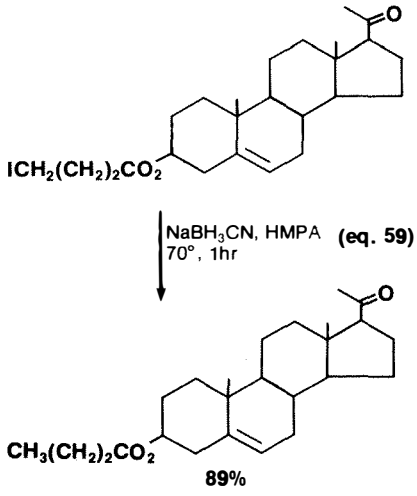
Sodium cyanoborohydride, synthesized from sodium borohydride and hydrogen cyanide, is a white crystalline solid, mp 240° (eq. 58).[63]



(eq. 58)

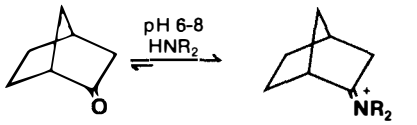
Unlike other hydride reagents, it is stable in acid solutions down to pH 3. It is soluble in tetrahydrofuran, methanol, water and in dipolar aprotic solvents (HMPA, DMF, sulfolane). It possesses a remarkable functional-group selectivity.

Sodium cyanoborohydride efficiently and selectively reduces alkyl halides to alkanes,[64] imines to amines,[65] and tosylhydrazones derived from aldehydes and ketones to the corresponding alkanes,[66] all in excellent yields (eqs. 59-61).



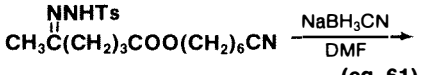
(eq. 59)

89%



(eq. 60)

63% (pure *endo*)



(eq. 61)

$CH_3(CH_2)_4COO(CH_2)_6CN$

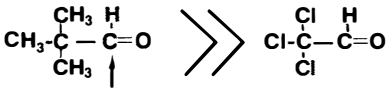
96%

7. Borane

Reductions involving complex borohydrides and their substituted derivatives discussed in the earlier sections (1-6) appear to involve transfer of the hydride moiety from the complex anion to an electron-deficient center of the functional group. Consequently, these are called nucleophilic or basic reducing agents.

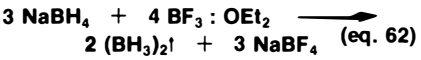
preferential attack by $NaBH_4$

The reactions involving borane, a strong Lewis acid, are expected to involve a preferential electrophilic attack at the centers of highest electron density. Hence, it is an electrophilic or acidic reducing agent.



preferential attack by B_2H_6

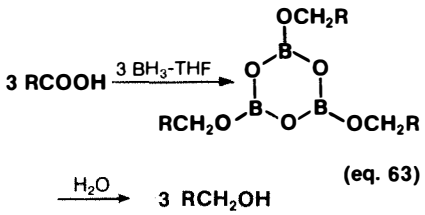
Diborane is sparingly soluble in ethyl ether and diglyme. It readily dissolves in tetrahydrofuran in which it exists as the borane-tetrahydrofuran addition compound. A standard solution of borane-THF in tetrahydrofuran can be prepared conveniently by treating sodium borohydride in diglyme with boron trifluoride etherate and passing the gas as generated into tetrahydrofuran (eq. 62).[67]



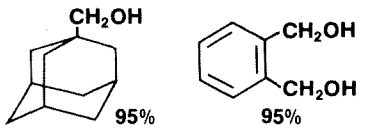
(eq. 62)

The exploration of the reducing characteristics of borane in THF has revealed a number of interesting features of this acidic reducing agent, quite different from those of the basic borohydride anion.[68-70]

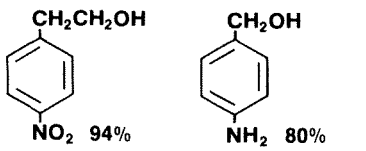
Aliphatic and aromatic carboxylic acids are reduced rapidly and quantitatively to the corresponding alcohols by borane in tetrahydrofuran, either at 0° or 25° (or even at -78°). (In view of the usual inertness of carboxylic acids toward many reducing agents, this high reactivity toward borane must be considered exceptional.) The reaction is applicable to a variety of structures such as sterically hindered acids, di- and polycarboxylic acids, phenolic acids, amino acids, etc. (eq. 63).[71]



(eq. 63)

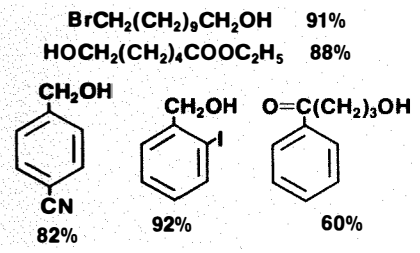


95% 95%

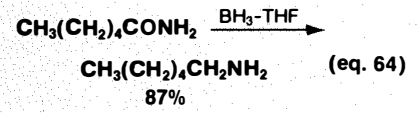


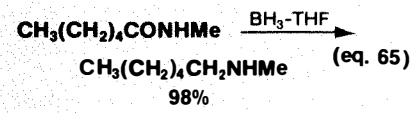
94% 80%

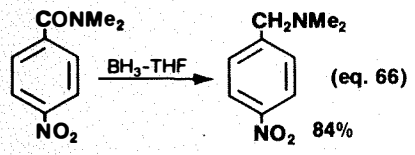
Borane-THF can tolerate a variety of functional groups and a number of functionalized alcohols have been prepared from the corresponding carboxylic acids in excellent isolated yields.



Another major application of borane-THF is the facile reduction of primary, secondary, and tertiary amides to the corresponding amines. Here again the reaction can tolerate many functional groups (eqs. 64-66).[72]



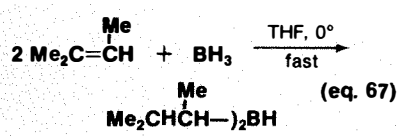


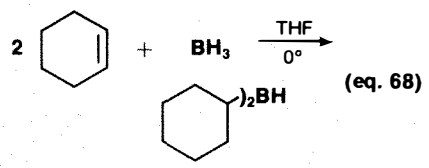


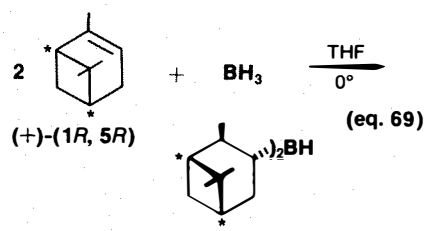
Until recently, the majority of borane reductions were carried out in tetrahydrofuran as the solvent. The recently introduced borane-methyl sulfide complex[73] has several advantages over borane-THF. It is exceptionally stable and is soluble in a variety of aprotic solvents such as ethyl ether, tetrahydrofuran, hexane, toluene, methylene chloride, diglyme, etc. Further, the reactivity of borane-methyl sulfide towards organic functional groups parallels that of borane-THF. Consequently, it is an advantageous reagent for the reduction of many organic functional groups.[74]

8. Dialkylboranes

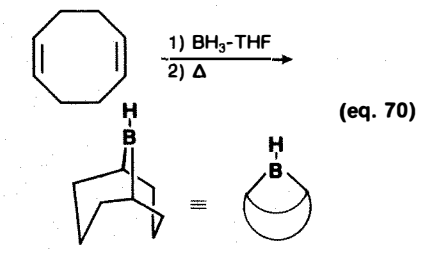
Hydroboration of certain hindered olefins or structurally suited dienes yields dialkylboranes preferentially. Thus, hydroboration of 2-methyl-2-butene rapidly forms the dialkylborane, disiamylborane (Sia_2BH).[75] The addition of the third mole of olefin is very sluggish. Similarly, dicyclohexylborane ($CHex_2BH$) and diisopinocampheylborane (IPC_2BH) (an asymmetric dialkylborane) can be prepared by the hydroboration of the corresponding olefins.[76] More recently, diisopinocampheylborane has been synthesized in very high purity (chemical as well as optical, eqs. 67-69).[77]



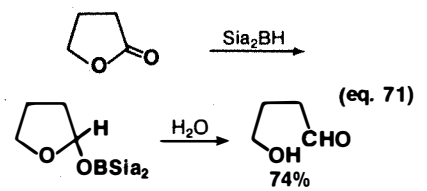




Cyclic hydroboration of 1,5-cyclooctadiene yields a bicyclic dialkylborane, 9-borabicyclo[3.3.1]nonane (9-BBN).[78] It exhibits certain unique physical and chemical characteristics. It is a white crystalline solid (mp 154-155°), thermally stable, relatively insensitive to air and soluble in a variety of organic solvents (eq. 70).

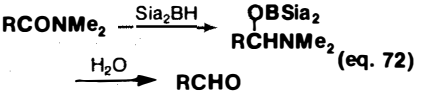


A systematic examination of the reducing characteristics of these dialkylboranes (disiamylborane and 9-BBN) towards representative organic functional groups has revealed a number of possible applications for these reagents in selective reductions.[79] One of the major applications of disiamylborane is the selective reduction of lactone to hydroxyaldehyde (eq. 71).[80]

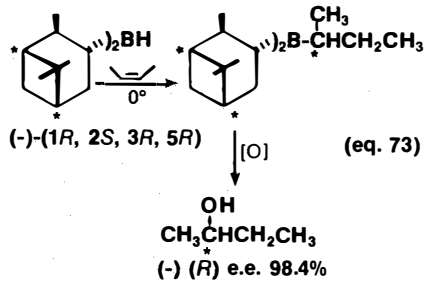


The reaction appears to be general. A number of interesting applications of this reagent for this type of transformation have been reported.[79a]

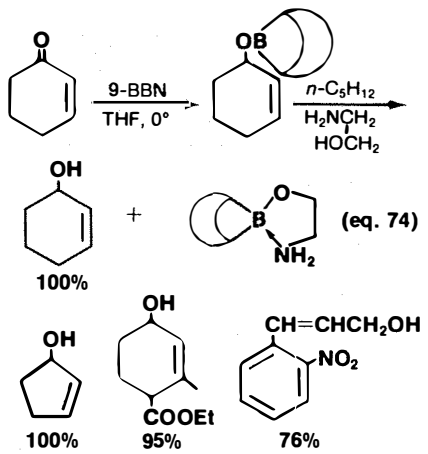
Preliminary investigations indicate that disiamylborane exhibits promise for the selective reduction of tertiary amides to the corresponding aldehydes (eq. 72).[79a]



Recently, diisopinocampheylborane of high optical purity has been examined for the asymmetric reduction of a representative series of alkyl methyl ketones. Asymmetric induction in the alcohol products in the range of 9 to 37% was observed.[81] Even more important, this new reagent achieves the asymmetric hydroboration of *cis*-2-butene to give, after oxidation, 2-butanol of optical purity as high as 98.4% (eq. 73).[77]



9-Borabicyclo[3.3.1]nonane reduces α,β-unsaturated aldehydes and ketones rapidly and quantitatively to the corresponding allylic alcohols. The development of a unique nonaqueous work-up procedure renders possible the isolation of the alcohols in excellent yields. Unlike conventional reagents, the mildness of 9-BBN permits the presence of almost any other functional group, such as ester, amide, carboxylic acid, nitro, halogen, and nitrile (eq. 74).[82]

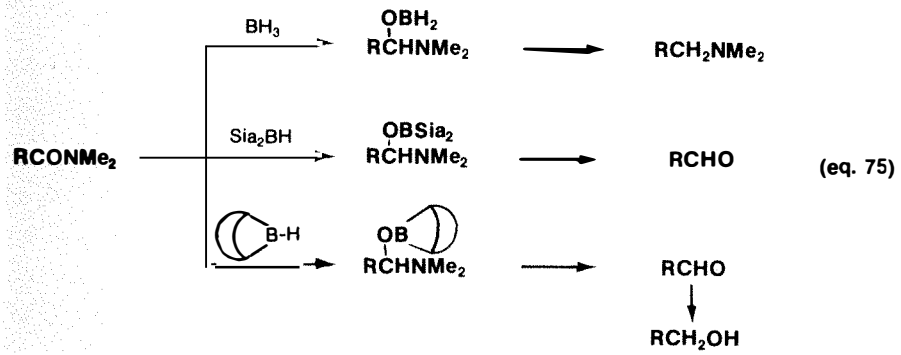


Reduction of tertiary amides to alcohols represents another promising area of application for 9-BBN yet to be explored in detail. It should be pointed out that we are now in a position to control the course of this reaction to get three different products by using various reagents (eq. 75).

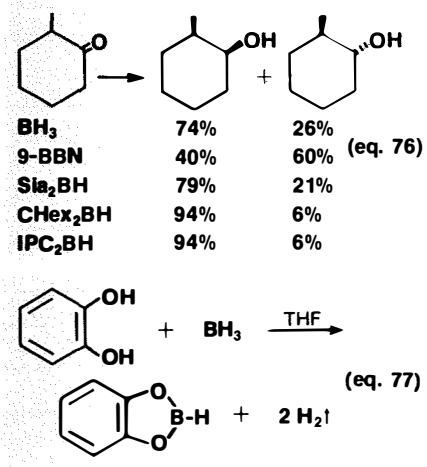
Dialkylboranes are consistent reagents for introducing steric control in the reduction of cyclic ketones. Increasing the size of the alkyl substituent(s) on boron enhances the stereoselectivity dramatically (eq. 76).[83]

9. Catecholborane and Chloroborane

Several heterosubstituted boranes also exhibit valuable properties as reducing agents. Thus, catechol reacts with borane to produce a new useful reducing agent, catecholborane (CB) (eq. 77).[84,85]



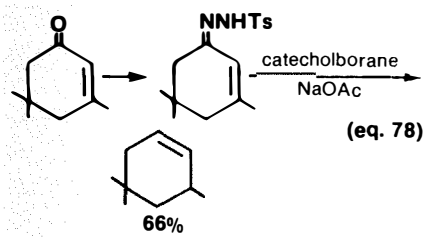
(eq. 75)



(eq. 76)

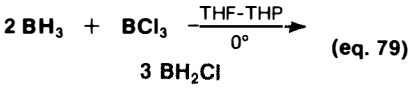
(eq. 77)

The reducing characteristics of this new reagent have been explored in detail.[86] The reagent is quite useful for the deoxygenation of α,β-unsaturated aldehydes and ketones through the reduction of their tosylhydrazones (eq. 78).[87]

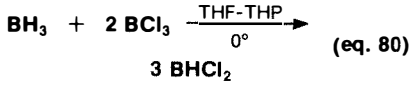


(eq. 78)

Procedures have been developed for the convenient synthesis of mono- and dichloroboranes (eqs. 79 and 80).[88]

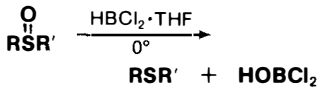


(eq. 79)



(eq. 80)

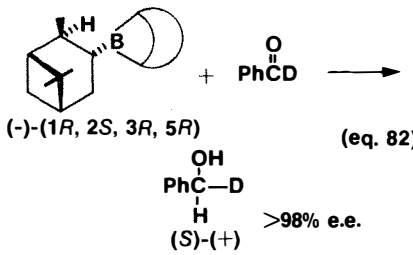
Aliphatic sulfoxides are rapidly deoxygenated to the corresponding sulfides in excellent yields by dichloroborane in tetrahydrofuran at 0° in a matter of minutes. The reaction can tolerate a variety of other reactive functional groups such as ketone, ester and amide (eq. 81).[89]



(eq. 81)

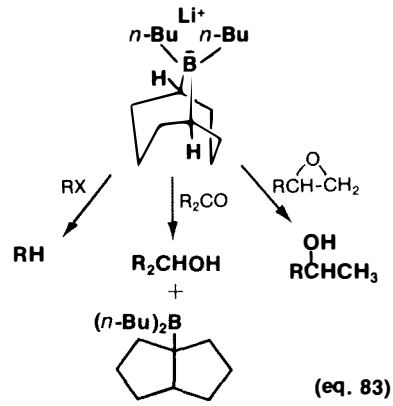
10. Trialkylboranes and "Ate" Complexes

Recently, certain trialkylboranes have been found to be effective reagents for the reduction of aldehydes to the corresponding alcohols. Especially interesting is the asymmetric reduction of benzaldehyde-α-*d* to benzyl-α-*d* alcohol by chiral *B*-isopinocampheyl-9-borabicyclo[3.3.1]nonane (eq. 82).[90]



(eq. 82)

Certain "ate" complexes derived from *B*-alkyl-9-BBN derivatives, such as lithium di-*n*-butyl-9-borabicyclo[3.3.1]nonane "ate" complex, have been discovered to be efficient reducing agents (eq. 83).[91]



(eq. 83)

V. SUMMARY

The systematic exploration of the reducing characteristics of various hydride reagents that have evolved during the course of forty years (1939-1979) has led to better understanding and appreciation of the scope and applicability of each reagent. The reactivities of hydride reagents toward various organic functional groups at 0-25° under standard conditions are summarized in Table 2. Symbol (+) indicates rapid reaction; symbol (-) indicates very slow or insignificant reaction; symbol (±) indicates a borderline case, the reactivity being sen-

Table II. Summary of behavior of various functional groups toward the hydride reagents

	$NaBH_4$ in ethanol	Li(O-*t*-Bu)$_3$AlH	$NaBH_4$ + LiCl in diglyme	$NaBH_4$ + $AlCl_3$ in diglyme	BH_3 in THF	Sia_2BH in THF	9-BBN in THF	AlH_3 in THF	LI(OMe)$_3$AlH in THF	$LiAlH_4$ in THF	$LiEt_3BH$ in THF
Aldehyde	+	+	+	+	+	+	+	+	+	+	+
Ketone	+	+	+	+	+	+	+	+	+	+	+
Acid chloride	R	+	+	+	—	—	+	+	+	+	+
Lactone	—	±	+	+	+	+	+	+	+	+	+
Epoxide	—	±	+	+	+	±	±	+	+	+	+
Ester	—	±	+	+	±	—	±	+	+	+	+
Acid	—	—	—	+	+	—	±	+	+	+	—
Acid salt	—	—	—	—	—	—	—	+	+	+	—
tert-Amide	—	—	—	—	+	+	+	+	+	+	+
Nitrile	—	—	—	—	+	—	±	+	+	+	+
Nitro	—	—	—	—	—	—	—	—	+	+	+
Olefin	—	—	—	—	+	+	+	—	—	—	—

R = Reacts with solvent; reduced in nonhydroxylic solvent

sitive to the structure of the functional group (both steric and electronic effects). A quick inspection of Table 2 reveals that by judicious choice of reducing agent it should be possible to reduce one group selectively in the presence of a second or to carry out the reverse operation. A word of caution is in order. The reactivities of the various functional groups can be greatly altered by the structures containing them. Consequently, these generalizations must be used with caution in predicting the behavior of greatly modified systems.

VI. CONCLUSIONS

Forty years ago it was first discovered that diborane reduces aldehydes and ketones rapidly. Unfortunately, the chemical rarity of diborane at the time prevented organic chemists from utilizing this reagent as a reducing agent. Subsequently, the development of practical synthetic routes to diborane, the discovery of sodium borohydride and, later, lithium aluminum hydride made such hydride reducing agents readily available. There then resulted rapid progress in the development of new reducing agents and in the exploration of their scope and applicability in organic synthesis. Still, we are in constant search of new selective reducing agents that are capable of reacting with a specific functional group. Today an organic chemist has a choice of specific hydride reagents for achieving specific synthetic transformations. Even more important, the majority of these reagents are now commercially available to facilitate their application by chemists.[92]

ACKNOWLEDGEMENT

We wish to acknowledge the generous financial support of the U.S. Army Research Office, North Carolina, through a series of grants for our program on "Selective Reductions" from the inception of this program to the present.

References and Notes:

1) Based in part on the symposium lecture delivered before the Organic Division at the Centennial Meeting of the American Chemical Society, New York (March 1976).
2) H.C. Brown, H.I. Schlesinger, and A.B. Burg, *J. Am. Chem. Soc.*, **61**, 673 (1939).
3) For an extensive review of our earlier results, see (a) H.C. Brown, *J. Chem. Educ.*, **38**, 173 (1961); (b) H.C. Brown, *Moderni Sivilupi Della Sintesi Organica*. Conferenze X, Corso Estivo di Chimica, Academica Nationale dei Lincei, Rome, 1968, pp 31-50; (c) H.C. Brown, "Boranes in Organic Chemistry," Cornell University Press, Ithaca, N.Y., 1972.
4) (a) N.G. Gaylord, "Reduction with Complex Metal Hydrides," Interscience Publishers, Inc., New York, N.Y., 1956; (b) E. Schenker, "Newer Methods of Preparative Organic Chemistry," Vol. IV, W. Foerst, Ed., Verlag Chemie GmbH, Weinheim/Bergstr., 1968, pp 196-335; (c) H.C. Brown, "Organic Syntheses via Boranes," Wiley-Interscience, New York, N.Y., 1975; (d) G.M.L. Cragg, "Organoboranes in Organic Synthesis," Marcel Dekker, New York, N.Y., 1973, p 319; (e) H.O. House, "Modern Synthetic Reactions," 2nd ed., Benjamin, Menlo Park, Ca., 1972, p 45; (f) E.R.H. Walker, *Chem. Soc. Rev.*, **5**, 23 (1976); (g) C.F. Lane, *Chem. Rev.*, **76**, 773 (1976).
5) (a) J. Bouis and H. Carlet, *Justus Liebigs Ann. Chem.*, **124**, 352 (1862); (b) C. Schorlemmer, *ibid.*, **177**, 303 (1875); (c) P.A. Levene and F.A. Taylor, *J. Biol. Chem.*, **35**, 281 (1918); (d) A.J. Hill and E.H. Nason, *J. Am. Chem. Soc.*, **46**, 2236 (1924); (e) H.T. Clarke and E.E. Dreger, *Org. Synth., Coll. Vol. 1*, 304 (1941).
6) (a) H. Thoms and C. Mannich, *Ber.*, **36**, 2544 (1903); (b) F.C. Whitmore and T. Otterbacker, *Org. Synth., Coll. Vol. 2*, 317 (1943).
7) F.Y. Wiselogle and H. Sonneborn III, *Org. Synth., Coll. Vol. 1*, 90 (1941).
8) A. Verley, *Bull. Soc. Chim. Fr.*, 37, 537, 871 (1925).
9) H. Meerwein and R. Schmidt, *Justus Liebigs Ann. Chem.*, **444**, 221 (1925).
10) W. Ponndorf, *Z. Angew. Chem.*, **39**, 138 (1926).
11) H. Lund, *Ber.*, **70**, 1520 (1937).
12) For an extensive review on Meerwein-Ponndorf-Verley reduction, see A.L. Wilds, *Org. React.*, **2**, 178 (1944).
13) (a) L. Bouveault and G. Blanc, *Bull. Soc. Chim. Fr.*, **31**, 674 (1904); (b) P.A. Levene and C.H. Allen, *J. Biol. Chem.*, **27**, 443 (1916); (c) S.G. Ford and C.S. Marvel, *Org. Synth., Coll. Vol. 2*, 372 (1943).
14) A.B. Burg and H.I. Schlesinger, *J. Am. Chem. Soc.*, **59**, 780 (1937).
15) A. Stock, "Hydrides of Boron and Silicon," Cornell University Press, Ithaca, N.Y., 1933.
16) A. Stock and C. Massenze, *Ber.*, **45**, 3539 (1912).
17) H.I. Schlesinger and A.B. Burg, *J. Am. Chem. Soc.*, **53**, 4321 (1931).
18) H.I. Schlesinger, R.T. Sanderson, and A.B. Burg, *ibid.*, **62**, 3421 (1940).
19) H.I. Schlesinger and A.B. Burg, *ibid.*, **62**, 3425 (1940).
20) H.I. Schlesinger, H.C. Brown, B.A. Abraham, N. Davidson, A.E. Finholt, R.A. Lad, J. Knight, and A.M. Schwartz, *ibid.*, **75**, 191 (1953).
21) H.I. Schlesinger and H.C. Brown, *ibid.*, **75**, 219 (1953).
22) H.I. Schlesinger, H.C. Brown, J.R. Gilbreath, and J.J. Katz, *ibid.*, **75**, 195 (1953).
23) H.I. Schlesinger, H.C. Brown, H.R. Hoekstra, and L.R. Rapp, *ibid.*, **75**, 199 (1953).
24) H.I. Schlesinger, H.C. Brown, and E.K. Hyde, *ibid.*, **75**, 209 (1953).
25) H.C. Brown, H.I. Schlesinger, I. Sheft, and D.M. Ritter, *ibid.*, **75**, 192 (1953).
26) H.I. Schlesinger, H.C. Brown, and A.E. Finholt, *ibid.*, **75**, 205 (1953).
27) A.E. Finholt, A.C. Bond, Jr., and H.I. Schlesinger, *ibid.*, **69**, 1199 (1947).
28) W.G. Brown, *Org. React.*, **6**, 469 (1951).
29) H.C. Brown, P.M. Weissman, and N.M. Yoon, *J. Am. Chem. Soc.*, **88**, 1458 (1966).
30) S.W. Chaikin and W.G. Brown, *ibid.*, **1**, 122 (1949).
31) H.M. Bell and H.C. Brown, *ibid.*, **88**, 1473 (1966).
32) R.O. Hutchins, F. Cistone, B. Goldsmith, and P. Heuman, *J. Org. Chem.*, **40**, 2018 (1975).
33) R.F. Nystrom, S.W. Chaikin, and W.G. Brown, *J. Am. Chem. Soc.*, **71**, 3245 (1949).
34) N.M. Yoon and J.S. Cha, *J. Korean Chem. Soc.*, **21**, 108 (1977).
35) H.C. Brown and B.C. Subba Rao, *J. Org. Chem.*, **22**, 1136 (1957).
36) J. Kollonitsch, P. Fuchs, and V. Gabor, *Nature*, **173**, 125 (1954).
37) J. Kollonitsch, P. Fuchs, and V. Gabor, *ibid.*, **175**, 346 (1955).
38) (a) H.C. Brown and B.C. Subba Rao, *J. Am. Chem. Soc.*, **78**, 2582 (1956); (b) Recent ^{11}B NMR examination of such solutions in diglyme indicates the presence of $NaBH_4$, NaB_2H_7, $NaAlCl_3 \cdot BH_4$ and $NaAlCl_3H$—all present at the same time.

$$AlCl_3 + NaBH_4 \underset{\text{diglyme}}{\rightleftharpoons} NaCl_3Al \cdot BH_4$$

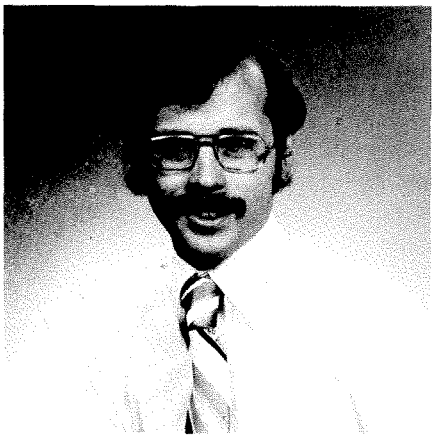
$$NaCl_3Al \cdot BH_4 + NaBH_4 \rightarrow NaAlCl_3H + NaB_2H_7$$

Further reaction will only proceed if this system is disturbed; see H. Nöth, "Proceedings of Hydride Symposium. II.," Metalgesellschaft AG, Frankfurt, 1974, p 51.
39) N.M. Yoon, H.J. Lee, J. Kong, and J.S. Chung, *J. Korean Chem. Soc.*, **19**, 468 (1975).
40) H.C. Brown, E.J. Mead, and C.J. Shoaf, *J. Am. Chem. Soc.*, **78**, 3616 (1956).
41) C.A. Brown, *ibid.*, **95**, 4100 (1973).
42) C.A. Brown, S. Krishnamurthy, and S.C. Kim, *Chem. Commun.*, 373 (1973).
43) For a review on this subject, see S. Krishnamurthy, *Aldrichimica Acta*, 7, 55 (1974).
44) H.C. Brown, S. Krishnamurthy, and J.L. Hubbard, *J. Am. Chem. Soc.*, **100**, 3343 (1978).
45) H.C. Brown and S. Krishnamurthy, *ibid.*, **95**, 1669 (1973).
46) S. Krishnamurthy, R.M. Schubert, and H.C. Brown, *ibid.*, **95**, 8486 (1973).
47) M.P. Cooke, Jr. and R.M. Parlman, *J. Org. Chem.*, **40**, 531 (1975).
48) S. Krishnamurthy and H.C. Brown, *ibid.*, **41**, 3064 (1976).
49) S. Krishnamurthy, *J. Organometal. Chem.*, **156**, 171 (1978).
50) H.C. Brown and S.C. Kim, *J. Org. Chem.*, **42**, 1482 (1978).
51) H.C. Brown and S.C. Kim, *Synthesis*, 635 (1977).
52) C.A. Brown and S. Krishnamurthy, *J. Organometal. Chem.*, **156**, 111 (1978).
53) P. Binger, G. Benedikt, G.W. Rotermund, and R. Köster, *Justus Liebigs Ann. Chem.*, **717**, 21 (1968).
54) E.J. Corey, S.M. Albonico, U. Koelliker, T.K. Schaaf, and R.K. Varma, *J. Am. Chem. Soc.*, 93, 1491 (1971).
55) H.C. Brown, S. Krishnamurthy, and J.L. Hubbard, *J. Organometal. Chem.*, in press.
56) H.C. Brown and W.C. Dickason, *J. Am. Chem. Soc.*, **92**, 709 (1970).
57) H.C. Brown and S. Krishnamurthy, *ibid.*, **94**, 7159 (1972).
58) H.C. Brown, S. Krishnamurthy, and S.C. Kim, unpublished results.
59) (a) B. Ganem, *J. Org. Chem.*, **40**, 2846 (1975); (b) J.M. Fortunato and B. Ganem, *ibid.*, **41**, 2194 (1976).
60) S. Krishnamurthy and H.C. Brown, *J. Am. Chem. Soc.*, **98**, 3383 (1976).
61) C.A. Brown and S. Krishnamurthy, Abstracts, 175th National Meeting of the American Chemical Society, Anaheim, Ca., March 1978, ORGN 23.
62) S. Krishnamurthy, F. Vogel, and H.C. Brown, *J. Org. Chem.*, **42**, 2534 (1977).
63) (a) G. Wittig, *Justus Liebigs Ann. Chem.*, **573**, 209 (1951); (b) R.C. Wade, E.A. Sullivan, J.R. Berchied, Jr., and K.F. Purcell, *Inorg. Chem.*, **9**, 2146 (1970).
64) R.O. Hutchins, D. Kandasamy, C.A. Maryanoff, D. Masilamani, and B.E. Maryanoff, *J. Org. Chem.*, **42**, 82 (1977).
65) R.F. Borch, M.D. Bernstein, and H.D. Durst, *J. Am. Chem. Soc.*, 93, 2897 (1971).
66) R.O. Hutchins, C.A. Milewski, and B.E. Maryanoff, *ibid.*, **95**, 3662 (1973).
67) G. Zweifel and H.C. Brown, *Org. React.*, **13**, 1 (1963).
68) H.C. Brown and B.C. Subba Rao, *J. Am. Chem. Soc.*, **82**, 681 (1960).
69) H.C. Brown and W. Korytnik, *ibid.*, **82**, 3866 (1960).
70) H.C. Brown, P. Heim, and N.M. Yoon, *ibid.*, **92**, 1637 (1970).
71) N.M. Yoon, C.S. Pak, H.C. Brown, S. Krishnamurthy, and T.P. Stocky, *J. Org. Chem.*, **38**, 2786 (1973).
72) H.C. Brown and P. Heim, *ibid.*, **38**, 912 (1973).
73) L.M. Braun, R. Braun, H.R. Crissman, M. Opperman, and R.M. Adams, *ibid.*, **36**, 2388 (1971).
74) (a) C.F. Lane, *Aldrichimica Acta*, **8**, 20 (1975); (b) S. Krishnamurthy and K.L. Thompson, *J. Chem. Educ.*, **54**, 778 (1977); (c) C.F. Lane, H.L. Myatt, J. Daniels, and H. Hopps, *J. Org. Chem.*, 39, 3052 (1974).
75) H.C. Brown and G. Zweifel, *J. Am. Chem. Soc.*, **83**, 1241 (1961).
76) G. Zweifel and H.C. Brown, *ibid.*, **86**, 393 (1964).
77) H.C. Brown and N.M. Yoon, *Israel J. Chem.*, **15**, 12 (1977).
78) E.F. Knights and H.C. Brown, *J. Am. Chem. Soc.*, **90**, 5280, 5281 (1968).
79) (a) H.C. Brown, D.B. Bigley, S.K. Arora, and N.M. Yoon, *ibid.*, **92**, 7161 (1970); (b) H.C. Brown, S. Krishnamurthy, and N.M. Yoon, *J. Org. Chem.*, **41**, 1778 (1976).
80) H.C. Brown and D.B. Bigley, *J. Am. Chem. Soc.*, **83**, 486 (1961).

81) H.C. Brown and A.K. Mandal, *J. Org. Chem.*, **42**, 2996 (1977).
82) (a) S. Krishnamurthy and H.C. Brown, *J. Org. Chem.*, **40**, 1864 (1975); (b) *ibid.*, **42**, 1197 (1977).
83) H.C. Brown and V. Varma, *ibid.*, **39**, 1631 (1974).
84) H.C. Brown and S.K. Gupta, *J. Am. Chem. Soc.*, **93**, 1816 (1971).
85) C.F. Lane and G.W. Kabalka, *Tetrahedron*, **32**, 981 (1976).
86) G.W. Kabalka, J.D. Baker, Jr., and G.W. Neal, *J. Org. Chem.*, **42**, 512 (1977).
87) G.W. Kabalka, D.T.C. Yang, and J.D. Baker, Jr., *ibid.*, **41**, 574 (1976).
88) (a) H.C. Brown and P.A. Tierney, *J. Inorg. Nucl. Chem.*, **9**, 51 (1959); (b) D.J. Pasto and P. Balasubramanian, *J. Am. Chem. Soc.*, **89**, 295 (1967); (c) H.C. Brown and N. Ravindran, *J. Org. Chem.*, **42**, 2533 (1977).
89) H.C. Brown and N. Ravindran, *Synthesis*, 42 (1972).
90) (a) M.M. Midland, A. Tramontano, and S.A. Zderic, *J. Organometal. Chem.*, **156**, 203 (1978); (b) M.M. Midland, A. Tramontano, and S.A. Zderic, *J. Am. Chem. Soc.*, **99**, 5211 (1977).
91) (a) Y. Yamamoto, H. Toi, S.I. Murahashi, and I. Moritani, *J. Am. Chem. Soc.*, **97**, 2558 (1975); (b) Y. Yamamoto, H. Toi, A. Sonoda, and S.I. Murahashi, *ibid.*, **98**, 1965 (1976); *Chem. Commun.*, 672 (1976).
92) Available from Aldrich Chemical Co., Inc., Milwaukee, Wisconsin 53233.

Trialkylborohydrides in Organometallic Syntheses

J.A. Gladysz
Department of Chemistry
University of California
Los Angeles, CA 90024



Trialkylborohydrides have been well established as potent hydride donors toward a variety of organic electrophiles.[1] Lithium triethylborohydride (Super-Hydride®) has been shown to be an exceptionally clean reagent for the reductive displacement of alkyl halides[2] and tosylates[3] and reductive ring opening of epoxides.[4] Hindered trialkylborohydrides such as lithium trisiamylborohydride (siamyl = 3-methyl-2-butyl) can reduce ketones such as 3-methylcyclohexanone with ≥99.6% stereoselectivity.[5] Other applications include the use of K(*sec*-$C_4H_9)_3BH$ (K-Selectride®) for the 1,4-reduction of enones[6] and chiral trialkylborohydrides for executing asymmetric reductions.[7]

A somewhat different line of research involving trialkylborohydride reagents has been under investigation in our laboratory. We have been interested in their reactivity toward inorganic and organometallic electrophiles. With substrates containing metal-metal or heteroatom-heteroatom bonds, rapid and high-yield cleavage to two nucleophilic anionic species occurs in many cases. Since transition metal anions, main-group metal anions, and metalloid anions are key intermediates in organometallic syntheses, our studies impact upon a broad front of synthetic chemistry.

It was our interest in nucleophilic attack upon coordinated CO that first led us to study the reactions of trialkylborohydrides with metal carbonyl complexes. A variety of reactions had been observed previously between $NaBH_4$ and metal carbonyl complexes.[8] We thought that a hydride source which was soluble in organic solvents and contained only one transferable hydride per mole would yield better defined chemistry.

One of the first useful reactions observed was the cleavage of metal carbonyl dimers to metal carbonyl anions (eqs. 1-4).[9,10] Transition metal anions play a pivotal role in the construction of metal-carbon and metal-metal bonds. They are highly nucleophilic species which may be readily alkylated, acylated, or metalated by reaction with an appropriate electrophile.

Conventionally, 1% Na/Hg amalgam or other heterogeneous metal reductants have been employed for the conversion of metal carbonyl dimers to metal carbonyl anions.[11] The problems involved are mainly ones of manipulation and handling. When Na/Hg is utilized, mercury-containing by-products are sometimes produced.[12] The use of $Li(C_2H_5)_3BH$, however, enables the rapid, room-temperature, one-flask synthesis of anions $Li[Co(CO)_4]$, $Li[(C_5H_5)Mo(CO)_3]$, and $Li[Mn(CO)_5]$ in near-quantitative yield under homogeneous conditions. Only the volatile by-products H_2 and $(C_2H_5)_3B$ are produced (eqs. 1-3).

Many elegant and useful synthetic transformations utilizing organometallics prepared from $[(C_5H_5)Fe(CO)_2]^-$ have been described in the literature.[13] The generation of $Li[(C_5H_5)Fe(CO)_2]$ *via* $Li(C_2H_5)_3BH$ or Li(*sec*-$C_4H_9)_3BH$ (L-Selectride®), however, requires longer reaction times (2hr) and ≥50% HMPA cosolvent (eq. 4). This is likely a consequence of the higher reduction potential of $[(C_5H_5)Fe(CO)_2]_2$ relative to the other metal carbonyl dimers. However, potassium trialkylborohydrides are stronger hydride donors, and K(*sec*-$C_4H_9)_3BH$ and $K(C_2H_5)_3BH$ were found to effect the synthesis of $K[(C_5H_5)Fe(CO)_2]$ in THF (eq. 5). Reaction times were 3hr at room temperature or 0.5hr at 45-65°C.

$$(CO)_4Co\text{-}Co(CO)_4 + 2\,LI(C_2H_5)_3BH \longrightarrow 2\,\underline{LI[Co(CO)_4]} + 2\,(C_2H_5)_3B + H_2 \qquad \text{(eq. 1)}$$

$$(CO)_5Mn\text{-}Mn(CO)_5 + 2\,LI(C_2H_5)_3BH \longrightarrow 2\,\underline{LI[Mn(CO)_5]} + 2\,(C_2H_5)_3B + H_2 \qquad \text{(eq. 2)}$$

$$(C_5H_5)(CO)_3Mo\text{-}Mo(CO)_3(C_5H_5) + 2\,LI(C_2H_5)_3BH \longrightarrow 2\,\underline{LI[(C_5H_5)Mo(CO)_3]} + 2\,(C_2H_5)_3B + H_2 \qquad \text{(eq. 3)}$$

$$(C_5H_5)(CO)_2Fe\text{-}Fe(CO)_2(C_5H_5) + 2\,Li(C_2H_5)_3BH \xrightarrow{HMPA} 2\,\underline{Li[(C_5H_5)Fe(CO)_2]} + 2\,(C_2H_5)_3B + H_2 \qquad \text{(eq. 4)}$$

$$(C_5H_5)(CO)_2Fe\text{-}Fe(CO)_2(C_5H_5) + 2\,K(sec\text{-}C_4H_9)_3BH \xrightarrow{3hr} 2\,\underline{K[(C_5H_5)Fe(CO)_2]} + 2\,(sec\text{-}C_4H_9)_3B + H_2 \qquad \text{(eq. 5)}$$

Potassium salts of other metal carbonyl anions, (*e.g.*, $K[(C_5H_5)Mo(CO)_3]$, $K[Mn(CO)_5]$; eqs. 6 and 7) can also be prepared with $K(sec\text{-}C_4H_9)_3BH$ and $K(C_2H_5)_3BH$. Sodium trialkylborohydrides are readily synthesized[14] and can be used similarly. Thus, transition metal anions can be prepared with a number of different counter-ions by the trialkylborohydride method. Triethylborohydrides are preferable to tri-*sec*-butylborohydrides because of the greater volatility of the borane by-product.

To demonstrate the preparative utility of these metal anion solutions, we have synthesized a number of derivatives.[9,10] These are compiled in Table I; full experimental details have been published.[10] Entries 1 and 10 depict the actual isolation of two anions as their air-stable "PPN$^+$", or $[(C_6H_5)_3P]_2N^+$, salts. Acylation reactions are illustrated in entries 4,5,7,9,13, and 14. Alkylation reactions and the formation of tin and silicon derivatives are also tabulated. Isolated yields are uniformly good.

We have investigated the *in situ* preparation of other metal carbonyl anion derivatives. Protonation of $Li[Mn(CO)_5]$ and $Li[(C_5H_5)Mo(CO)_3]$ with the nonaqueous, nonoxidizing acid CF_3SO_3H affords quantitative spectroscopic yields of $H[Mn(CO)_5]$ and $H[(C_5H_5)Mo(CO)_3]$, respectively (eqs. 8 and 9).[15]

Transition metal hydrides are key intermediates in numerous stoichiometric and catalytic reactions, and have been the object of a variety of structural, spectroscopic, and theoretical studies.[8] Since the conventional preparation of anhydrous $H[Mn(CO)_5]$ requires extensive vacuum-line manipulations,[16] our *in situ* synthesis offers obvious advantages. We have used it to study several $H[Mn(CO)_5]$ reactions.[15]

Trialkylborohydrides also enable the preparation of metal carbonyl anions from other organometallic precursors.[10] Eqs. 10 and 11 provide two such examples.

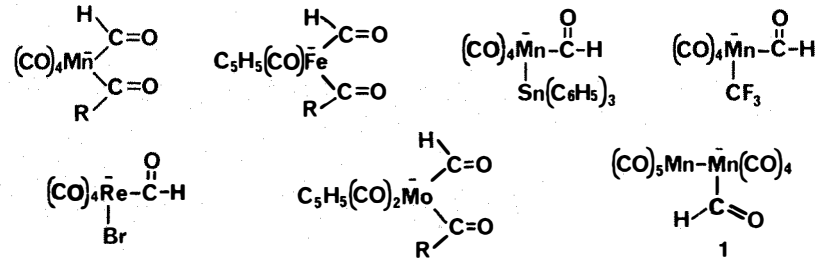
We anticipate that such reactions may prove of occasional synthetic utility. For instance, $[Mn(CO)_5]Br$ undergoes much more rapid exchange with ^{13}CO than $[Mn(CO)_5]_2$. Thus, the preparation of ^{13}CO-labeled $[Mn(CO)_5]R$ species would be most readily accomplished *via* initial conversion of $[Mn(CO)_5]_2$ to $[Mn(CO)_5]Br$. After ^{13}CO exchange, the desired product could be obtained in a one-flask operation from labeled $[Mn(CO)_5]Br$.

A major focus of research in our laboratory has been the preparation and characterization of reactive ligand types believed to be present on the reaction coordinate between CO/H_2 and alkanes and alcohols in Fischer-Tropsch-type processes.[17] There has been a great deal of attention focused upon formyl ligands as the probable initially formed catalyst-bound species.[17]

Trialkylborohydrides provide an excellent means of generating anionic formyl complexes according to the generalized eq. 12. Because most anionic formyl complexes rapidly decompose at room temperature, reactions must be carried out below 0°C and the products characterized by low temperature spectroscopy. Figure 1 illustrates the variety of unstable metal formyl complexes prepared by this method.[18-20] Not surprisingly, we believe anionic formyl complexes are intermediates in many of our metal carbonyl anion syntheses. Species **1** is formed in 99% yield when $[Mn(CO)_5]_2$ is treated with one equivalent of $Li(C_2H_5)_3BH$ at -20°C; warming to room temperature and the addition of a second equivalent of $Li(C_2H_5)_3BH$ affords two equivalents of $Li[Mn(CO)_5]$ quantitatively.[9]

Figure 1

UNSTABLE ANIONIC FORMYL COMPLEXES PREPARED WITH $Li(C_2H_5)_3BH$



1

The metal carbonyl dimer $[Re(CO)_5]_2$ did not cleave upon reaction with $Li(C_2H_5)_3BH$. Instead, a thermally stable binuclear rhenium formyl complex was obtained, which proved *isolable* (eq. 13).[21] Rhenium is known to form stronger metal-metal and metal-ligand bonds than manganese.

Anionic formyl complexes can undergo further reduction by trialkylborohydrides. Organic products, presumably derived from the formyl ligand, include formaldehyde and methanol.[21] When $Fe(CO)_5$ was treated with 2 equivalents of $K(sec\text{-}C_4H_9)_3BH$, the formyl complex $K[(CO)_4Fe(COH)]$ (**2**) was rapidly formed;[22] refluxing the reaction mixture for 3hr in THF afforded $K_2[Fe(CO)_4]$ in quantitative yield as an analytically pure precipitate (eq. 14).[23] The highly nucleophilic tetracarbonylferrate dianion, $[Fe(CO)_4]^=$ has been proven to be of considerable value in organic and inorganic syntheses.[11,24] A number of useful organic transformations employing $Na_2[Fe(CO)_4]$ or $Na_2[Fe(CO)_4]\cdot$dioxane have been developed by Collman and coworkers.[24] Although $K_2[Fe(CO)_4]$ has not been as extensively utilized, its preparation is distinctly easier and it is not pyrophoric. To provide additional characterization, we carried out the homologation reaction depicted in eq. 15 and the derivatization with $AuCl[P(C_6H_5)_3]$ depicted in eq. 16.[23]

Trialkylborohydrides may prove useful in the synthesis of other transition metal dianions. Following an initial report by Shore,[25] we were able to prepare the cluster dianion $K_2[H_2Ru_4(CO)_{12}]$ according to eq.

$$(C_5H_5)(CO)_3Mo\text{-}Mo(CO)_3(C_5H_5) + 2\,K(sec\text{-}C_4H_9)_3BH \longrightarrow 2\,K[(C_5H_5)Mo(CO)_3] + 2\,(sec\text{-}C_4H_9)_3B + H_2 \quad \text{(eq. 6)}$$

$$(CO)_5Mn\text{-}Mn(CO)_5 + 2\,K(sec\text{-}C_4H_9)_3BH \longrightarrow 2\,K[Mn(CO)_5] + 2\,(sec\text{-}C_4H_9)_3B + H_2 \quad \text{(eq. 7)}$$

$$Li[Mn(CO)_5] + CF_3SO_3H \longrightarrow H[Mn(CO)_5] + CF_3SO_3Li \quad \text{(eq. 8)}$$

$$Li[(C_5H_5)Mo(CO)_3] + CF_3SO_3H \longrightarrow H[(C_5H_5)Mo(CO)_3] + CF_3SO_3Li \quad \text{(eq. 9)}$$

$$[Mn(CO)_5]Br + 2\,Li(C_2H_5)_3BH \longrightarrow Li[Mn(CO)_5] + LiBr + 2\,(C_2H_5)_3B + H_2 \quad \text{(eq. 10)}$$

$$[(C_5H_5)Mo(CO)_3]Cl + 2\,Li(C_2H_5)_3BH \longrightarrow Li[(C_5H_5)Mo(CO)_3] + LiCl + 2\,(C_2H_5)_3B + H_2 \quad \text{(eq. 11)}$$

17.[26] Exploratory reactions indicate that trialkylborohydrides are not sufficiently strong reductants to produce metal carbonyl trianions and tetraanions of the type reported by Ellis.[27]

Recently, we have found that trialkylborohydrides can also be used to form ***neutral*** formyl complexes from metal carbonyl cations according to the generalized eq. 18.[28] These reactions, and the properties of the products, are under active investigation. The neutral formyl $(C_5H_5)Re(CO)(NO)(COH)$ (**3**), whose preparation is depicted in Scheme I, has a half-life of *ca.* 3hr at room temperature. The addition of a second equivalent of $Li(C_2H_5)_3BH$ affords **4**, the first bis(formyl) complex prepared. Reaction of **3** with $BH_3 \cdot THF$ reduces the formyl ligand to a methyl ligand (Scheme I).

In only one instance have we observed a trialkylborohydride to cleanly attack a metal carbonyl complex at a site other than coordinated CO. The reaction of **5** with $Li(C_2H_5)_3BH$ afforded the novel metallocycle **6**, presumably *via* intermediate **7** (eq. **19**).[29] We undertook an X-ray crystal-structure determination of the PPN^+ salt of **6** to confirm its structure. Metallocycle **6** is not merely a curiosity; it serves as a pivotal intermediate in our recently described approach to α-silyloxyalkyl and α-hydroxyalkyl metal complexes.[29] α-Hydroxyalkyl ligands are believed to be key mechanistic branch points in Fischer-Tropsch-type processes.[17]

Having established that trialkylborohydrides can effect the net cleavage of metal-metal bonds, we decided to see if metalloid-metalloid bonds could be broken as well. Gray, elemental selenium consists of polymeric, unbranched helical chains.

$$L_nM\text{-}C{=}O + Li(C_2H_5)_3BH \longrightarrow Li^+\,L_nM^-\text{-}\overset{O}{\overset{\|}{C}}\text{-}H + (C_2H_5)_3B \qquad \text{(eq. 12)}$$

$$(CO)_5Re\text{-}Re(CO)_5 \xrightarrow{Li(C_2H_5)_3BH} Li^+(CO)_5Re\text{-}\underset{\displaystyle H\text{-}C{=}O}{\overset{\displaystyle |}{\overset{\displaystyle -}{Re}}}(CO)_4 \cdot THF \qquad \text{(eq. 13)}$$

$$Fe(CO)_5 \xrightarrow[3hr,\ THF,\ \Delta]{2\ K(sec\text{-}C_4H_9)_3BH} \underline{K_2[Fe(CO)_4]}\downarrow \qquad 100\% \qquad \text{(eq. 14)}$$

$$K_2[Fe(CO)_4] \xrightarrow[3)\ CH_3COOH]{1)\ n\text{-}C_8H_{17}Br;\ 2)\ P(C_6H_5)_3} \text{1-nonanal} \qquad 100\% \qquad \text{(eq. 15)}$$

$$K_2[Fe(CO)_4] \xrightarrow{2\ AuCl[P(C_6H_5)_3]} [Fe(CO)_4][AuP(C_6H_5)_3]_2 \qquad 82\% \qquad \text{(eq. 16)}$$

$$H_4Ru_4(CO)_{14} + 2\ K(sec\text{-}C_4H_9)_3BH \longrightarrow \underline{K_2[H_2Ru_4(CO)_{12}]} + 2\ (sec\text{-}C_4H_9)_3B + 2\ H_2 \qquad \text{(eq. 17)}$$

$$[L_nM\text{-}C{=}O]^+ + Li(C_2H_5)_3BH \longrightarrow L_nM\text{-}\overset{O}{\overset{\|}{C}}\text{-}H + (C_2H_5)_3B + Li^+ \qquad \text{(eq. 18)}$$

Scheme I. Formation and Further Reductions of Neutral Formyl 3

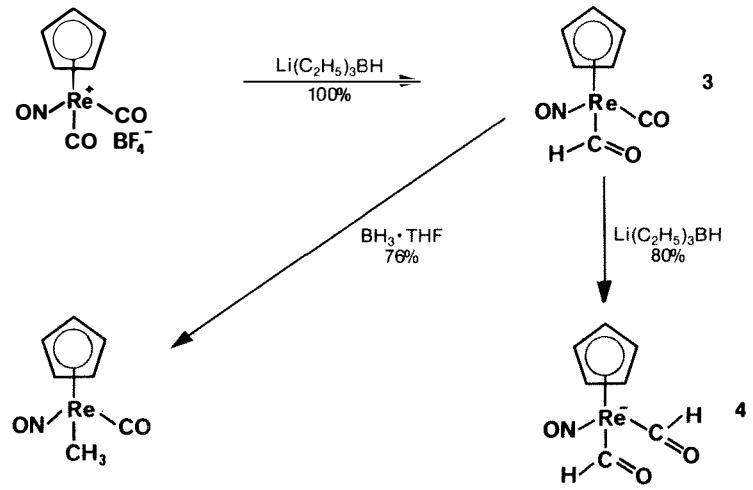


TABLE I. SUMMARY OF TRANSITION METAL MONOANION DERIVATIVES PREPARED

Entry	Starting Carbonyl	Hydride Reagent	Monoanion Produced	Electrophile Added	Product Formed	Isolated Yield (%)
1	$[Co(CO)_4]_2$	$Li(C_2H_5)_3BH$	$Li[Co(CO)_4]$	$[(C_6H_5)_3P]_2N^+Cl^-$	$[(C_6H_5)_3P]_2N^+[Co(CO)_4]^-$	79
2	$[Co(CO)_4]_2$	$Li(C_2H_5)_3BH$	$Li[Co(CO)_4]$	$(C_6H_5)_3SnCl$	$[Co(CO)_4]Sn(C_6H_5)_3$	83
3	$[(C_5H_5)Mo(CO)_3]_2$	$Li(C_2H_5)_3BH$	$Li[(C_5H_5)Mo(CO)_3]$	CH_3I	$[(C_5H_5)Mo(CO)_3]CH_3$	77
4	$[(C_5H_5)Mo(CO)_3]_2$	$Li(C_2H_5)_3BH$	$Li[(C_5H_5)Mo(CO)_3]$	$(CH_3O)COCOCl$	$[(C_5H_5)Mo(CO)_3]COCO_2CH_3$	77
5	$[(C_5H_5)Mo(CO)_3]_2$	$Li(sec\text{-}C_4H_9)_3BH$	$Li[(C_5H_5)Mo(CO)_3]$	$(CH_3O)COCOCl$	$[(C_5H_5)Mo(CO)_3]COCO_2CH_3$	77
6	$[(C_5H_5)Mo(CO)_3]_2$	$Li(C_2H_5)_3BH$	$Li[(C_5H_5)Mo(CO)_3]$	$(C_6H_5)_3SnCl$	$[(C_5H_5)Mo(CO)_3]Sn(C_6H_5)_3$	76
7	$[Mn(CO)_5]_2$	$Li(C_2H_5)_3BH$	$Li[Mn(CO)_5]$	$C_6H_5COCOCl$	$[Mn(CO)_5]COCOC_6H_5$	92
8	$[Mn(CO)_5]_2$	$Li(C_2H_5)_3BH$	$Li[Mn(CO)_5]$	$(C_6H_5)_3SnCl$	$[Mn(CO)_5]Sn(C_6H_5)_3$	88
9	$[Mn(CO)_5]_2$	$Li(C_2H_5)_3BH$	$Li[Mn(CO)_5]$	$(CH_3O)COCOCl$	$[Mn(CO)_5]COCO_2CH_3$	81
10	$[Mn(CO)_5]_2$	$K(sec\text{-}C_4H_9)_3BH$	$K[Mn(CO)_5]$	$[(C_6H_5)_3P]N^+Cl^-$	$[(C_6H_5)_3P]_2N^+[Mn(CO)_5]^-$	78
11	$[Mn(CO)_5]_2$	$K(sec\text{-}C_4H_9)_3BH$	$K[Mn(CO)_5]$	$(CH_3)_3SiBr$	$[Mn(CO)_5]Si(CH_3)_3$	60-80
12	$[(C_5H_5)Fe(CO)_2]_2$	$K(sec\text{-}C_4H_9)_3BH$	$K[(C_5H_5)Fe(CO)_2]$	$(C_6H_5)_3SnCl$	$[(C_5H_5)Fe(CO)_2]Sn(C_6H_5)_3$	93
13	$[(C_5H_5)Fe(CO)_2]_2$	$K(sec\text{-}C_4H_9)_3BH$	$K[(C_5H_5)Fe(CO)_2]$	$C_6H_5CH{=}CHCOCl$	$[(C_5H_5)Fe(CO)_2]COCH{=}CHC_6H_5$	72
14	$[(C_5H_5)Fe(CO)_2]_2$	$K(sec\text{-}C_4H_9)_3BH$	$K[(C_5H_5)Fe(CO)_2]$	C_6H_5COCl	$[(C_5H_5)Fe(CO)_2]COC_6H_5$	67
15	$[(C_5H_5)Fe(CO)_2]_2$	$K(C_2H_5)_3BH$	$K[(C_5H_5)Fe(CO)_2]$	CH_3I	$[(C_5H_5)Fe(CO)_2]CH_3$	56

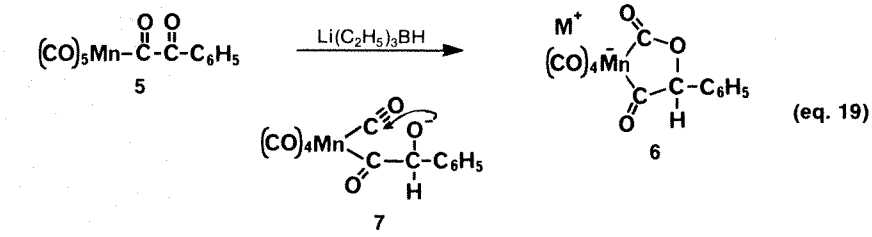
While it is only partially reduced by $NaBH_4$,[30] $Li(C_2H_5)_3BH$ rapidly converts Se_x to Li_2Se or Li_2Se_2 (depending upon stoichiometry) according to eqs. 20 and 22.[31] Alkyl halides could then be added to the heterogeneous suspensions (optimally in the presence of *t*-butyl alcohol cosolvent) and dialkyl selenides and dialkyl diselenides obtained in 50-90% yields (eqs. 21 and 23).[31]

This one-flask preparation of R_2Se and R_2Se_2 compounds offers distinct advantages over many previous methods. Alkali metal-ammonia reduction converts Se_x to $Se^=$ or $Se_2^=$, but is obviously a more cumbersome procedure. Sodium formaldehyde sulfoxylate ("Rongalite") can also reduce selenium but requires an aqueous solvent system.[31]

We have undertaken a more extensive investigation of the reaction of sulfur (S_8) with trialkylborohydrides.[32,33] Although there exists a variety of means for the introduction of sulfur into organic molecules, research continues on the development of new sulfur transfer reagents and methods. When $Li(C_2H_5)_3BH$ is simply syringed onto sulfur or a sulfur/THF suspension, Li_2S or Li_2S_2 formation occurs over a two-minute period as depicted in eqs. 24 and 25. Significantly, these reaction mixtures are homogeneous, whereas commercial anhydrous Li_2S is insoluble in THF. While there may be some association between the sulfur anions and the byproduct $(C_2H_5)_3B$, experiments[33] indicate that the homogeneity is primarily due to supersaturation.

A variety of electrophiles have been added to these reaction mixtures. Some of the organosulfur compounds thus prepared are tabulated in Table II.[32,33] Although the synthesis of simple dialkyl sulfides is adequately served by inexpensive $Na_2S \cdot 9H_2O$, this reagent is, of course, incompatible with electrophiles requiring strictly anhydrous conditions. Notably, our Li_2S preparation undergoes facile acylation (entries 5 and 6), providing a distinct improvement over existing synthetic methods for diacyl sulfides.[34] While anhydrous alkali metal sulfides are commercially available, they are exceedingly hygroscopic, and thus, our one-flask *in situ* synthesis offers obvious advantages.

Alkali metal disulfides are not commercially available. Methods for their preparation (*e.g.*, Li/NH_3) are cumbersome and sometimes afford mixtures of polysulfide salts. Hence, alkylation of Na_2S_2 has been reported to proceed only in fair yield.[33] As is evident from Table IIB, our disulfide yields are uniformly high. Thus, disulfides may be readily prepared from nonsulfur-containing precursors. Particularly for the diacyl disulfides (entries 13 and 14) are the literature procedures markedly simplified.[35]



(eq. 19)

$$Se + 2\,Li(C_2H_5)_3BH \longrightarrow \underline{Li_2Se} + 2\,(C_2H_5)_3B + H_2 \quad \text{(eq. 20)}$$

$$Li_2Se + 2\,RX \longrightarrow \underline{R_2Se} + 2\,LiX \quad \text{(eq. 21)}$$

$$2\,Se + 2\,Li(C_2H_5)_3BH \longrightarrow \underline{Li_2Se_2} + 2\,(C_2H_5)_3B + H_2 \quad \text{(eq. 22)}$$

$$Li_2Se_2 + 2\,RX \longrightarrow \underline{R_2Se_2} + 2\,LiX \quad \text{(eq. 23)}$$

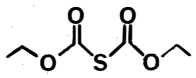
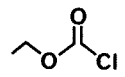
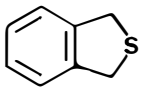
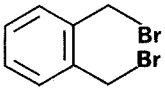
$$S + 2\,Li(C_2H_5)_3BH \longrightarrow \underline{Li_2S} + 2\,(C_2H_5)_3B + H_2 \quad \text{(eq. 24)}$$

$$2\,S + 2\,Li(C_2H_5)_3BH \longrightarrow \underline{Li_2S_2} + 2\,(C_2H_5)_3B + H_2 \quad \text{(eq. 25)}$$

$$RSSR + 2\,Li(C_2H_5)_3BH \longrightarrow 2\,\underline{RSLi} + 2\,(C_2H_5)_3B + H_2 \quad \text{(eq. 26)}$$

$$RSeSeR + 2\,Li(C_2H_5)_3BH \longrightarrow 2\,\underline{RSeLi} + 2\,(C_2H_5)_3B + H_2 \quad \text{(eq. 27)}$$

TABLE II. REPRESENTATIVE ORGANOSULFUR COMPOUNDS PREPARED

Entry	Product	Electrophile	Yield (%)[a]	Reaction Conditions[b]
		A. Sulfides		
1	$(C_6H_5CH_2)_2S$	$C_6H_5CH_2Cl$	[94]	3hr
2	$(n\text{-}C_4H_9)_2S$	$n\text{-}C_4H_9I$	71	5hr
3	$(n\text{-}C_5H_{11})_2S$	$n\text{-}C_5H_{11}Br$	71	5hr
4	$(sec\text{-}C_4H_9)_2S$	$sec\text{-}C_4H_9I$	63	12hr reflux
5	$(CH_3CO)_2S$	CH_3COCl	87	2hr
6			51	2.5hr
7			[63]	1.5hr
		B. Disulfides		
8	$(C_6H_5CH_2)_2S_2$	$C_6H_5CH_2Br$	[89] 85	5hr
9	$(H_2C{=}CHCH_2)_2S_2$	$H_2C{=}CHCH_2Br$	[93]	2hr reflux
10	$(n\text{-}C_4H_9)_2S_2$	$n\text{-}C_4H_9I$	[87] 78	1hr
11	$(n\text{-}C_5H_{11})_2S_2$	$n\text{-}C_5H_{11}Br$	99	2hr reflux
12	$(sec\text{-}C_4H_9)_2S_2$	$sec\text{-}C_4H_9I$	[73]	2hr reflux
13	$(C_6H_5CO)_2S_2$	C_6H_5COCl	85	1hr reflux
14	$(CH_3CO)_2S_2$	CH_3COCl	[82]	0.5hr

[a]Yields are based upon starting sulfur and are not optimized. Bracketed values are ^1H NMR yields; others are isolated yields.

[b]Room temperature unless noted.

Disulfides and diselenides are rapidly cleaved by $Li(C_2H_5)_3BH$ to thiolates and selenolates, respectively (eqs. 26 and 27).[31-33] These reactions enable facile syn-

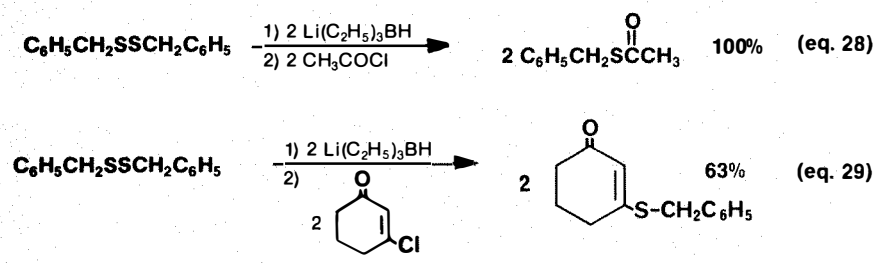
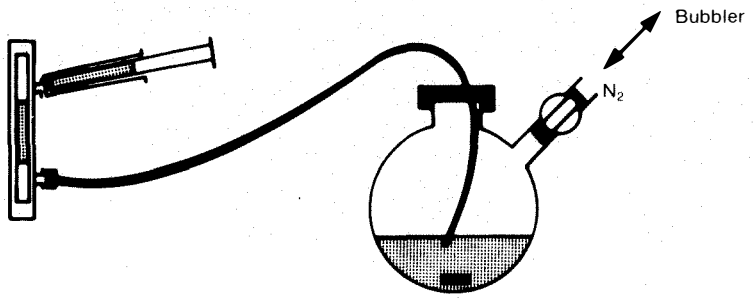


Figure II

APPARATUS FOR IR MONITORING OF REACTIONS



theses of unsymmetrical sulfides and selenides. Thus, the sequential treatment of dibenzyl disulfide with $Li(C_2H_5)_3BH$ and CH_3I gave benzyl methyl sulfide in 75% yield. Benzyl acetyl sulfide was obtained in 100% yield by the reaction of dibenzyl disulfide with $Li(C_2H_5)_3BH$ and acetyl chloride (eq. 28).[32,33] Eq. 29 depicts the formation of a vinyl sulfide *via* an addition-elimination reaction.[33]

APPARATUS

Metal carbonyl compounds have strong and characteristic IR bands in the 1800-2100 cm^{-1} region. Although the reactions we describe can be run in good yield in the absence of spectroscopic monitoring, the simple apparatus detailed in Figure II enables reactions to be titrated to 100% yields. Solutions of the metal carbonyl reactant are placed in a Schlenk flask which is fitted with a septum and a Teflon needle. A standard 0.1-mm-cavity NaCl IR cell is mated to the other end of the needle with a machined Teflon plug. To the other IR cell inlet is attached a (gas-tight) syringe. A slight positive nitrogen pressure is maintained *via* the side arm of the Schlenk flask. Reagents and reactants are added as needed through the septum. By pumping the syringe, the reaction mixture can be spectroscopically sampled at any time.

Such an apparatus might also see use in purely organic transformations. For instance, it should be as (or more) effective as TLC in monitoring the disappearance of a carbonyl-containing compound.

CONCLUSION AND PROGNOSIS

A number of rapid, high-yield, multi-step, single-flask synthetic sequences utilizing trialkylborohydrides have been described. Most of the transformations detailed result in the formation of a metal-carbon or heteroatom-carbon bond. Other applications include the synthesis of metal hydrides, mixed metal compounds, and formyl complexes.

We anticipate that trialkylborohydrides may also be of use in the generation of phosphorus- and silicon-based anions. Our own efforts are focused on the applications of some of the organometallic species described herein to organic synthesis. Although the potential of metal carbonyl reagents has long been recognized by organic chemists, their inaccessibility by standard bench-top techniques has often discouraged their use. In light of the studies summarized in this article, we hope this will no longer be the case.

ACKNOWLEDGEMENTS

I wish to thank the donors of the Petroleum Research Fund, administered by the American Chemical Society, The Department of Energy, The National Science Foundation, and the UCLA Research Committee for support of the various investigations reported in this article. Most importantly, I would like to express my gratitude to the following coworkers for bringing this chemistry to fruition: Jim Garbe, John Hornby, Bryan Jick, Dennis Johnson, Jim Merrifield, Jay Selover, Wilson Tam, Greg Williams, Rick Wong, and Victor Wong.

References and Notes:

1) S. Krishnamurthy, *Aldrichimica Acta*, 7, 55 (1974).
2) H.C. Brown and S. Krishnamurthy, *J. Am. Chem. Soc.*, **95**, 1669 (1972).
3) S. Krishnamurthy and H.C. Brown, *J. Org. Chem.*, **41**, 3065 (1976).
4) H.C. Brown, S. Krishnamurthy, and R.A. Coleman, *J. Am. Chem. Soc.*, **94**, 1750 (1972).
5) S. Krishnamurthy and H.C. Brown, *ibid.*, **98**, 3384 (1976).
6) J.M. Fortunato and B. Ganem, *J. Org. Chem.*, **41**, 2194 (1976).
7) S. Krishnamurthy, F. Vogel, and H.C. Brown, *ibid.*, **42**, 2534 (1977).
8) See H.D. Kaesz and R.B. Saillant, *Chem. Rev.*, **72**, 231 (1972).
9) J.A. Gladysz, G.M. Williams, W. Tam, and D.L. Johnson, *J. Organometal. Chem.*, **140**, Cl (1977).
10) J.A. Gladysz, G.M. Williams, W. Tam, D.L. Johnson, D.W. Parker, and J.C. Selover, *Inorg. Chem.*, **18**, in press (1979).
11) J.E. Ellis, *J. Organometal. Chem.*, **86**, 1 (1975).
12) R.B. King, *J. Inorg. Nucl. Chem.*, **25**, 1296 (1963).
13) M. Rosenblum, *Acc. Chem. Res.*, **7**, 122 (1974).
14) H.C. Brown, S. Krishnamurthy, and J.L. Hubbard, *J. Am. Chem. Soc.*, **100**, 3343 (1978).
15) J.A. Gladysz, W. Tam, G.M. Williams, D.L. Johnson, and D.W. Parker, *Inorg. Chem.*, **18**, in press (1979).
16) R.B. King and F.G.A. Stone, *Inorg. Synth.*, **7**, 198 (1963).
17) G.H. Olivé and S. Olivé, *Angew. Chem., Int. Ed. Engl.*, **15**, 136 (1976); *J. Mol. Catal.*, **3**, 443 (1977/78); W.A. Goddard, S.P. Walch, A.K. Rappé, T.H. Upton, and C.F. Melius, *J. Vac. Sci. Technol.*, **14**, 416 (1977).
18) J.A. Gladysz and J.C. Selover, *Tetrahedron Lett.*, 319 (1978).
19) D.W. Parker, unpublished results.
20) J.A. Gladysz and J.H. Merrifield, *Inorg. Chim. Acta.*, **30**, L317 (1978).
21) J.A. Gladysz and W. Tam, *J. Am. Chem. Soc.*, **100**, 2545 (1978).
22) Other researchers have also noted the formation of salts of **2** by the reaction of $Fe(CO)_5$ with trialkylborohydrides or related hydride donors: C.P. Casey and S.M. Neumann, *J. Am. Chem. Soc.*, **98**, 5395 (1976); S.R. Winter, G.W. Cornett, and E.A. Thompson, *J. Organometal. Chem.*, **133**, 399 (1977).
23) J.A. Gladysz and W. Tam, *J. Org. Chem.*, **43**, 2279 (1978).
24) J.P. Collman, *Acc. Chem. Res.*, **8**, 342 (1975).
25) K. Inkrott and S.G. Shore, *J. Am. Chem. Soc.*, **100**, 3955 (1978).
26) W.K. Wong, unpublished results.
27) J.E. Ellis, C.P. Parnell, and G.P. Hagen, *J. Am. Chem. Soc.*, **100**, 3605 (1978).
28) W. Tam, W.K. Wong, and J.A. Gladysz, *J. Am. Chem. Soc.*, **101**, in press (1979).
29) J.A. Gladysz, J.C. Selover, and C.E. Strouse, *J. Am. Chem. Soc.*, **100**, 6766 (1978).
30) J.M. Lalancette, A. Frêche, J.R. Brindle, and M. Laliberté, *Synthesis*, 526 (1976).
31) J.A. Gladysz, J.L. Hornby, and J.E. Garbe, *J. Org. Chem.*, **43**, 1204 (1978).
32) J.A. Gladysz, V.K. Wong, and B.S. Jick, *Chem. Commun.*, 838 (1978).
33) J.A. Gladysz, V.K. Wong, and B.S. Jick, submitted for publication in *Tetrahedron*.
34) M. Mikolajczyk, P. Kielbasinski, and H.M. Schiebel, *J. Chem. Soc., Perkin Trans. 1*, 564 (1976); S. Motoki and H. Satsumabayashi, *Bull. Chem. Soc. Jpn.*, **45**, 2930 (1972); W.A. Bonner, *J. Am. Chem. Soc.*, **72**, 4270 (1950).
35) R.L. Frank and J.R. Blegen, *Org. Syn., Coll. Vol. 3*, 116 (1955); L. Field and J.E. Lawson, *J. Am. Chem. Soc.*, **80**, 838 (1958).

About the Author

John A. Gladysz is a native of Galesburg, Michigan. He earned his B.S. degree at the University of Michigan and his Ph.D. at Stanford University. In 1974, he joined the UCLA Faculty as an Assistant Professor. His research interests encompass a wide area of synthetic chemistry, emphasizing organometallic compounds and new preparative methods (high pressure chemistry, metal atom chemistry).

Page intentially blank

Aldrichimica Acta

Volume 12, Number 2, 1979

Spin Trapping. See page 23.
A Businessman's Look at PMN. See page 35.

chemists helping chemists in research & industry
aldrich chemical co.

Aldrichimica Acta

Volume 12, Number 2, 1979
A publication of ALDRICH CHEMICAL COMPANY, INC.

Main Sales Office:
940 West Saint Paul Ave.
Milwaukee, Wisconsin 53233
Telephone: (414) 273-3850
Order Desk: (800) 558-9160 Toll-free
TWX: (910) 262-3052
Telex: 26 843

East Coast Service and Distribution Center:
159 Forrest Street
Metuchen, New Jersey 08840
Telephone: (201) 549-6300
TWX: (710) 998-0575

In Canada:
Aldrich Chemical Co. (Canada), Ltd.
1500 Stanley Street, Suite 405
Montreal, Quebec H3A 1R3
Telephone: (514) 845-9289
Eastern & Atlantic: (800) 361-6141 Toll-free
TWX: (610) 421-4608

In Great Britain:
Aldrich Chemical Company, Ltd.
The Old Brickyard, New Road
Gillingham, Dorset
SP8 4JL, England
Telephone: 074-76 2211
Telex: (851) 417238

In West Germany/Continental Europe:
EGA-Chemie KG
7924 Steinheim am Albuch
West Germany
Telephone: (07329) 6011
Telex: (841) 714838

In Belgium/Continental Europe:
Aldrich-Europe
B-2340 Beerse
Belgium
Telephone: 014/611431
Telex: (846) 32540

In Japan:
Aldrich Japan
c/o Tokyo Danchi Sohko Kanrito
4-1, 3-chome, Heiwajima, Ohta-ku
Tokyo, Japan
Telephone: 768-0555
Telex: (781) 246-6143

In Israel:
Sigma Israel Chemical Co.
P.O. Box 37673
Tel Aviv, Israel 61360
Telephone: 03-612315
Telex: (922) 35645

About Our Cover:

Unlike many works bought by our chemist-collector, this painting (oil on canvas, 40 x 50 inches) poses no problems of authorship or iconography; it was signed and dated 1629 by Jan Pynas, and the subject is not in doubt: 'Potiphar's Wife Accusing Joseph.' Jan Pynas was one of a group of artists known as the 'Pre-Rembrandtist' and his works are rare; only about fifteen works are known for certain, and of these only one other is in the United States.

What surprised us was that our chemist bought another work depicting Joseph, one of his least likeable heroes in the Bible. Our chemist is fond of quoting Maurice Samuel who wrote that Joseph's only good *personal* deed ever was to resist the advances of Potiphar's wife, and to be undersexed is not sufficient to be considered a truly good person. Why then, we asked our chemist, did he buy this work? Only because of its quality. It is beautiful in color — light pinks and greens and a sheer white in Joseph's robe — and so telling in its psychological insights: Potiphar is obviously in doubt, and so is his wife!

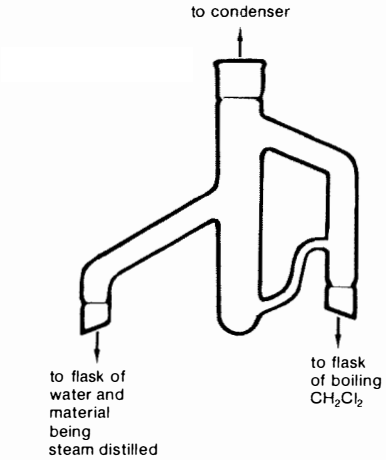
Are you interested in our Acta covers? *Selections from the Bader Collection*, with 30 duotone reproductions, many of previous Acta covers, and an introduction by Professor Wolfgang Stechow is available to all chemist art-lovers.

Also, many paintings reproduced on our Acta covers were shown at the Milwaukee Art Center in an exhibition, "The Bible Through Dutch Eyes," arranged by Dr. Bader in 1976. The fully illustrated catalog with 66 black-and-white and 4 full-color reproductions contains many art historical and Biblical comments.

Many of the early issues of the *Aldrichimica Acta* have become very rare. Please do not throw your issues away. In time, we believe that complete sets will become valuable, and — if you do not want to keep them — there probably are chemists near you who would be interested.

Lab Notes

Steam distillation of a compound of low volatility requires condensation of a large volume of water; this normally makes isolation of the desired compound, by extraction or filtration, tedious.



The arrangement shown[1] obviates the need to collect a large volume of water. The compound steam-distills into the condenser where it undergoes continuous extraction by dichloromethane.[2] A progressively more concentrated solution of the compound accumulates in the CH_2Cl_2 flask; this solution is simply run through a small cotton-wool plug and evaporated[3] leaving the desired material.

With this device we concentrated into about 200ml of CH_2Cl_2 a quantity of 1,5-dibenzocyclooctadiene that would have required filtration from tens of liters of water.[4]

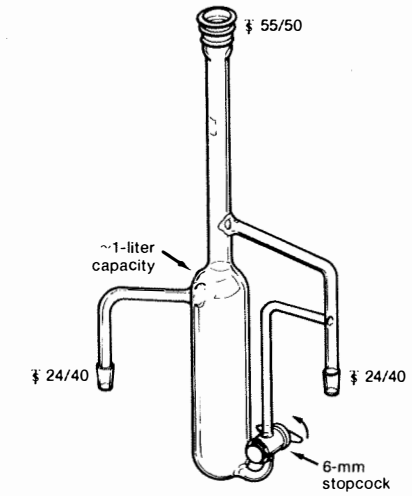
References:

1) This device was designed by Dr. A.C. Mackey, then a graduate student at the University of Toronto.
2) CH_2Cl_2 is the only common heavier-than-water organic solvent that seems to be noncarcinogenic and nontoxic: *Chemical and Engineering News*, July 24, 1978, p 7.
3) E. Lewars, *Aldrichimica Acta*, **8**, 38 (1975).
4) P. Yates, E.G. Lewars, and P.H. McCabe, *Can. J. Chem.*, **48**, 788 (1970).

Professor E.G. Lewars
Trent University
Peterborough, Ontario K9J 7B8
Canada

Editor's note:

We have found this continuous steam distillation/extraction apparatus quite useful, so as a service to chemists who may have need for it, we offer the device shown below, accompanied by an instruction sheet.

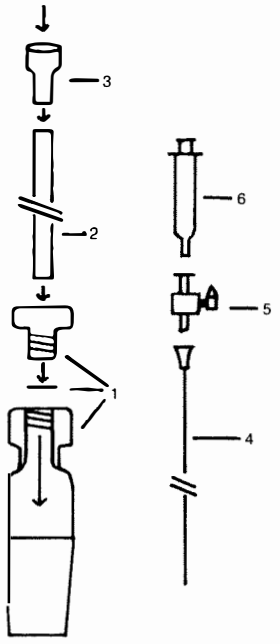


The accompanying drawing details an apparatus which we use to sample a reaction in progress without interruption of the reaction, or if run under inert atmosphere, without introduction of air.

The arrangement is particularly suitable for use with high-temperature reactions where hot organic solvents would attack a septum cap attached directly to the flask *via* a sidearm or adapter.

By attaching the septum cap to a Pyrex glass tube and inserting this into the adapter (as one would a thermometer), the tube, which now extends out from the pot, acts as an air-cooled condenser, protecting the septum.

The needle is then inserted through the septum cap and manipulated to allow sample removal. After a sample has been taken the needle is withdrawn from the solution and the luer-lock is closed to allow syringe removal without admitting air to the pot.



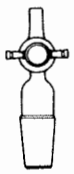
(1) Thermometer adapter assembly
(2) Pyrex glass tube of appropriate length and diameter
(3) Septum cap
(4) Heavy-gauge needle of appropriate length
(5) Luer-lock
(6) Syringe of appropriate volume

In taking successive samples, the syringe must be "pumped" several times to flush traces of the previous sample from the syringe and needle.

Michael D. Tufano
Corporate Research Laboratories
UOP Incorporated
Des Plaines, IL 60016

Editor's note:

This sampling assembly is easily constructed from materials normally available in the laboratory. To chemists who would make use of the described assembly frequently, we recommend Aldrich's septum-inlet adapter with Teflon stopcock.



Cont'd on page 36

"Please Bother Us!"

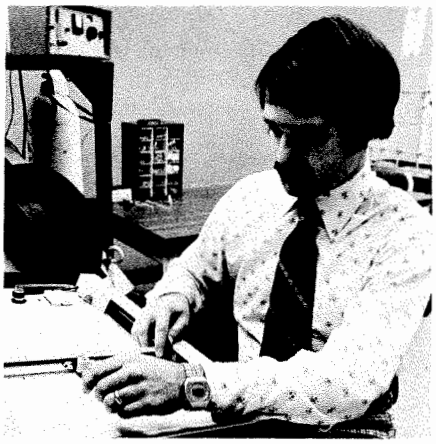
by Ayhan Bader.

Recently Dr. Colin F. Chignell, the chief of the Laboratory of Environmental Biophysics at the N.I.H. suggested that we offer α-(4-pyridyl 1-oxide)-*N*-*tert*-butylnitrone (4-POBN), a new spin trap uniquely useful for the identification of hydroxyl radicals in solution, reported by Janzen *et al.*, *J. Am. Chem. Soc.*, **100**, 2923 (1978). Unfortunately, Professor Janzen's method of preparation given in a footnote of that communication to the editor, is very sketchy. Well, when a compound as interesting as 4-POBN is suggested to us, we don't let lack of experimental details deter us — and we have now made it.

It was no bother at all, just a pleasure to be able to help.

Spin Trapping

C. Anderson Evans
Varian Associates
East Coast EPR Applications Laboratory
25 Hanover Road
Florham Park, New Jersey 07932



Since its discovery some thirty-four years ago electron spin resonance (ESR) has proven to be a useful tool for studies in chemical, physical, and biological systems.[1] The ability of ESR to detect low concentrations of free radicals and its sensitivity to their environment and molecular motions have contributed greatly to its popularity. A limitation in the application of ESR to solution studies has been the difficulty in producing sufficient quantities of reactive free radicals to make possible direct ESR detection. Various methods have been employed to overcome this problem including high-energy *in situ* radiolyses,[2] high-intensity photolyses,[3] and rapid-flow techniques.[4] However, these techniques are rather expensive or cumbersome and do not appear to be generally applicable. Until recently, therefore, most research in ESR in the solution phase was limited to that involving relatively stable free-radical systems.

In 1968 the technique of spin trapping was introduced by Professor Edward Janzen's group at the University of Georgia as well as by other groups around the world, either simultaneously or a short time afterwards.[5] Since that time publications in this area have proliferated[6] with applications appearing in the fields of polymerization,[7] radiation chemistry,[8] biology,[9] and general solution chemistry.[10]

Interest in biological applications of spin trapping is picking up, with several laboratories presently devoting a significant portion of their research effort to the detection of free-radical processes in biological systems. Because of this increased interest and because existing general reviews of the technique are now some eight years old,[11] it seems appropriate to discuss some of the recent work that has been done using the spin-trapping technique. Particular attention will be given to the spin traps that have been used. Biological applications will be discussed in some detail and a cautionary note is given to help in avoiding potential pitfalls in the application of the technique.

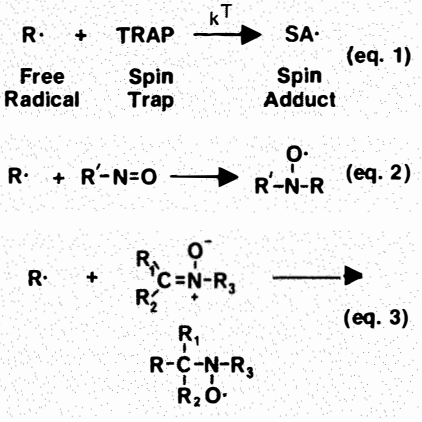
THE TECHNIQUE

The technique of spin trapping makes use of a diamagnetic compound (the spin trap) which reacts with a free radical (the spin) giving rise to a relatively stable, ESR-observable free radical (the spin adduct, eq. 1). In favorable cases the free radical, R·, can be identified from the ESR parameters [*e.g.*, hyperfine coupling constants (hfsc), g-factor] of SA·. Thus spin trapping extends the capabilities of ESR in that previously unobservable free radicals (or, at least, radicals observable only with difficulty) can now be studied as their respective spin adducts in a somewhat more leisurely fashion.

The spin traps that have been most commonly employed are those designed so that on reaction with a free radical a nitroxide is produced. Typically, spin traps are either nitroso compounds[11a] (eq. 2) or nitrones[11b] (eq. 3).

The actual experimental procedure employed in spin-trapping experiments depends on a number of factors such as the manner of radical production, the inertness of the solvent and reagents with respect to the spin trap, the lifetime of the spin adducts, how much or what kind of deoxygenation (if any) is required. Usually deoxygenation by bubbling purified nitrogen or argon gas through the solution is sufficient for spin-trapping purposes. In some cases degassing by the freeze-pump-thaw vacuum technique is necessary if a very low oxygen level is required or if volatile reagents are involved.

An apparatus that has proven rather generally useful for us in spin trapping and other organic applications of electron spin



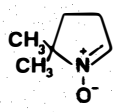
resonance is shown in figure 1.[12] This consists of a "U"-tube (a) which connects *via* a 7/25 tapered ground-glass joint to a Varian "flat cell" [Fig. 1 (b)] for aqueous or high dielectric solvents, or to a standard ESR round cell [Fig. 1 (c)] if a low dielectric (nonlossy) solvent is used. In a typical experiment one positions the "U"-tube vertically and a solution of the spin trap is placed in one chamber of the "U"-tube and the radical producer in the other. The chambers are stoppered with rubber septa through which long (#18 or #20) syringe needles are inserted. A stream of purified nitrogen or argon gas is then passed through the solutions for 15-30 minutes. If a flat cell is used it may be attached during the outgassing procedure since the gas can escape through the opposite end of the cell. Since the round cell has no secondary opening it must be flushed with nitrogen or argon gas just prior to attachment to the "U"-tube. When outgassing is complete the system is stoppered and the contents of the "U"-tube and sample cell are thoroughly mixed and shaken down into the ESR cell, which is inserted into the microwave cavity of the ESR spectrometer. Relatively simple modifications of this basic experimental design allow the use of vacuum degassing, three- (or more) component mixing, etc.

SPIN TRAPS

As mentioned earlier spin traps are usually either nitroso compounds or nitrones. By far the most popular nitroso compound has been 2-methyl-2-nitrosopropane or, trivially, nitroso-*tert*-butane (NtB). Nitroso compounds have an inherent advantage over nitrones for radical identification in that the added group lies immediately adjacent to the nitroxide center and therefore can easily give rise to additional hyperfine splitting. For example, reaction of ethyl radical with NtB gives the ethyl adduct of NtB (NtB-Et) (eq. 4). The ESR spectrum of this nitroxide [Fig. 2 (a)] shows the unpaired electron resonance split first into three lines of equal intensity by interaction with the nitrogen (nuclear spin = 1) and then into three lines of a 1:2:1 intensity ratio by interaction with the two equivalent methylene hydrogens of the ethyl group. A long-range splitting from the methyl hydrogens shows up as a 1:3:3:1 pattern superimposed on the nine major lines and helps to identify the radical trapped.

The nitrone which has been used most in spin-trapping studies is phenyl *N-tert*-butyl nitrone (PBN). This is probably due to the fact that it has a good shelf stability, has been commercially available for a long time, and was the first nitrone to be used in this manner. However, PBN does not distinguish between alkyl radicals particularly well, its spin adducts generally consisting of triplet of doublets with a relatively small variation in the doublet splitting as a function of trapped radical. An example of a typical ESR spectrum is shown in Fig. 2 (b) for the ethyl adduct of PBN (PBN-Et) (eq. 5).

A nitrone which has shown more sensitivity to the structure of the radical is 5,5-dimethyl-1-pyrroline-*N*-oxide (DMPO),



DMPO

introduced by Janzen in 1972.[13] Examples of the spectra obtained on trapping different types of radicals with DMPO are shown in Fig. 3.

It is interesting to consider the origin of the variation in the proton hyperfine splitting observed as a function of structure of the trapped free radical. The magnitude of this interaction is governed by the Heller-McConnell equation (eq. 6),[14] where B_0 and B_2 are constants ($B_0 \cong 0$ and $B_2 \cong 26$ Gauss for nitroxides) and θ is the dihedral angle formed by the C-N *p*-orbital and the N-C βH planes (Fig. 4). Thus, each group *R* added to the spin trap will have different stereoelectronic characteristics and will therefore give rise to a different value for θ.

The spin trap DMPO is structured so that the conformation of its adducts places the β-hydrogen in a nearly eclipsing relationship with the nitrogen *p*-orbital (*i.e.*, θ is small and $A_{H\beta}$ is large). As a result, small changes in the bulk of R· give rise to relatively large variations in $A_{H\beta}$. This is illustrated in the "scatter plot" of A_N *vs.*

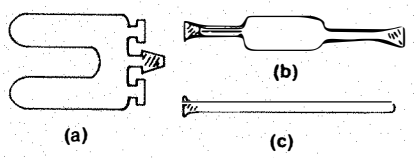
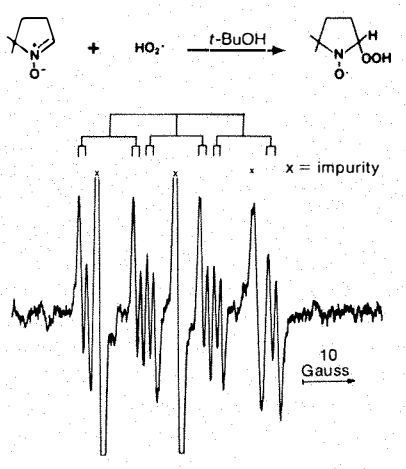
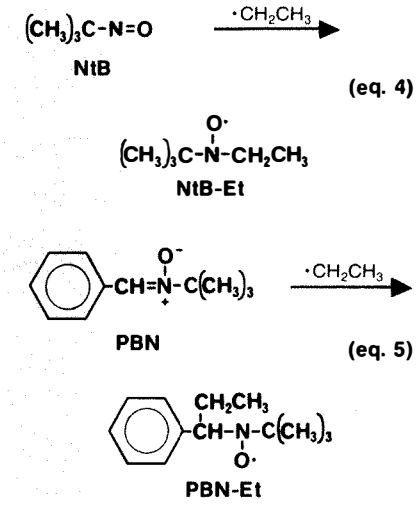


Figure 1





$$A_{H\beta} = B_0 + B_2 \cos^2\theta \quad \text{(eq. 6)}$$

$A_{H\beta}$ for a number of adducts to DMPO (Fig. 5). In this kind of plot, the better the scatter the better is the spin trap for purposes of identification of the trapped radical. The range of hfsc's for the same adducts to PBN is indicated on the plot.

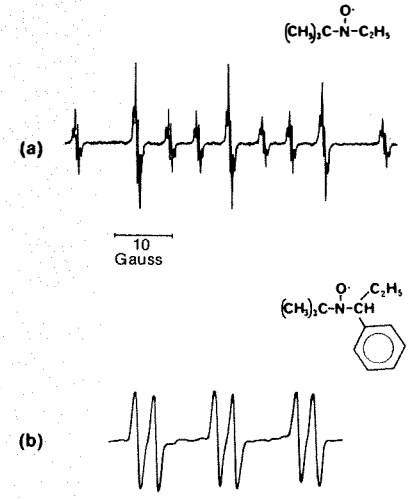


Figure 2

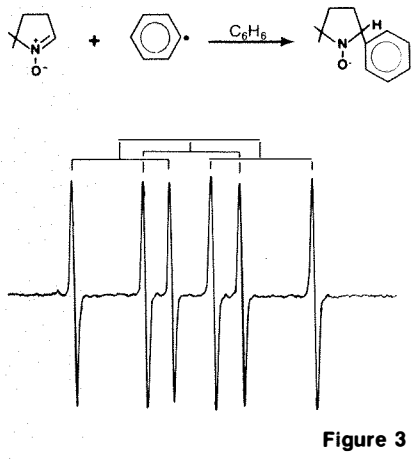
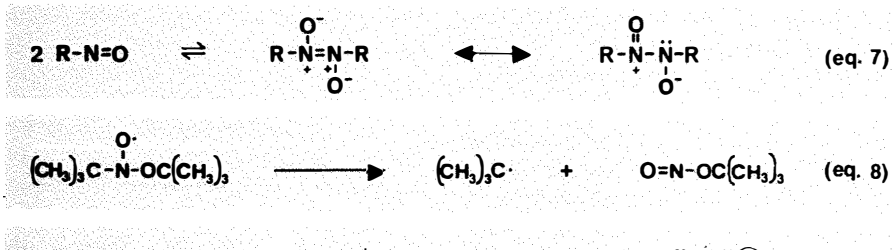


Figure 3



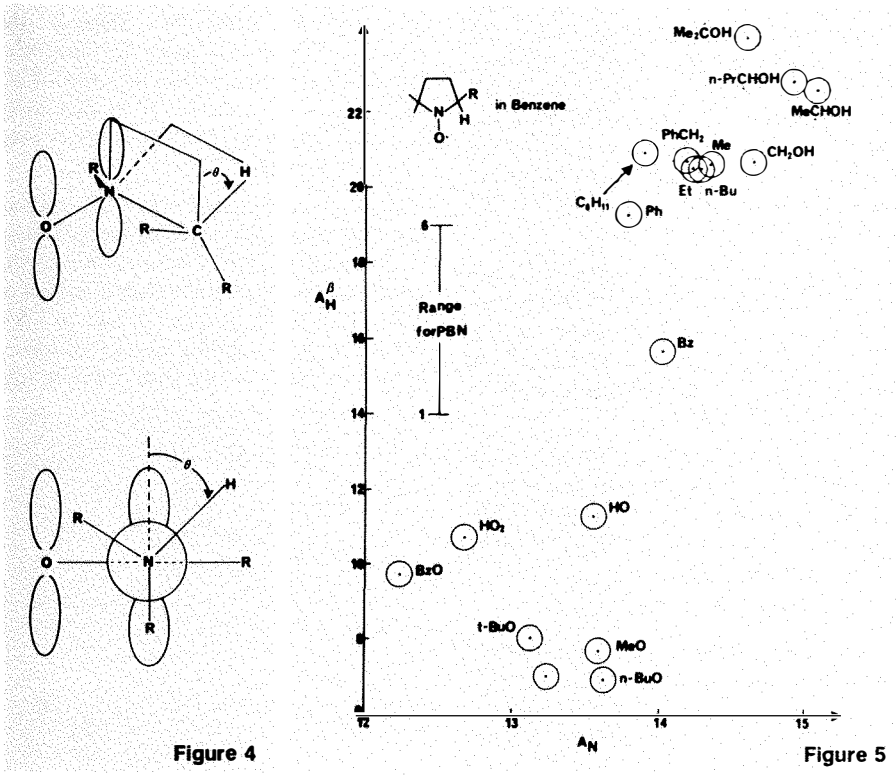


Figure 4

Figure 5

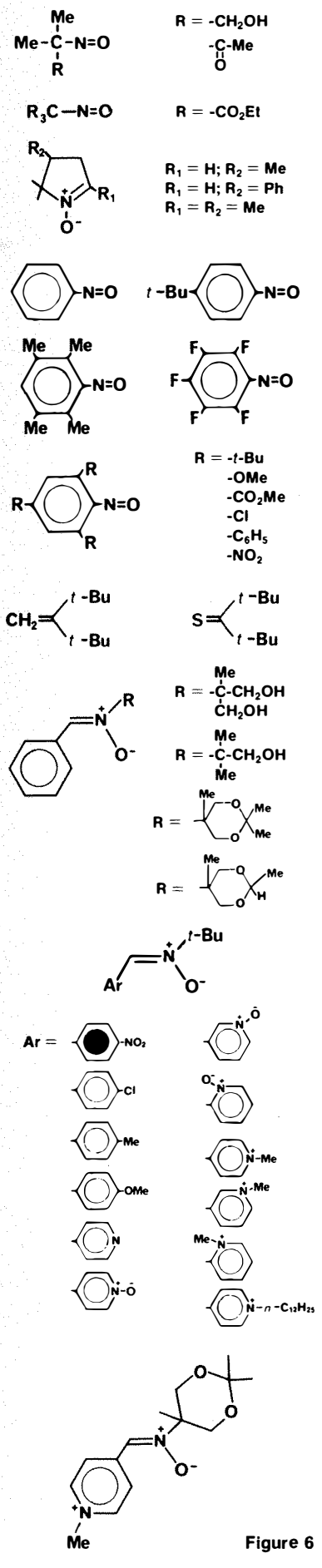


Figure 6

OTHER SPIN TRAPS

The three spin traps discussed above have been the ones most utilized by researchers up to this point. Although a great deal of tailored synthesis has been done for the technique of spin labelling,[15] very little has been done to configure spin traps to suit the exact problem under investigation. With the advent of investigational activity in the biological area, it is likely that this situation will be changing over the next few years.

A number of other traps have been used in problems investigated by spin trapping, particularly in the early days of the development of the technique.[5,16] These will not be discussed specifically, but the structures of some of these traps are shown in Figure 6.

Janzen has recently published the preparations of a number of traps which seem to be quite good for trapping hydroxyl radicals.[17]

RELATIVE MERITS OF NITROSO VERSUS NITRONE SPIN TRAPS

Earlier it was mentioned that nitroso compounds are generally more capable than nitrones of providing a "fingerprint" of the trapped radical because the added group lies closer to the unpaired electron center. However nitroso compounds have the disadvantage of being both thermally and photochemically unstable.[11b,16b,18] In addition they possess a low-energy visible absorption band which makes it nearly impossible to use them for photochemical studies. One of the consequences of this instability is that the ESR spectra of spin adducts of nitroso compounds invariably show the presence of impurity nitroxides which may obscure certain regions of the spectra and hinder interpretations. It should be noted that aromatic nitroso compounds show much more desirable properties in this regard.[16b]

There are other problems associated with the use of nitroso compounds in spin-trapping applications. Nitroso compounds have a tendency to form dimers which are inert towards radical trapping (eq. 7).[16b] Thus, in any quantitative applications it is necessary to take this equilibrium into account. Nitroso compounds seem somewhat unreliable in spin-trapping applications involving oxygen-centered radicals. For example, it has been shown[18] that the *tert*-butoxy adduct of NtB is unstable, decomposing to give a *tert*-butyl radical and *tert*-butyl nitrite (eq. 8).

In contrast to nitroso compounds, nitrones have absorption bands firmly in the ultraviolet which render them suitable for a number of photochemical studies. In general, use of wavelengths longer than 300nm completely avoids direct photolysis of the spin trap. Indeed, photolysis of benzene solutions of PBN for over two hours with a low-pressure mercury lamp gives no detectable ESR signal.[19] Nitrones are monomeric and, to my knowledge, show no tendency to dimerize. Many of the spin adducts produced from nitrones are stable for long periods (the phenyl spin adduct of PBN has a half-life of several weeks; the dodecyl adduct, several years[19]). The most serious disadvantage of nitrones is their tendency to undergo reactions with nucleophiles. A weak signal of the acetoxyl adduct of PBN can be detected from reaction of sodium acetate with PBN.[20] This probably arises from nucleophilic addition of acetate to PBN with subsequent oxidation of the anion produced (eq. 9).

One concludes from this discussion that there is no such thing as the ideal spin trap. One trap will be good for a given application and another will be good for a different application. It seems, therefore, that it would be good to have a kit of spin traps from which a researcher could select the trap appropriate for his experimental needs. This is one of the reasons that I hope the custom design of spin traps will accelerate in order that a larger number of spin traps will become available.

SPIN ADDUCTS

The spin-trapping reaction has been studied extensively within Janzen's group and a review of this aspect of spin trapping has appeared.[21] A large number of rate constants have now been determined for the formation reaction (eq. 1) principally by Janzen, Evans, *et al.*[22] and by Schmid and Ingold.[23] A limited amount of data has been made available by other workers in the field[24]. This rate constant data is summarized in Table I.

All rate constants for the spin-trapping reaction have been measured either by direct competition or by determining a rate constant ratio in which some other rate constant is a "known" quantity. Thus, it is doubtful that any spin-trapping rate constant is correct to better than a factor of 2 and a safer margin of error would be to say that the listed quantities are correct to within an order of magnitude. All values so far fall in the extremes of 1×10^5 to 5×10^8 M^{-1} sec^{-1}.

It is appropriate to remark that preliminary flash photolysis-ESR results[25] on the system *tert*-butoxy-PBN (eq. 10) indicate a $k^T \cong 2 \times 10^6$ M^{-1} sec^{-1} at 25°, in good agreement with the earlier work of Janzen and Evans.[22b]

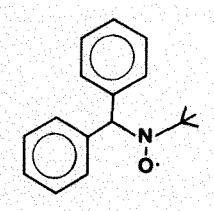
Very little information on activation parameters has been obtained for the spin-trapping reaction, but it appears that energies of activation will fall in the range of 1-5 kcal/mole.[23b]

DECAY OF SPIN ADDUCTS

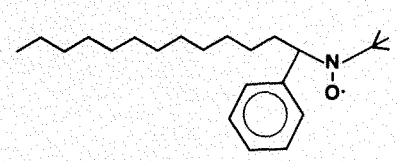
A number of decay routes are possible for spin adducts. In the following discussion, some reference will be made to nitroxides which are not spin adducts, *per se*. However, it is felt that data which is available for these nitroxides has a bearing on the decay of spin adducts.

Spin adducts which have a hydrogen attached to the α-carbon can decay by disproportionation (eq. 11). The mechanism for this decay pathway has been worked out by Ingold and co-workers.[26] For diethyl nitroxide, the decay involves the initial formation of a dimer which decomposes to products. The decay is rather fast ($k = 1 \times 10^4$ M^{-1} sec^{-1} at 25° in benzene). For more substituted nitroxides, the decay is slower (*n*-hexyl *tert*-butyl nitroxide: $k \leqslant 100$ M^{-1} sec^{-1} at 40° in benzene)[23a] and is probably "a straightforward disproportionation not involving the formation of an intermediate dimer."[26c] Indeed, the decrease in decay rate seems to continue as the degree of substitution and size of attached groups increase.[19,27] In fact some spin adducts are so stable they are at least partially isolable.[19,27]

In preliminary work aimed at studying the effect of the size of the added radical on spin adduct lifetime, I have compared the relative persistence of the phenyl adduct of PBN (I) and the dodecyl adduct of PBN (II). The phenyl adduct has a half-life of several months in benzene whereas the



I



II

dodecyl adduct evidently has a half-life of several years.[19] Similar results were obtained for the phenyl and dodecyl adducts of DMPO, although these adducts were much less stable.[19]

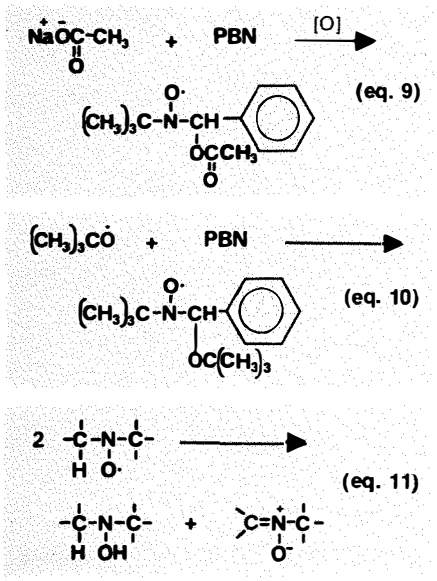


TABLE I. RATE CONSTANTS FOR THE SPIN-TRAPPING REACTION

$$R\cdot + TRAP \xrightarrow{k^T} SA\cdot$$

Spin Trap	Radical	T (°C)	k^T ($M^{-1}sec^{-1}$)	Reference
PBN	*t*-BuO·	25	5×10^6	22,44
	Ph·	25	2×10^7	22,44
	BzO·	40	3×10^7	22,44
	CH_3·	25	4×10^6	22,44
	RCH_2·	40	1.3×10^5	23
DMPO	*t*-BuO·	25	4×10^8	22,44
	Ph·	25	7×10^7	22,44
	BzO·	40	8×10^7	22,44
	$PhCH_2$·	25	2×10^7	22,44
	RCH_2·	40	2.5×10^6	23
NtB	*t*-BuO·	25	2×10^6	22,44
	CH_3O·	-45	1.3×10^8	24e
	$(CH_3)_3OC{=}O$	40	1×10^6	24a
	RCH_2·	40	9×10^6	23

It may not be too obvious to remark that the stable nitroxides used for spin labels are almost exclusively those in which all of the hydrogens on the α-carbons have been substituted.

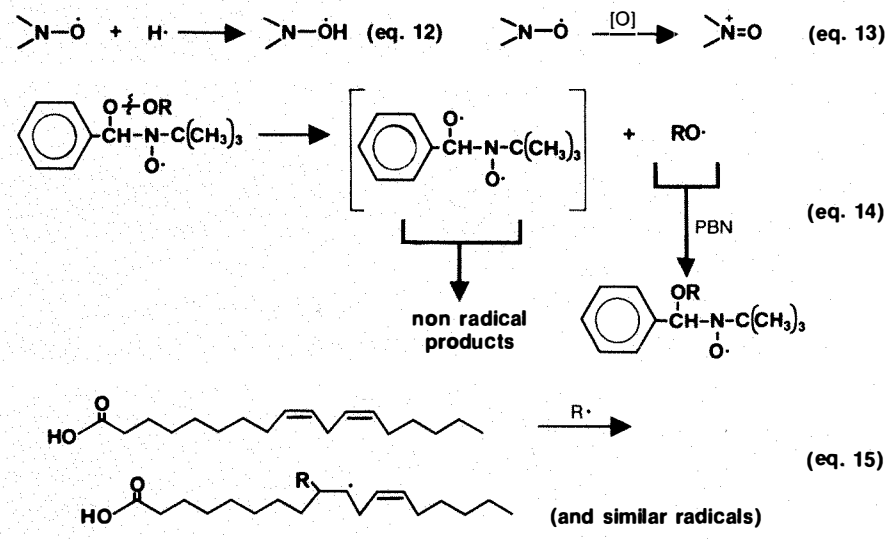
There are some other ways in which the spin adduct can decay. One of the most common is by means of a reduction of the spin adduct (shown formally in equation 12 as reaction of the nitroxide with a hydrogen atom). The observation of this reaction is becoming more common now that the use of spin traps in biological systems is increasing. This is, of course, because of the endogenous reducing agents present in many biological preparations. The most common reductant is ascorbate, but there may be others (such as dithionite) which are not naturally occurring, but may have been added in the preparative procedure. One positive aspect of the disappearance of spin adduct due to reduction is that the skeletal structure of the adduct is generally preserved. Therefore, it may be possible to regenerate the ESR spectrum by means of an appropriately chosen oxidative procedure. It might even be possible to isolate the reduced adduct and to study it by other techniques such as NMR.

It is, of course, possible to oxidize nitroxides[28] (eq. 13), but this appears to be less common than reduction, particularly in biological systems. It may well be that nitroxides which have been one-electron oxidized are more prone to undergo cleavage than are the reduced species. If this is the case, skeletal integrity will not be preserved and it will be difficult to regenerate the original nitroxide.

Spin adducts may decay by means of cleavage of a portion of the nitroxide as a free radical. This was mentioned earlier for the *tert*-butoxy adduct of NtB (eq. 8). This may also be a problem when certain groups which add to the spin trap contain weak chemical bonds (*e.g.*, -O-O-, -N=N-). For example, alkylperoxy radical adducts of PBN are difficult to observe except at low temperatures.[29] One exception was the adduct derived from n-$C_{18}H_{37}O_2\cdot$ and PBN, which was observed at room temperature. The decay pathway for these adducts may well involve breaking of the O-O bond. At room temperature, alkoxy radical adducts are observed instead of alkylperoxy adducts (eq. 14).

SELECTED APPLICATIONS OF SPIN TRAPPING TO BIOLOGY

The presence of free radicals in biological systems has been postulated for some time. Conventional ESR has not been heavily utilized to study these radical processes because of the short lifetime and consequent low concentrations of the free

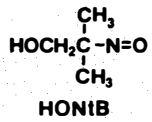


radicals involved. In recent years spin trapping has spurred interest in the application of ESR to biological problems and several successful studies have been reported. One of the more common kinds of studies concerns free radicals produced by high-energy radiation of aqueous solutions of peptides,[30] amino acids,[31] nucleic acids,[32] etc., in the presence of a spin trap. These have been discussed in some detail in a recent review.[33]

In this article I will briefly discuss the application of spin trapping to the study of lipid peroxidation and to the detection of superoxide ($O_2\dot{-}$) and hydroxyl radicals. This is in no way intended to be a comprehensive review. These papers and others are discussed in considerably greater detail in the review by Janzen.[33]

LIPID PEROXIDATION

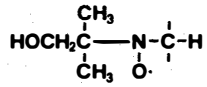
In one of the earliest applications of spin trapping to a problem of biological interest, de Groot *et al.* examined the production of radicals in the anaerobic reaction of lipoxygenase with linoleic acid using 2-methyl-2-nitrosopropanol (HONtB)



HONtB

as spin trap.[34] The nitroso alcohol (HONtB) was chosen as spin trap because of its greater solubility in water over NtB.

The reaction of interest in this work was the formation of dimeric linoleic acid which was shown to require hydroperoxylinoleic acid. Garssen *et al.*[35] had proposed a mechanism for this dimerization involving a linoleic acid radical. When linoleic acid was incubated aerobically with lipoxygenase and HONtB an ESR spectrum consisting of a triplet of doublets was observed. The ESR spectrum indicated an interaction of the unpaired electron with a nitrogen (A_N 16.0 Gauss) and a proton (A_N 2.0 Gauss), consistent with the basic structure III. The reaction could also be



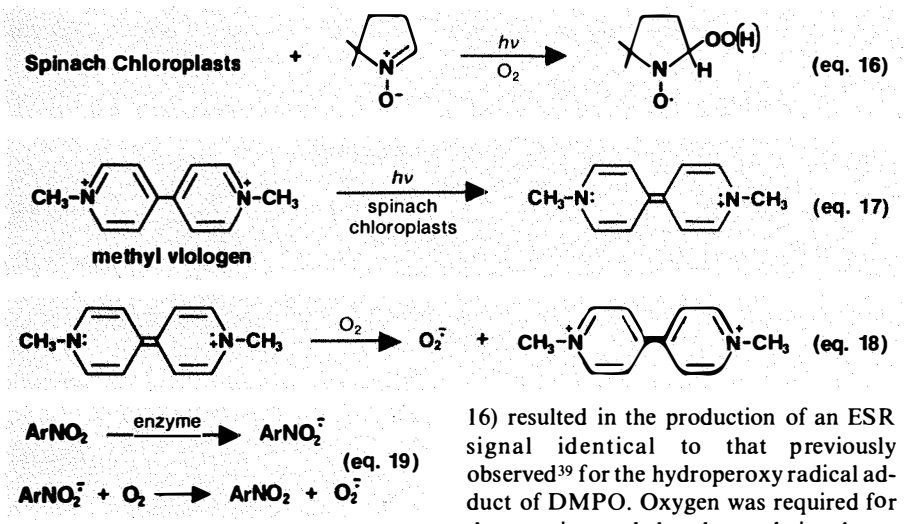
III

carried out anaerobically without the enzyme. In this experiment, a degassed solution of linoleic acid and spin trap was prepared and mixed with a degassed solution of hydroperoxylinoleic acid. An ESR spectrum identical with the one described above was obtained.

The workers were able to assign a more precise structure to the radical giving rise to the ESR spectrum by means of experiments using deuterated linoleic acids. When 11,11-d_2-linoleic acid was used in place of linoleic acid the ESR spectrum was unchanged. However, when either 9,10,11,11,12,13,-d_6- or 9,10,12,13-d_4-linoleic acids were used, the doublet splitting disappeared and the ESR spectrum consisted of three lines. The authors concluded that a linoleic acid radical at either C-13 or C-9 appeared to have been trapped. Of course, there is no *a priori* reason to exclude trapping at C-10 or C-12. Radicals derived from addition reactions to the double bond (eq. 15) are consistent with the above experiments whereas radicals derived from hydrogen abstraction at C-11 are not.

Other experiments carried out with deuterated compounds established that the radical was derived from linoleic acid and not from the hydroperoxide.

It should be reemphasized at this point that nitroso compounds are notoriously unreliable as traps of oxygen-centered radicals. It would perhaps be advisable to reinvestigate this system using nitrone spin traps to see if other radicals present in the



reaction could be detected. This system was reexamined recently, but again, only a nitroso trap was used.[36]

Perhaps the most powerful application of spin trapping to the lipid peroxidation area has been due to Piette and coworkers.[37] These workers have explored radical production in rat liver microsomes using both PBN and DMPO as spin traps. The liver microsomal NADPH-dependent lipid peroxidation system was shown to produce free radicals from a variety of substrates, *viz.*, methanol, ethanol, propanol, acetone, acetonitrile, DMSO, linoleic acid and the well known carcinogens, dimethylnitrosamine and diethylnitrosamine.[37a] The authors also showed that a good signal could be obtained when the common buffering agent, Tris, was used. This latter result further demonstrates that all components of the system must be checked in order that the true source of radicals giving rise to a particular spin adduct be identified.

Lai and Piette[37b] have also demonstrated hydroxyl radical production in the microsomal system.

SUPEROXIDE DETECTION

Singly-reduced oxygen, superoxide ($O_2^{\cdot-}$), has been postulated as an intermediate in a host of biochemical redox reactions. Because of its importance, a great deal of attention is being paid to the detection of superoxide anion by spin trapping.[33]

The first paper in this area was the paper by Harbour and Bolton,[38] who studied superoxide production in spinach chloroplasts. Indeed, it now appears that this paper was the one which triggered much of the current interest in spin-trapping applications to biological problems.

Harbour and Bolton found that red light (λ >600nm) illumination of spinach chloroplasts in the presence of DMPO (eq. 16) resulted in the production of an ESR signal identical to that previously observed[39] for the hydroperoxy radical adduct of DMPO. Oxygen was required for the reaction and the observed signal was much larger in the presence of methyl viologen, a species known to accept electrons from the primary acceptor of photosystem I. The methyl viologen functions by taking the electron from the photosynthetic chain and forming the methyl viologen radical cation (eq. 17). This radical in turn reduces molecular oxygen to form the superoxide radical (eq. 18).

A recent work from the National Biomedical ESR Center describes the detection of superoxide during the aerobic liver microsomal reduction of nitro compounds[40] (eq. 19). Both DMPO and PBN were used as spin traps. The mechanism for production of superoxide is very similar to that given above for methyl viologen.

Buettner and Oberley have published a paper in which lifetimes of the $O_2^{\cdot-}$ (or $HO_2^{\cdot}$) adduct of DMPO were measured under a variety of conditions.[41] A method for quickly purifying the commercially available DMPO is presented. This paper should prove to be valuable since it aids in defining the limits of observation of superoxide by spin trapping.

HYDROXYL RADICAL DETECTION

Hydroxyl radical is one of the most powerful oxidizing radicals occurring in biological systems. DMPO and PBN have been shown[39] to be effective traps for this radical.

One of the more intriguing observations of hydroxyl has been in the Fe^{+2}-bleomycin-DMPO system.[42] Bleomycin[43] is a multifunctional anticancer antibiotic known to induce strand breakage in DNA. The efficiency of strand breakage is markedly increased when reducing agents are added.

When a solution of $FeSO_4$, bleomycin and DMPO is placed in the cavity of an ESR spectrometer the characteristic signal of the hydroxyl radical adduct to DMPO is observed. Control experiments verify that the entire system is necessary to produce the signal, *i.e.*, Fe^{+2} or bleomycin alone with DMPO does not give rise to the ESR spectrum. The authors propose that the hydroxyl radical is the actual toxic species giving rise to the DNA strand breaks. These strand breaks are somewhat "site-specific" because bleomycin is bound to DNA and the hydroxyl radical is released in the vicinity of the site of strand breakage.

SOME CAUTIONARY NOTES TO PRACTITIONERS OF SPIN TRAPPING

It seems to be somewhat of a law of nature that the easier a technique is to perform, the more subject to abuse are the interpretations of the results. Spin trapping is in most cases rather easy to do experimentally and, accordingly, may well fall under the jurisdiction of the above law. It seems appropriate, therefore, to lay out some guidelines which may be helpful in avoiding some of the more common pitfalls.

1. The observation of an ESR signal in a spin-trapping experiment is not *prima facie* evidence that one has trapped the radical of greatest interest to the researcher.

Thus, *the highest priority in any spin-trapping experiment is assignment of the ESR signal(s).*

2. The observation of a spin adduct corresponding to the radical of greatest interest to the researcher does not necessarily mean that the ESR signal arose by means of the pathway of greatest interest to the observer.

Considerable testing needs to be done to assure that the spin adduct did indeed get there by the proposed mechanism. One simple test is to vary the concentration of the spin trap to determine the kinetic order of the reaction in spin trap. It should be quite general that the *overall reaction should tend toward zeroth order in spin trap as the concentration of spin trap is increased.*[44] It may not be too obvious to remark that observation of zero order dependence of spin trap is not 100% assurance of the radical nature of the adduct formation. It is, however, a step in the right direction.

3. Corollary to #1. The lack of observation of an ESR signal does not mean that the radical of interest is not present.

It may be that the spin adduct is unstable, the trapping rate is too slow relative to other pathways for the radical, or there might be a number of other reasons for the

failure to observe the adduct of interest. Some ideas for dealing with this and the other problems above are discussed in Janzen's review.[33]

To summarize, spin trapping is a powerful technique for the indirect ESR observation of many reactive free radicals. As with all techniques, some care should be taken to cross-check results whenever possible.

References and Notes:

1) (a) J.E. Wertz and J.R. Bolton, "Electron Spin Resonance," McGraw-Hill, New York, 1972; (b) H.M. Swartz, J.R. Bolton, and D.C. Borg, "Biological Applications of Electron Spin Resonance," Wiley-Interscience, New York, 1972.
2) See, for example, the classic paper by R.W. Fessenden and R.H. Schuler, *J. Chem. Phys.*, **39**, 2147 (1963).
3) A representative paper is by J.K. Kochi and P. Krusic, *J. Am. Chem. Soc.*, **93**, 846 (1971).
4) See, for example, W.T. Dixon and R.O.C. Norman, *Proc. R. Soc. London Ser. A.*, 97 (1963).
5) (a) E.G. Janzen and B.J. Blackburn, Abstracts of the 156th Meeting of the ACS, Atlantic City, N.J., Sept., 1968, No. ORGN-86; (b) E.G. Janzen and B.J. Blackburn, *J. Am. Chem. Soc.*, **90**, 5909 (1968); (c) G.R. Chalfont, M.J. Perkins, and A. Horsfield, *ibid.*, **90**, 7141 (1968); (d) C. Lagercrantz and S. Forschult, *Nature*, **218**, 1247 (1968).
6) It now appears that there are some 200 publications in spin trapping and applications. A complete list in the form of a titled bibliography will be available soon from the author.
7) Polymerization example: T. Kunitake and S. Murakami, *J. Polym. Sci., Polym. Chem. Ed.*, **12**, 67 (1974).
8) Radiation chemistry example: F.P. Sargent and E.M. Gardy, *Can. J. Chem.*, **54**, 275 (1976).
9) Biological chemistry example: G.R. Buettner, L.W. Oberley, and S.W.H.C. Leuthauser, *Photochem. Photobiol.*, **28**, 693 (1978).
10) Solution chemistry example: C. Lagercrantz and S. Forschult, *Acta Chem. Scand.*, **23**, 811 (1969).
11) (a) M.J. Perkins, in "Essays on Free Radical Chemistry," R.O.C. Norman, Ed., *Chem. Soc. Spec. Publ.*, **24**, 97 (1970); (b) E.G. Janzen, *Acc. Chem. Res.*, **4**, 31 (1971); (c) C. Lagercrantz, *J. Phys. Chem.*, **75**, 3466 (1971).
12) G.A. Russell, E.G. Janzen, and E.T. Strom, *J. Am. Chem. Soc.*, **86**, 1807 (1964).
13) (a) E.G. Janzen and J.I.-P. Liu, *J. Mag. Res.*, **9**, 510 (1973); (b) E.G. Janzen, C.A. Evans, and J.I.-P. Liu, *ibid.*, **9**, 513 (1973).
14) C. Heller and H.M. McConnell, *J. Chem. Phys.*, **32**, 1535 (1960).
15) (a) C. Chignell, *Aldrichimica Acta*, **7**, 1 (1974); (b) L. Berliner, Ed., *Spin Labelling*, Vol. 1 and 2, Academic Press, New York, 1976; (c) I.C.P. Smith, ref. 1 (b), pp 483-539.
16) (a) W. Ahrens and A. Berndt, *Tetrahedron Lett.*, 4281 (1973); (b) S. Terabe, K. Kuruma, and R. Konaka, *J. Chem. Soc. Perkin Trans. II*, 1252 (1973); (c) E.G. Janzen, R.L. Dudley, and R.V. Shetty, *J. Am. Chem. Soc.*, **101**, 243 (1979).
17) E.G. Janzen, Y.Y. Wang, and R.V. Shetty, *J. Am. Chem. Soc.*, **100**, 2923 (1978) and references therein.
18) A. Macker, Th.A.J.W. Wajer, and Th.J. DeBoer, *Tetrahedron*, **24**, 1623 (1968).
19) C.A. Evans, unpublished work.
20) A.R. Forrester, quoted in ref. 11(b), p 115. In reproducing this experiment only very low levels of nitroxides were produced (ref. 19).
21) E.G. Janzen, C.A. Evans, and E.R. Davis in "Organic Free Radicals," W.A. Pryor, Ed., *ACS Symposium Series*, **69**, 433 (1978).
22) (a) E.G. Janzen, C.A. Evans, and Y. Nishi, *J. Am. Chem. Soc.*, **94**, 8236 (1972); (b) E.G. Janzen and C.A. Evans, *ibid.*, **95**, 8205 (1973); (c) E.G. Janzen and C.A. Evans, *ibid.*, **97**, 205 (1975); (d) E.G. Janzen, D.E. Nutter, Jr., and C.A. Evans, *J. Phys. Chem.*, **79**, 1983 (1975).
23) (a) P. Schmid and K.U. Ingold, *J. Am. Chem. Soc.*, **99**, 6434 (1977); (b) P. Schmid and K.U. Ingold, *ibid.*, **100**, 2493 (1978).
24) (a) M.J. Perkins and B.P. Roberts, *Chem. Commun.*, 173 (1973); (b) M.J. Perkins and B.P. Roberts, *J. Chem. Soc. Perkin Trans. II*, 297 (1974); (c) M.J. Perkins and B.P. Roberts, *ibid.*, 77 (1975); (d) P. Ledwith, P.J. Russell, and L.H. Sutcliffe, *Proc. R. Soc. London Ser. A*, **332**, 151 (1973). (e) P. Sargent, *J. Phys. Chem.*, **81**, 89 (1977).
25) T.M. Chiu, C.A. Evans, J.R. Bolton, and S.K. Wong, unpublished work at the University of Western Ontario, London, Ontario.
26) (a) K. Adamic, D.F. Bowman, T. Gillan, and K.U. Ingold, *J. Am. Chem. Soc.*, **93**, 902 (1971); (b) D.F. Bowman, J.L. Brokenshire, T. Gillan, and K.U. Ingold, *ibid.*, **93**, 6551 (1971); (c) D.F. Bowman, T. Gillan, and K.U. Ingold, *ibid.*, **93**, 6555 (1971).
27) (a) M. Iwamura and N. Inamoto, *Bull. Chem. Soc. Jpn.*, **40**, 702, 703 (1967); (b) M. Iwamura and N. Inamoto, *ibid.*, **43**, 856, 860 (1970).
28) A.R. Forrester, J.M. Hay, and R.H. Thomson, "Organic Chemistry of Stable Free Radicals," Academic Press, London, 1968, p 225.
29) M.V. Merritt and R.A. Johnson, *J. Am. Chem. Soc.*, **99**, 3713 (1977).
30) H. Taniguchi and H. Hatano, *Chem. Lett.*, 531 (1974); *ibid.*, 9 (1975).
31) (a) C. Lagercrantz and S. Forschult, *Nature*, **218**, 1247 (1968); (b) S. Rustgi, A. Joshi, H. Moss, and P. Riesz, *Int. J. Radiat. Biol.*, **31**, 415 (1977).
32) A. Joshi, S. Rustgi, and P. Riesz, *Int. J. Radiat. Biol.*, **30**, 151 (1976).
33) E.G. Janzen in "Free Radicals in Biology," Volume IV, W.A. Pryor, Ed., 1979.
34) J.J.M.C. de Groot, G.J. Garssen, J.F.G. Vliegenthart, and J. Boldingh, *Biochim. Biophys. Acta*, **326**, 297 (1973).
35) G.J. Garssen, J. Vliegenthart, and J. Boldingh, *Biochem. J.*, **122**, 327 (1971).
36) H. Aoshima, T. Kajiwara, A. Hatanaka, and H. Hatano, *J. Biochem.*, **82**, 1559 (1977).
37) (a) A.N. Saprin and L.H. Piette, *Arch. Biochem. Biophys.*, **180**, 480 (1977); (b) C.-S. Lai and L.H. Piette, *Biochem. Biophys. Res. Commun.*, **78**, 51 (1977).
38) J.R. Harbour and J.R. Bolton, *Biochem. Biophys. Res. Commun.*, **64**, 803 (1975).
39) J.R. Harbour, V. Chow, and J.R. Bolton, *Can. J. Chem.*, **52**, 3549 (1974).
40) R.C. Sealy, H.M. Swartz, and P.L. Olive, *Biochem. Biophys. Res. Commun.*, **82**, 680 (1978).
41) G.R. Buettner and L.W. Oberley, *ibid.*, **83**, 69 (1978).
42) L.W. Oberley and G.R. Buettner, *FEBS Lett.*, **97**, 47 (1979).
43) J.L. Fox, *Chem. Eng. News*, **56**, 21 (1978).
44) C.A. Evans, Ph.D. Thesis, University of Georgia, 1974.

About the Author

C. Anderson Evans received his Ph.D. degree from the University of Georgia in 1974. He received his post doctoral training at the Centre D'Études Nucléaire, Grenoble, France under a Fulbright-Hays Fellowship, 1973-1974 and at the University of Western Ontario, London, Ontario, 1974-1976. His current interests include magnetic resonance, spin trapping, NMR/ESR applications to biological problems and computer applications to instrumentation.

A Small Chemical Businessman Looks At Premanufacture Notification (PMN)

Kenneth W. Greenlee
President, Chemsampco, Inc.
4692 Kenny Road
Columbus, Ohio 43214

One of the most worrisome aspects of operating a small- or medium-size chemical company today is the enormous proliferation of government regulations. Of these, the PMN (premanufacturing notification) proposed by TOSCA for all new products to be used individually regardless of quantity is the most serious: if finalized as now proposed, it is bound to stifle innovation.

Perhaps the clearest analysis we have seen of this has been Dr. Ken Greenlee's presentation at a public meeting called by the EPA in Cleveland, Ohio on February 7, 1979. Dr. Greenlee is one of the country's ablest chemists running a chemical company, Chemsampco, in Columbus, Ohio. Dr. Greenlee's presentation would be hilariously funny if only the problem were not so serious: we have to smile reading this, despite our worries.

Alfred Bader

As head of a small chemical company I am well aware that chemicals can be dangerous, but also that they can be handled with safety. I am also well aware that staying in business is a precarious venture, and small economic changes may spell life or death for a company. The proposed PMN rules could make a large change.

I am appalled by what EPA seems to be laying on us . . . what will be especially severe upon *small* chemical businesses . . . and I predict that it will cut chemical innovation in half. Before you scorn this "wild guess" of mine, take a good look at the wild guesses EPA is asking us to make in the proposed forms for PMN (premanufacturing notification) procedures! Now, besides criticizing the proposed rules, I mean to offer some specific remedies; for a starter, I'd say to exempt quantities produced in less than 10,000lbs., across the board.

At first, PMN sounded so simple. I visualized sending a postcard or short letter to EPA saying, "I plan to make u-name-it acid for commercial purposes in 90 days unless you object." EPA would look at it briefly and generally reply "Okay." Such a quick answer could be possible if EPA will hire practical chemists, biologists and toxicologists capable of "separating the sheep from the goats."

On the other hand, one couldn't fault EPA for asking for a little help. It is reasonable for them to ask us to share whatever property and toxicology data we may have on hand. But the depth and breadth of the questioning in those formidable 38 pages of PMN forms make it clear that they want *much, much more* than you are likely to have on hand.

Also, they make it clear that they mean to have it. On page 2225 of the document which we're here to discuss I read "Section 5 and these rules require manufacturers to submit complete and valid notices ..... if a person does not submit a complete and valid notice he may be subject to penalties up to $25,000 per day." (!)

Now I ask you: who devises the notice forms? Who decides what information to ask for? Who decides whether the notices are complete and valid? You know; not an independent firm of experts, not a panel of referees; EPA does it all!

Section 5 of TOSCA (Toxic Substances Control Act) makes it clear that no registration procedure is intended to be set up under PMN. Moreover, EPA affirms, in the preamble to their proposed rules, that "Section 5 does not establish a certification or registration program . . . . rather it requires a manufacturer to notify EPA . . . . and submit information . . . which EPA can use." But another section declares that the statutory 90-day waiting period can be extended even for minor technical flaws . . . indefinitely . . . until EPA determines that the flaws are mended. Now I ask you, doesn't that sound just like a *bona fide* certification deal?

TOSCA specifies that the application of PMN must not be unduly burdensome on industry. Yet EPA estimates that the cost of completing their forms will be in the range of $2,500 to $41,400; and presumably this is just for the clerical and "library research" work of assembling existing data and "paper" projections. Creating data to complete the forms could cost (according to some estimates) one-quarter-of-a-million dollars.

It is clear that PMN is bad news for small chemical companies. My own had to grow a dozen years before it made an annual profit as large as EPA's estimated maximum cost of PMN for just one product. Large companies may anticipate sales volumes large enough to justify such costs in addition to the usual R & D costs, but small ones cannot.

We small companies can continue to operate in the research and development area of chemistry, until that, too, becomes overregulated. But, how can we hope to break through that medium-volume range where PMN is required but the costs are too high for us to bear?

On page 2263 of the preamble we see that the EPA Administrator, Douglas Costle, has determined that "..... this document does not . . . require preparation of an

economic impact analysis . . . .," because (it appears) of its low cost to industry. Well, its impact on the small chemical business community may be like that of a ton of brick.

Anyone who has carefully read the proposed rules, explanations and forms (an ordeal that takes hours) gets these impressions about the questions and the data they ask for:

1) Some will require great expense.
2) Some can't be obtained until after you're in production.
3) Some open up the realm of pure conjecture.
4) Some violate the traditions and practices of confidentiality. Here, a prime example is the requirement of process flow diagrams which are among our most closely guarded secrets.

Honestly, it seems as if EPA is asking for every conceivable piece of information no matter how difficult it is to obtain or how sacred or how ridiculous. If they were consciously trying to stifle innovation (hence progress) in the chemical industry (at least in the small business area), they would be on the right track.

In their eagerness to cover the whole waterfront they have come up with many ambiguities and contradictions which call for rethinking or rewriting.

Examples:

Page 2269 "Submitter must contact each person whom he firmly believes will purchase . . ." Now, "firmly believes" is so subjective that you would be justified in contacting none at all!

Page 2269 "Submitter must state (to said person) that he is not under legal obligation to provide . . . . (but) . . . EPA . . . may require (him) to provide . . . ." In the upshot, is it a legal obligation, or is it not?

Page 2305 "Are there any structurally related chemical substances which you have not discussed here? ( )yes ( )no. If yes, explain why." Does this refer to substances which have been made (or found) and studied, or to all such (there could be thousands) which are capable of existence? Does it ask why they exist or why you didn't discuss them? The implication is that you should know about them all and discuss them.

My preannounced topic of major concern was the treatment of chemical intermediates in PMN. Now, in small chemical manufacturing businesses, quick turnabouts in customer requirements, raw material availability and costs, actions by competitors, etc. call for rapid adaptation by the manufacturer. New processes or radical changes in old ones may be needed - - - and accomplished - - - almost overnight. Our ability to move fast is the chief reason for our success - - - our existence.

Changes in processes mean new intermediates, some of which will be subject to PMN rules. A 90-to 180-day delay in manufacture of such an intermediate could cause a critical interruption in output of the final product, and conceivably could make the new intermediate a dead letter before its production could begin!

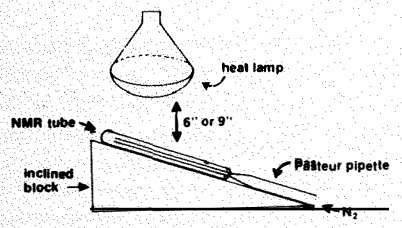
To be considered a nonisolated intermediate, the chemical (it seems) must not be removed from the reactor in which it is made (page 2248), and at first this seems reasonable. But, frequently *reversed addition* is required for good yields or safety; in that case, the intermediate chemical must be pumped from the original reactor into another one, or to a holding tank from which it is added back (at a controlled rate) to the same reactor, now charged with a different reactant. Such slightly variant procedures should not make these intermediates subject to PMN.

My own company has submitted 66 chemicals for the "inventory", half of which are intended for intermediate use only. We are generating new ones at a rate of 1 or 2 per month, some with useful lives of less than 6 months. It actually seems that PMN treatment for just one of them could consume our entire R & D budget for a whole year. Is there any wonder that I am apprehensive?

With that question, which is really a cry for help, I should stop. I could go on and on. But, others should get their chance to speak up and I hope they will.

Lab Notes, *cont'd*

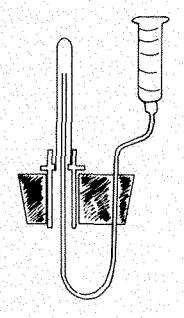
The problems associated with cleaning and drying dirty NMR tubes have been alleviated by the following procedure.



The soiled tubes are rinsed several times with a solvent which solubilizes the residue (if any), then twice with acetone. The problem now arises as to the mode of drying. Oven drying is time consuming and not very efficient. One solution is to dry the NMR tubes under an infrared heat lamp at a distance of 6 to 9 inches. Dry N_2 gas is circulated through the tubes *via* a long (9-in) Pasteur pipette. The tubes are positioned for drying on a grooved and inclined wooden block. Drying is completed in about ten minutes. Spectra run after this procedure do not show any residual water or acetone peaks even under conditions of long-term Fourier Transform acquisition.

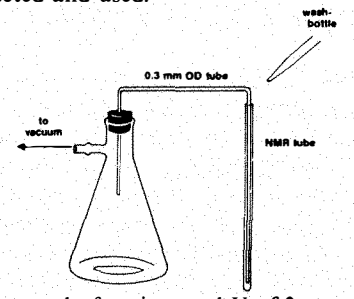
Joseph Piarulli
Sterling Chemical Laboratories
Yale University
New Haven, CT 06520

Commercially available washers for NMR tubes are convenient, but also fragile and expensive. An almost unbreakable version can be made quickly from a rubber stopper, a syringe barrel, a long (12-in) 14- or 16-gauge blunt needle, and a polyethylene "quick disconnect," used to join lengths of rubber tubing. Assembled as shown in the accompanying diagram, with the NMR tube to be washed resting on the inner ledge of the "quick disconnect," the apparatus is inserted into a vacuum flask and the syringe barrel filled with solvent. Barrels of different sizes may be used according to the amount of solvent desired. Without the "quick disconnect" and using a somewhat shorter needle, the system may be used for rinsing uv spectrophotometer cells.



Edward W. Sheppard, Sr.
Research Chemist, Mobil Corp.
Corporate Research and Development
Princeton, NJ 08540

Most devices for cleaning NMR tubes are fragile and/ or cumbersome. Here is a practical version which is easily constructed and used:



One end of an inverted U of 3-mm o.d. glass tubing is inserted through a stopper into a filter flask. The NMR tube is filled

Cont'd on page 38

Page intentially blank

Page intentially blank

Aldrichimica Acta

Volume 12, Number 3, 1979

New Synthetic Reagents and Reactions. See page 43.
Choosing and Using Noble Metal Hydrogenation Catalysts. See page 53.

chemists helping chemists in research & industry
aldrich chemical co.

Aldrichimica Acta

Volume 12, Number 3, 1979
A publication of ALDRICH CHEMICAL COMPANY, INC.

Main Sales Office:
940 West Saint Paul Ave.
Milwaukee, Wisconsin 53233
Telephone: (414) 273-3850
Order Desk: (800) 558-9160 Toll-free
TWX: (910) 262-3052
Telex: 26 843

East Coast Service and Distribution Center:
159 Forrest Street
Metuchen, New Jersey 08840
Telephone: (201) 549-6300
TWX: (710) 998-0575

In Canada:
Aldrich Chemical Co. (Canada), Ltd.
1500 Stanley Street, Suite 405
Montreal, Quebec H3A 1R3
Telephone: (514) 845-9289
Eastern & Atlantic: (800) 361-6141 Toll-free
TWX: (610) 421-4608

In Great Britain:
Aldrich Chemical Company, Ltd.
The Old Brickyard, New Road
Gillingham, Dorset
SP8 4JL, England
Telephone: 074-76 2211
Telex: (851) 417238

In West Germany/Continental Europe:
EGA-Chemie KG
7924 Steinheim am Albuch
West Germany
Telephone: (07329) 6011
Telex: (841) 714838

In Belgium/Continental Europe:
Aldrich-Europe
B-2340 Beerse
Belgium
Telephone: 014/611431
Telex: (846) 32540

In Japan:
Aldrich Japan
c/o Tokyo Danchi Sohko Kanrito
4-1, 3-chome, Heiwajima, Ohta-ku
Tokyo, Japan
Telephone: 768-0555
TWX: (781) 246-6143

In Israel:
Sigma Israel Chemical Co.
P.O. Box 37673
Tel Aviv, Israel 61360
Telephone: 03-612315
Telex: (922) 35645

About Our Cover:

When we first looked at the painting reproduced on our cover, we were reminded of what we had written about another Acta cover (Volume 8, Number 4, 1975) and we were happy that our chemist-collector did not limit himself to one painting per subject.

"The Bible is the book of dreams, par excellence: dreams of individuals, dreams of a people, dreams of all mankind. It is surely no accident that the very first well known dream in the Bible is not that of a king or of a general but of a man at the lowest point in his life — homeless and hunted, yearning for God's promise that He would return him to his country.

The vision of a ladder with angels going up and down on it is unique in Biblical imagery, and so *Jacob's Dream* has aroused artists' imagination for centuries." This depiction (oil on canvas, 29 x 33$^1/_2$ inches) by Abraham Bloemaert, *ca.* 1620, was purchased in an antique store in The Hague where it was thought to be of a mythological subject, and painted in the nineteenth century. In fact, much of the extensive overpaint was nineteenth century, and it took careful restoration to bring out its original beauty. If only our chemist could find a good many more such dreams of paintings.

This painting and those on five other Acta covers are among twenty-four Dutch and Flemish paintings in an exhibition in honor of Professor Anna Harrison, past-president of the American Chemical Society, held at the Art Museum, Mount Holyoke College this autumn. If you would like the fully illustrated catalog please send your check for $3.00 to the Art Museum, Mount Holyoke College, South Hadley, MA 01075, and you will receive the catalog postpaid.

Are you interested in our Acta covers? *Selections from the Bader Collection*, with 30 duotone reproductions, many of previous Acta covers, and an introduction by Professor Wolfgang Stechow is available to all chemist art-lovers.

Also, many paintings reproduced on our Acta covers were shown at the Milwaukee Art Center in an exhibition, "The Bible Through Dutch Eyes," arranged by Dr. Bader in 1976. The fully illustrated catalog with 66 black-and-white and 4 full-color reproductions contains many art historical and Biblical comments.

Many of the early issues of the *Aldrichimica Acta* have become very rare. Please do not throw your issues away. In time, we believe that complete sets will become valuable, and — if you do not want to keep them — there probably are chemists near you who would be interested.

Lab Notes

There are many instances where it is difficult to prevent charcoal from passing through a filter bed prepared from many of the commonly used filter aids. This is particularly true, for example, when DMF is used as a solvent for a catalytic reduction with Pt or Pd on charcoal. In such cases, the use of a bed of magnesium sulfate (anhydrous reagent powder) helps overcome this difficulty.

Jules Freedman, Ph.D.
Organic Chemistry Department
Merrell Research Center
110 Amity Road
Cincinnati, Ohio 45215

A common problem is the vacuum filtration of products from hot, highly acidic solutions. It always seems that the filtration is 90% complete and then the filter paper disintegrates. Hot, highly caustic solutions and/or slurries are equally hard to handle. A convenient solution to this problem is to use polypropylene filter cloth. Impervious to most mineral acids and strong bases, it is easily cut with a pair of scissors into any size using the appropriate-size filter paper as a model. It is insoluble in almost all organic solvents, and therefore can be used again and again. A bed of Filter-Cel® or Dicalite® on the cloth works beautifully in clarifying solutions with activated charcoal. The cloth can be easily cleaned by washing or even boiling in a solvent like acetone.

Henry C. Koppel
Vice President, Production
Aldrich Chemical Company

Editor's Note:
For the convenience of our customers, Aldrich offers this filter cloth.

The Kuderna-Danish concentrator suffers from the disadvantage that the ground-glass joint between the evaporator flask and receiver tube represents a potential contamination site. Unless grease, a chemical spray coating (*e.g.*, Teflon®) or a Teflon sleeve is used to render the joint watertight, water vapor seeps in depositing chlorides and other salts. Both grease and chemical coatings themselves represent contaminants since they dissolve in certain organic solvents, and Teflon sleeves often leak and collect contaminants. This note describes a modification to the Kuderna-Danish concentrator which does away with the outside ground-glass joint between receiver tube and flask.

The modified apparatus is illustrated in Figure 1. Instead of being detachable the receiver tube is now physically joined to the evaporator flask and contains a ground-glass joint inside the tube using a Quickfit socket and cup piece. When the solution has been concentrated to a small enough volume to be contained in the receiver tube (usually about 4ml) the Snyder column is removed and a micro-Snyder column with an extension tube if necessary, is lowered through the top of the evaporator flask and inserted into the ground-glass joint leading to the receiver tube. Concentration of the solution is continued until the desired volume is obtained. Alternatively, the final concentration can be performed under reduced pressure or using a stream of nitrogen. The final concentrate is removed by pipette and either injected directly into the gas chromatograph or transferred for the next step, *e.g.*, the clean-up stage in pesticide residue analysis.

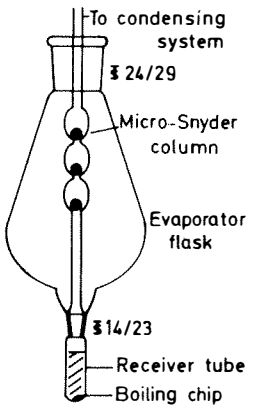


Fig. 1. Modified Kuderna-Danish concentrator showing the position of the micro-Snyder column for the final stage of the concentration process.

Apart from obviating the need for an outside joint between the receiver tube and evaporator flask the modification has another advantage. The micro-Snyder column, being enclosed completely by the evaporator flask, can operate more efficiently especially if the flask is evacuated by use of an adapter with vacuum take-off and outlet (*e.g.*, Quickfit plastic screwcap-type) for the top of the Snyder column placed at the outlet from the flask. Improving the efficiency of fractional distillation at this stage is vital if pesticides are not to be lost in the process.

R.D. Davies
Fuel Research Institute
P.O. Box 217
Pretoria, South Africa

The reciprocating motor supplied as part of the Aldrich Kugelrohr Distillation Apparatus (Cat. No. Z10,046-3) makes an extremely useful substitute for a conventional rotary motor used to drive the paddle stirrer in a reaction flask. Since the oscillating motor is either air- or vacuum-driven, there is little danger from electrical sparking and the motor will not burn out if the stirrer should stall.

Cont'd on page 49

"Please Bother Us."

by

Earlier this year I received a very interesting letter from Dr. J.A. Cotruvo, Director, Criteria and Standards Division of the Office of Drinking Water of the EPA in Washington, expressing his deep concern about the unavailability of Basic Fuchsin. Dr. Cotruvo explained that "this dye is used as an ingredient in the bacteriological medium m-Endo agar, which is used by most water treatment facilities on a regular basis for the enumeration of certain bacterial indicators of fecal pollution. National drinking water regulations allow for only one other alternative procedure (the Most Probable Number test), but this test is less precise and more expensive than that using m-Endo agar." I replied that the problem might have seemed funny if it wasn't so sad and serious. Basic Fuchsin used to be made by two large American companies which have discontinued its production (and that of many other low-volume stains and dyes) because of regulatory pressures!

In this case we were able to help. We are now manufacturing Basic Fuchsin on a modest scale, and will continue unless the EPA stops us.

It was no bother at all, just a pleasure to be able to help.

New Synthetic Reagents and Reactions*

George A. Olah
Hydrocarbon Research Institute
and Department of Chemistry
University of Southern California
Los Angeles, California 90007

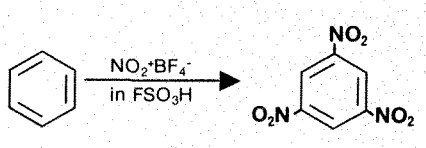
I. INTRODUCTION

Synthetic organic chemistry encompasses, besides multistep synthesis of complex target molecules (frequently natural products with specific stereochemistry), the development of simple, basic reactions and new methods for carrying out individual steps or preparing products.

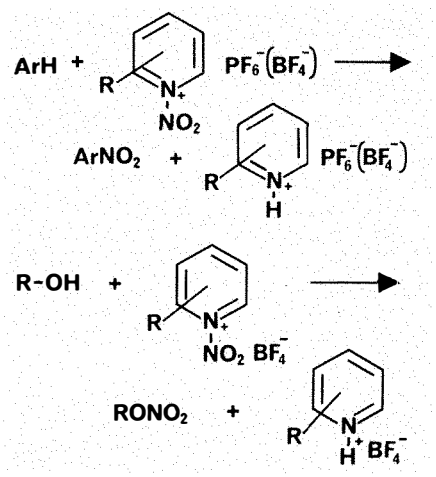
It is in this latter area that our synthetic investigations are centered, encompassing the study of basic (unit) reactions as well as development of new reagents.

II. NITRATION

Conventional nitration[1] of aromatic compounds uses mixed acid (mixture of nitric and sulfuric acid). In the reaction the water formed dilutes the acid; further, due to its strong oxidizing ability, mixed acid is ill-suited to nitrate many sensitive compounds. It also presents serious problems in spent-acid disposal. We have developed a series of efficient new nitrating agents and methods to overcome these difficulties. Readily prepared and isolated stable **nitronium salts**, such as $NO_2^+BF_4^-$ and $NO_2^+PF_6^-$, nitrate aromatics[2] in organic solvents generally in close-to-quantitative yields. **Alkyl nitrates**, such as $MeONO_2$,[3] $BuONO_2$ or acetone cyanohydrin nitrate, $Me_2C(CN)ONO_2$,[4] with BF_3 as catalyst are similarly effective and more selective nitrating agents. The powerful nature of nitronium salts as nitrating agents enables, for example, even trinitration[5] of benzene to trinitrobenzene.



Nitro-onium ions, such as $C_5H_5N^+NO_2$, readily prepared[6a,b] from suitable donors and nitronium salts, act as convenient **transfer nitrating reagents** in generally selective, clean reactions. Transfer nitrations are equally applicable to C- as well as to O-nitrations allowing, for example, safe, acid-free preparation of alkyl nitrates and polynitrates from alcohols (polyols).[6c]

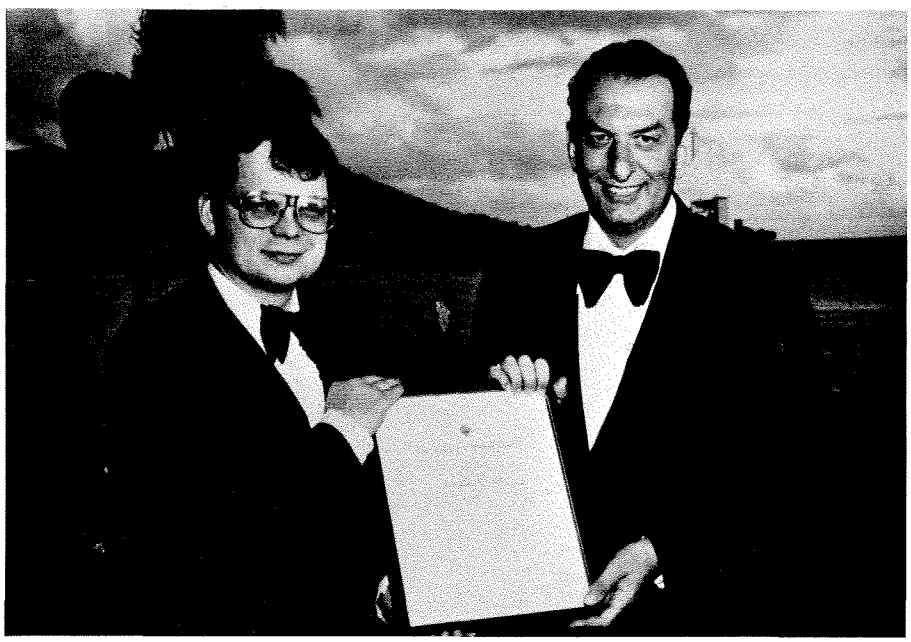


$$ArH + \overset{+}{N}O_2\bar{P}F_6 \longrightarrow ArNO_2 + HPF_6$$

$$ArH + CH_3ONO_2 \xrightarrow{BF_3} ArNO_2$$

or

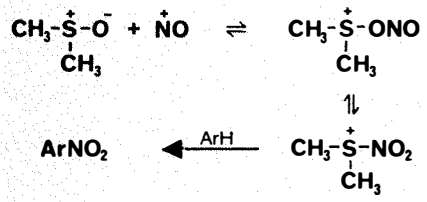
$$(CH_3)_2C(CN)ONO_2$$



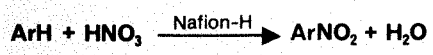
Professor George A. Olah (right) receiving the ACS Award for Creative Work in Synthetic Organic Chemistry sponsored by Aldrich, from Dr. Irwin Klundt, vice-president of Aldrich.

*Based on Lecture given upon receipt of the American Chemical Society Award for Creative Work in Synthetic Organic Chemistry, 1979, sponsored by the Aldrich Chemical Company, delivered at the ACS/CSJ Chemical Congress in Honolulu, Hawaii, April 4, 1979 (Paper ORGN 236).

A new nitration system in the form of nitrosonium $(NO)^+$ salts in DMSO was developed.[7] The S-nitro ⇌ S-nitrito equilibrium was also directly observed by ^{13}C and ^{15}N NMR spectroscopy.

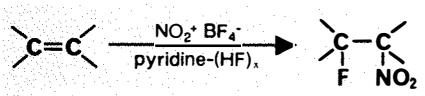


Solid superacid catalysts, comparable to or stronger than sulfuric acid, play a significant role in replacing conventional liquid acid (protic and Friedel-Crafts-type Lewis) catalysts in developing novel, clean, heterogeneous reactions. In the case of nitration, not only were alkyl nitrate nitrations carried out in this way, but also the **azeotropic nitration** of aromatic compounds with nitric acid was developed[4,5] over solid perfluorinated sulfonic acid catalysts (Nafion-H).



Water formed is continuously azeotroped off by excess of aromatics, thus preventing dilution of acid and allowing its extensive utilization.

Electrophilic nitration of olefins is also readily carried out[8a] with nitronium salts in pyridinium polyhydrogen fluoride as solvent. The reaction gives high yields of nitrofluorinated alkanes which subsequently can be dehydrofluorinated to nitroolefin.



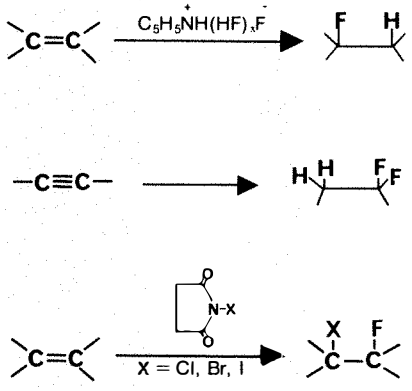
Some of the characteristic reactions of NO_2^+ and NO^+ salts are depicted in Figures I and II, respectively.

III. HALOGENATION

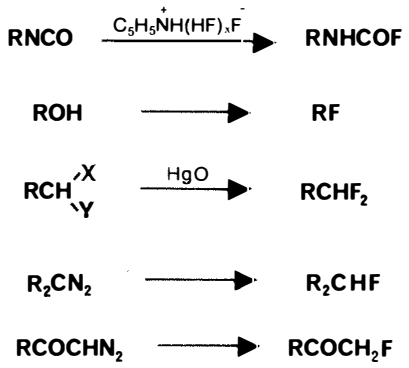
Fluorination of organic compounds still requires special techniques not generally feasible in the average laboratory. Reactions with the industrially most generally used and inexpensive fluorinating agent, anhydrous hydrogen fluoride, must be carried out under pressure in special equipment due to its relatively low boiling point (20° C) and corrosive nature.

We have found a simple way to enable carrying out anhydrous hydrogen fluoride reactions at atmospheric pressure in ordinary laboratory equipment (polyolefin or even glass) — by using the remarkably stable complex formed between pyridine and excess hydrogen fluoride. HF (70% w/w) and pyridine (30%) form a liquid complex, $C_5H_5NH^+(HF)_xF^-$, showing little vapor pressure at temperatures up to 60° C.[8b] The reagent (pyridinium polyhydrogen fluoride) thus enables[8(b-j)] one to carry out a wide variety of synthetically very useful fluorination reactions at atmospheric pressure under very simple experimental conditions. Examples of the usually high-yield reactions are:

Hydro- and Halofluorination of Olefins and Acetylenes

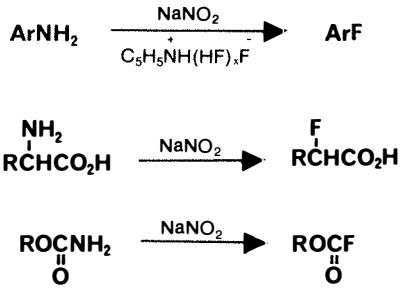


Fluorinations with Pyridinium Polyhydrogen Fluoride

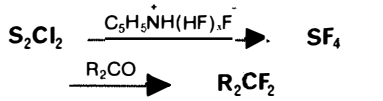


Where X and Y = Cl, Br, I

Deaminative Fluorination Reactions in Pyridinium Polyhydrogen Fluoride Solution



The pyridinium polyhydrogen fluoride reagent is also very convenient for the *in situ* preparation of inorganic fluorides such as SF_4.[9] Due to the good solvent properties



of pyridinium polyhydrogen fluoride, SF_4 fluorinations can be carried out *in situ* at atmospheric pressure.

Figure I.

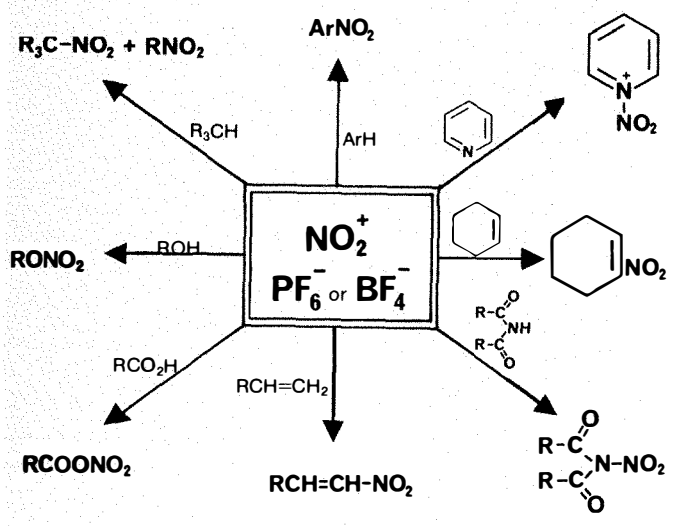
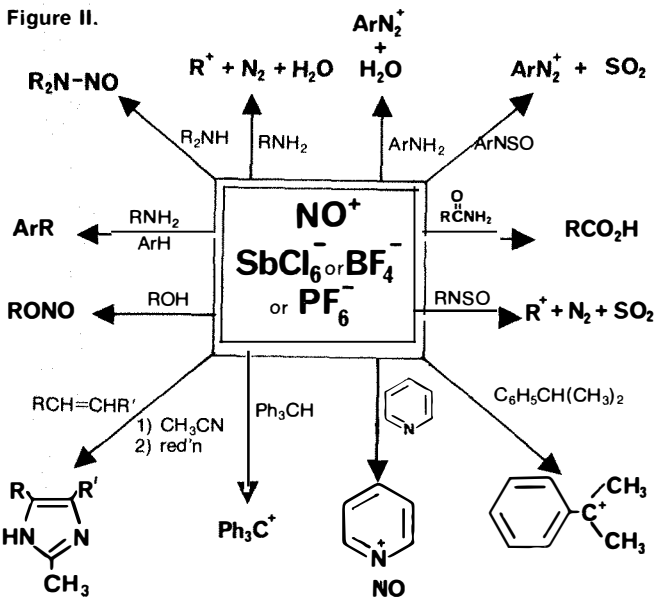
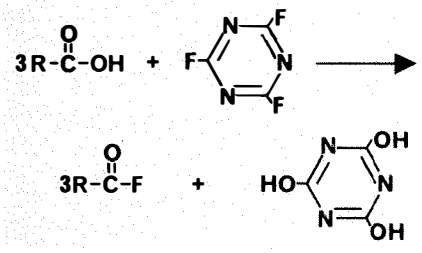


Figure II.

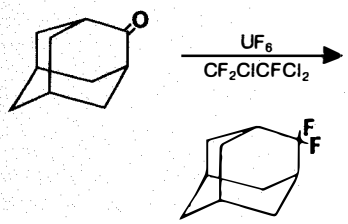


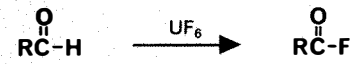
An alternative reagent, selenium **tetrafluoride** (SeF_4), which has an atmospheric boiling point of 106°, was also developed.[10] Fluorination of ketones, aldehydes, etc., proceeds in high yield. Since selenium compounds are generally toxic, the reagent must be handled with great care.

Cyanuric fluoride, another easily prepared fluorinating agent, is particularly advantageous in the preparation of acyl fluorides, including formyl fluoride.[11]

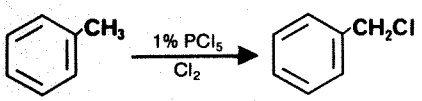


Uranium hexafluoride depleted of U^{235} is an abundant by-product of enrichment plants. It was found[12] to be highly soluble in fluorocarbons and halofluorocarbons, thus allowing its convenient use in atmospheric-pressure fluorination reactions (as well as in oxidations, *vide infra*).

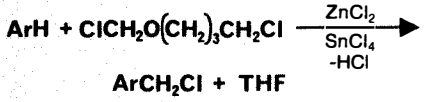




Due to the high carcinogenic activity of chloromethyl ethers,[13] **chloromethylation** reactions have presented significant problems in recent years. A simple substitute for the preparation of chloromethylarenes is the selective side-chain chlorination of methylarenes. Whereas many radical chlorinations are known, an exceedingly simple and efficient PCl_5-catalyzed side-chain chlorination of alkylbenzenes (and alkanes) was found.[14]



An alternative chloromethylating agent, 1-chloro-4-chloromethoxybutane, reacting *via* oxygen participation to give tetrahydrofuran as the by-product, is also very effective.[15]

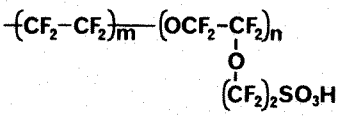


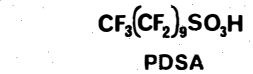
IV. ALKYLATION

In the Friedel-Crafts alkylation method using aluminum chloride or related metal halide catalysts, complex mixtures of products are generally formed due to consecutive and concurrent polyalkylation and isomerization-disproportionation processes. They are promoted by extensive carbocationic complex formation with the catalyst.[16]

In order to avoid much of the side reactions and complex formation that necessitate aqueous acid/caustic workup (generally accompanied by loss of the catalytic halide), high-acidity solid acid catalysts which allow clean heterogeneous reactions without workup problems have been used increasingly. My group[17] has found of particular utility, solid perfluorinated sulfonic acids such as the acid form of DuPont's ion-membrane Nafion resin (Nafion-H) or longer-chain perfluorinated alkanesulfonic acids such as perfluorodecanesulfonic acid (PDSA). If needed, the

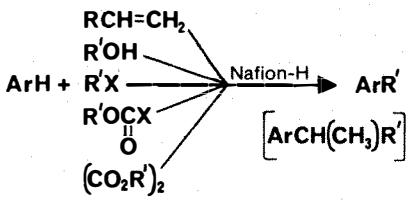
Solid Superacid Catalysts



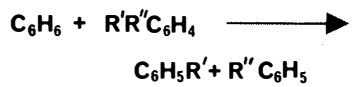


acidity of these acids, which is similar to that of liquid Magic Acid® (FSO_3H-SbF_5), can be further increased by complexing with higher-valency fluorides such as SbF_5, TaF_5, and NbF_5.[18]

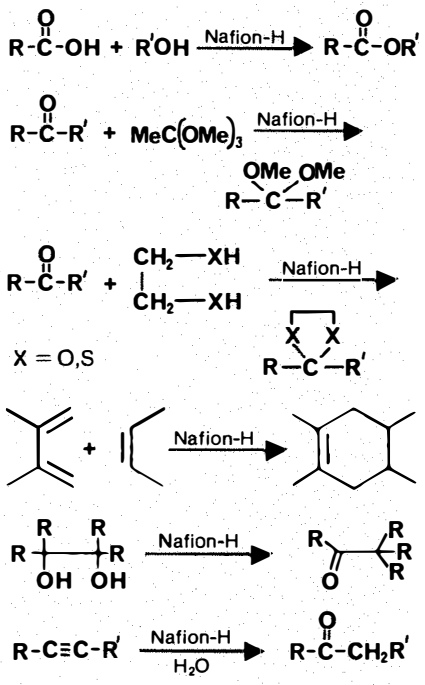
Alkylation of aromatics with olefins, alkyl halides, alcohols (including methyl alcohol), esters and the like takes place with ease over these catalysts.[19]



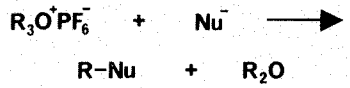
Transalkylation of aromatics with di- or polyalkylbenzenes can be carried out with equal ease.[20]



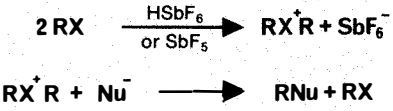
Solid superacid catalysts of the Nafion-H type also efficiently catalyze various reactions such as esterification, ketal (acetal) formation, Diels-Alder reactions, pinacol-pinacolone rearrangement and hydration of alkynes.[21]



For selective laboratory alkylations, we have also developed a series of ionic alkylating agents. Although Meerwein's[22] trialkyloxonium and dialkoxycarbenium tetrafluoroborate and hexachloroantimonate salts (as well as the conveniently soluble hexafluorophosphate salts used in our work[23]) are widely used as transfer alkylating agents, they lack selectivity and generally are incapable of C-alkylation.

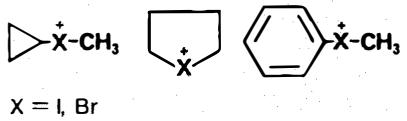


Dialkylhalonium salts such as dimethylbromonium and dimethyliodonium fluoroantimonate, prepared from excess alkyl halide with antimony pentafluoride or fluoroantimonic acid and isolated as stable salts, as well as the less stable chloronium salts obtainable in solution,



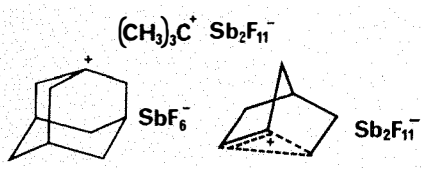
are very effective alkylating agents for heteroatom compounds (Nu = R_2O, R_2S, R_3N, R_3P, etc.), and for C-alkylation (arenes, alkenes). As the nature of the halogen atom can be varied, these salts provide useful selectivity in their alkylation reactions.[24]

A great variety of other halonium ions was also prepared, including the following:

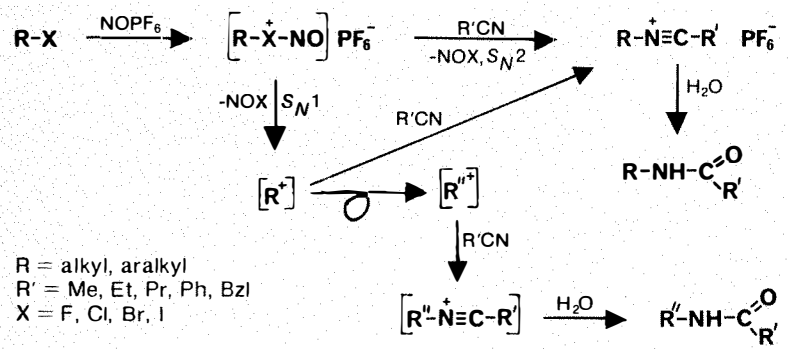


Their alkylating abilities were also studied.[24,25]

Not only onium ions, but also **carbocation salts,** can be prepared and used as highly reactive alkylating agents. The remarkably stable triphenylcarbenium salts are widely used as hydride-abstracting agents and as initiators for cationic polymerizations. Using methods developed for preparing stable carbocations in superacidic media and isolating the salts generally by addition of Freon-type solvents or by evaporation of solvent SO_2, SO_2ClF or SO_2F_2, we have isolated a series of stable salts.[26] Typical carbocation salts, generally isolated as the fluoroantimonates, include such simple tertiary ions as the *tert*-butyl and adamantyl cations,[27] as well as stabilized secondary ions, such as the norbornyl cation.

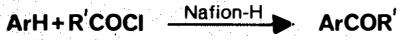


A particularly advantageous new technique is to carry out alkylation reactions with alkyl halides by initiation with nitrosonium salts. Using this reaction, a very mild form of the Ritter reaction was developed.[28]



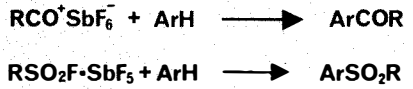
V. ACYLATION, SULFONYLATION

Solid superacidic catalysts of the Nafion-H type are also effective in bringing about Friedel-Crafts-type acylations with aroyl halides.[29] Interestingly, acetyl

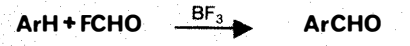


chloride gives predominantly ketene under the reaction conditions.

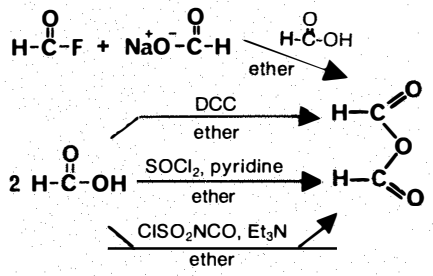
Isolated acyl salts, such as acetyl, propionyl and benzoyl salts, as well as similarly isolated sulfonyl halide-antimony pentafluoride complexes, are effective acylating (sulfonylating) agents.[30]



Acylation[31a] with acyl fluorides, generally catalyzed by boron trifluoride, also allows formylation, as formyl fluoride is a stable acyl halide of formic acid.



Formic anhydride was also prepared, characterized (by NMR and IR spectroscopy), and used as a new formylating agent.[32]

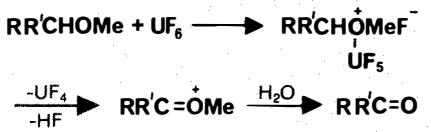


VI. OXIDATION AND OXYGENATION

During investigations of oxidation reactions, including electrophilic oxygenation of hydrocarbons, we have studied new oxidations with higher-valency fluorides (UF_6, WF_6, MoF_5, IF_5 and CoF_3),[12,33] peroxy compounds ($UO_4 \cdot 2H_2O$),[34] superacid-catalyzed hydrogen peroxide[35] and ozone reactions[36] (*i.e.*, with $H_3O_2^+$ and O_3H^+), as well as oxidations with NO_2^+.[7,37]

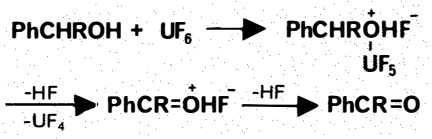
In spite of the availability of uranium hexafluoride depleted of fissionable ^{235}U and its remarkable properties, the study of the reactions of UF_6 with organic compounds remained virtually unexplored. The highly covalent nature of UF_6 makes it particularly suitable for reaction in nonaqueous solvents. Stable solutions of UF_6 in chlorofluorocarbons (Freons) or chlorohydrocarbons (methylene chloride or chloroform) can be used conveniently as they do not attack glass and are generally easy to handle.

Ethers undergo oxidative cleavage to form carbonyl compounds and alcohols. Furthermore, the direction of cleavage is predictable, thus the utility of ethers (such as benzyl or benzhydryl ethers) as protecting groups for alcohols is broadened. The oxidation of methyl ethers is of high yield and regiospecific. Trapping experiments with phenyllithium suggest the intermediacy of methoxycarbenium ions in the reaction.

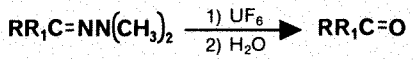


Benzyl and benzhydryl ethers are cleaved to the corresponding alcohols and benzaldehyde or benzophenone, respectively.

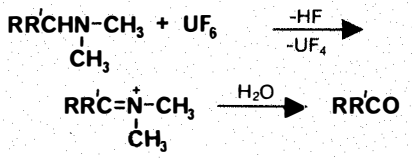
Benzyl alcohols are further readily oxidized to the corresponding carbonyl compounds.



Oxidative cleavage of protected carbonyl compounds such as tosylhydrazones and *N,N*-dimethylhydrazones also takes place with ease upon aqueous quenching of the initially formed UF_6 adducts.



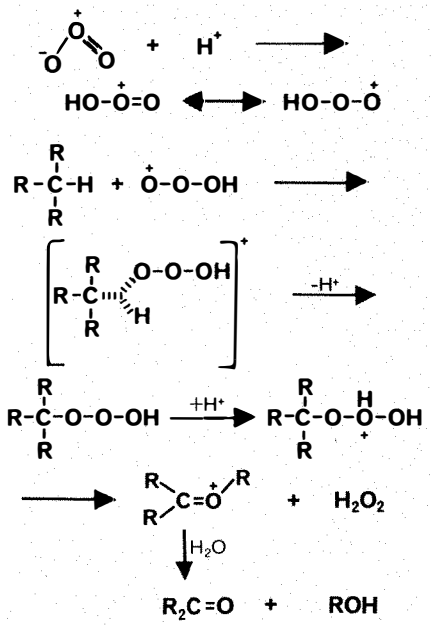
N,N-Dimethylalkyl(cycloalkyl)amines are also oxidized by UF_6 yielding, upon aqueous quenching, the corresponding carbonyl compounds.



WF_6, MoF_5, IF_5, and CoF_3 are capable of oxidations similar to those with UF_6 but are considerably less easily available and also tend to give more fluorination side reactions.

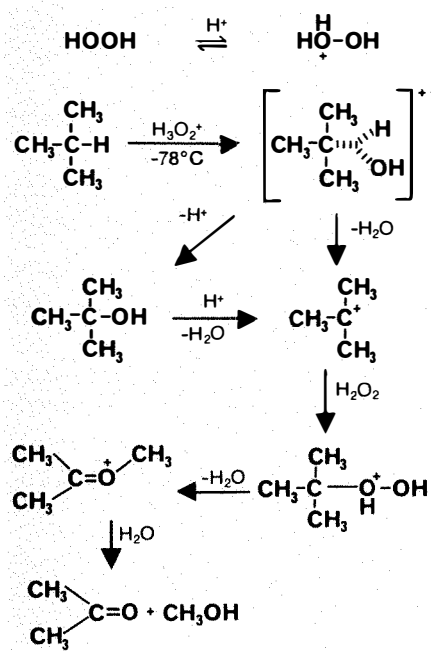
Both hydrogen peroxide and ozone readily protonate in superacids, giving the reactive electrophilic oxygenating agents H_2O^+-OH and $O{=}O^+$-OH, respectively.

Protonated ozone, upon reaction with a tertiary alkane *via* front-side insertion into the C-H bond, gives a very unstable trioxide which immediately undergoes acid-catalyzed cleavage rearrangement leading to the corresponding ketone and alcohol.

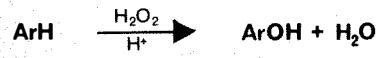


The reaction can be considered as the aliphatic equivalent of the well known cumene hydroperoxide reaction giving phenol and acetone.

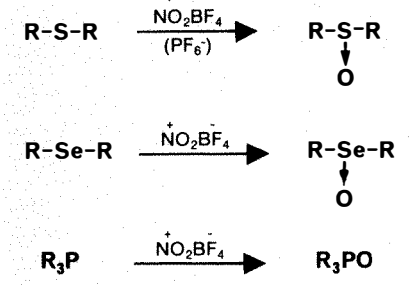
Protonated hydrogen peroxide similarly acts as an electrophilic hydroxylating agent, forming alcohols which can react further with hydrogen peroxide giving hydroperoxides and thus, acid-catalyzed cleavage rearrangement products.



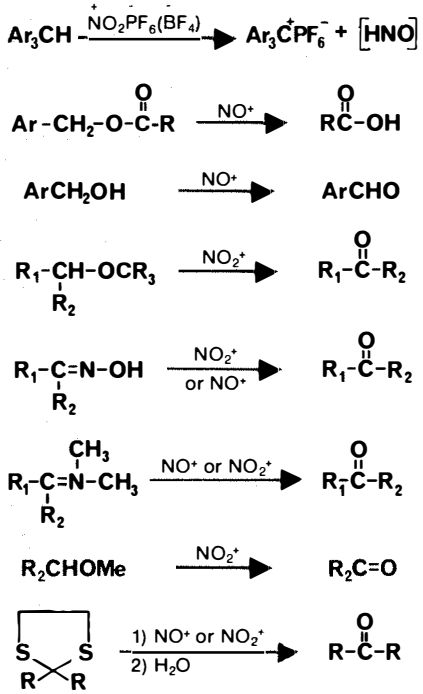
Benzene and alkylbenzenes are hydroxylated to phenols with high selectivity as the products are protonated in the acidic media and thus, are protected from further oxidation.



The nitronium ion, NO_2^+, is generally considered to function only as a nitrating agent. It was found,[7] however, that it possesses significant ambident reactivity and acts as an oxidizing agent. Dialkyl (aryl) sulfides and selenides, as well as trialkyl(aryl)phosphines, react with nitronium salts to give the corresponding oxides.



Another interesting aspect of our work relates to the utilization of stable nitronium (NO_2^+) and nitrosonium (NO^+) salts, particularly the PF_6^- and BF_4^- salts, as mild and selective hydride-abstraction and oxidative cleavage agents.[37] Representative examples are:



VII. MISCELLANEOUS REAGENTS

The utilization of **iodotrimethylsilane, $(CH_3)_3SiI$,**[38] (also studied independently by M. Jung[39]) and its simplified *in situ* analogs

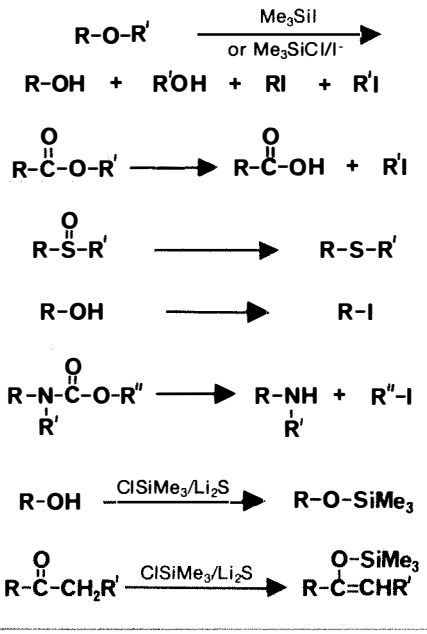
In situ **Iodotrimethylsilane Reagents**

$$(CH_3)_3Si\text{-}Si(CH_3)_3 + I_2$$

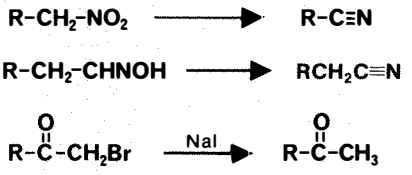
$$C_6H_5Si(CH_3)_3 + I_2$$

$$ClSi(CH_3)_3 + NaI \text{ (in } CH_3CN)$$

offer excellent preparative possibilities for mild, neutral, nonaqueous cleavage-hydrolysis reactions, deoxygenations, oxidations, halogenations, and the like. Some examples are:



Other recently[40] developed reagents from our laboratory include the solid, stable and quite soluble **trimethyl(ethyl)-aminesulfur dioxide complexes** $R_3N \cdot SO_2$. These "solid forms" of SO_2 make many dehydrogenation, reduction, and halogenation reactions readily available, avoiding the use of inconvenient, low-boiling, and difficult-to-handle sulfur dioxide. Examples are:



Acknowledgment

Support of our research by the National Science Foundation, the National Institutes of Health and the U.S. Army Office of Research is gratefully acknowledged.

References:

1) J.G. Hoggett, R.B. Moodie, J.R. Penton, and K. Schofield, "Nitration and Aromatic Reactivity," Cambridge University Press, Cambridge, 1971.
2) a) G.A. Olah, S.J. Kuhn, and S.H. Flood, *J. Am. Chem. Soc.*, **83,** 4581 (1961).
b) G.A. Olah and S.J. Kuhn, *ibid.*, **84,** 3684 (1962).
c) G.A. Olah, S.J. Kuhn, S.H. Flood, and J.C. Evans, *ibid.*, **84,** 3687 (1962).
3) a) G.A. Olah and H.C. Lin, *Synthesis,* 489 (1973).
b) G.A. Olah and H.C. Lin, *J. Am. Chem. Soc.*, **96,** 2892 (1974).
4) a) G.A. Olah and S.C. Narang, *Synthesis,* 690 (1978).
b) G.A. Olah, R. Malhotra, and S.C. Narang, *J. Org. Chem.*, **43,** 4628 (1978).
c) S.C. Narang and M.J. Thompson, *Aust. J. Chem.*, **31,** 1839 (1978).
5) G.A. Olah and H.C. Lin, *Synthesis,* 444 (1974).
6) a) G.A. Olah, J.A. Olah, and N.A. Overchuk, *J. Org. Chem.*, **30,** 3373 (1965).
b) C.A. Cupas and R.L. Pearson, *J. Am. Chem. Soc.*, **90,** 4742 (1968).
c) G.A. Olah, S.C. Narang, R.L. Pearson, and C.A. Cupas, *Synthesis,* 452 (1978).
7) G.A. Olah, B.G.B. Gupta, and S.C. Narang, *J. Am. Chem. Soc.*, in press.
8) a) G.A. Olah and M. Nojima, *Synthesis,* 785 (1973).
b) G.A. Olah, M. Nojima, and I. Kerekes, *ibid.*, 779 (1973).
c) *Idem, ibid.*, 780 (1973).
d) G.A. Olah and M. Nojima, *ibid.*, 786 (1973).
e) G.A. Olah and J. Welch, *ibid.*, 652 (1974).

f) *Idem, ibid.,* 653 (1974).
g) *Idem, ibid.,* 654 (1974).
h) *Idem, ibid.,* 896 (1974).
i) G.A. Olah and J. Welch, *J. Am. Chem. Soc.,* **97,** 208 (1975).
j) G.A. Olah, J. Welch, Y.D. Vankar, M. Nojima, I. Kerekes, and J. A. Olah, *J. Org. Chem.,* in press.
9) G.A. Olah, M.R. Bruce, and J. Welch, *Inorg. Chem.,* **16,** 2637 (1977).
10) G.A. Olah, M. Nojima, and I. Kerekes, *J. Am. Chem. Soc.,* **96,** 925 (1974).
11) G.A. Olah, M. Nojima, and I. Kerekes, *Synthesis,* 487 (1973).
12) a) G.A. Olah, J. Welch, and T.L. Ho, *J. Am. Chem. Soc.,* **98,** 6717 (1976).
b) G.A. Olah and J. Welch, *ibid.,* **100,** 5396 (1978).
13) a) B.L. Van Duisen, A. Sivak, B.M. Goldschmidt, C. Katz, and S. Melchionne, *J. Nat. Cancer Inst.,* **43,** 481 (1969).
b) R.T. Drew, V. Cappiello, S. Larkin, and M. Kuschner, 1970 Conference of the American Industrial Hygiene Association, Abstract 164.
14) G.A. Olah, P. Schilling, R. Renner, and I. Kerekes, *J. Org. Chem.,* **39,** 3472 (1974).
15) a) G.A. Olah, D.A. Beal, S.H. Yu, and J.A. Olah, *Synthesis,* 560 (1974).
b) G.A. Olah, D.A. Beal, and J.A. Olah, *J. Org. Chem.,* **41,** 1627 (1976).
16) G.A. Olah, "Friedel-Crafts Chemistry," Wiley-Interscience Publishers, New York, N.Y., 1973.
17) G.A. Olah, G. Messina, J. Bukala, J.A. Olah, and G.D. Mateescu, Abstracts, 1st North American Chemical Conference, Mexico City, Mexico, Dec. 1975, Paper PHSC153.
18) G.A. Olah and J. Kaspi, *J. Org. Chem.,* **42,** 3046 (1977).
19) a) J. Kaspi, D.D. Montgomery, and G.A. Olah, *ibid.,* **43,** 3147 (1978).
b) G.A. Olah and D. Meidar, *Nouveau J. Chim.,* 3, 269 (1979).
c) J. Kaspi and G.A. Olah, *J. Org. Chem.,* **43,** 3142 (1978).
d) G.A. Olah, R. Malhotra, D. Meidar, J.A. Olah, and S.C. Narang, *J. Catalysis,* in press.
20) a) G.A. Olah and J. Kaspi, *Nouveau J. Chim.,* **2,** 581 (1978).
b) *Idem, ibid.,* **2,** 585 (1978).
21) a) G.A. Olah, T. Keumi, and D. Meidar, *Synthesis,* 929 (1978).
b) G.A. Olah, G.F. Salem, S.C. Narang, and D. Meidar, *ibid.,* in press.
c) G.A. Olah, D. Meidar, and A.P. Fung, *ibid.,* 270 (1979).
d) G.A. Olah and D. Meidar, *ibid.,* 358 (1978).
e) *Idem, ibid.,* 671 (1978).
22) a) H. Meerwein, *Org. Syn.,* **46,** 120 (1966).
b) H. Meerwein, E. Battenberg, H. Gold, E. Pfeil, and G. Willfang, *J. Prakt. Chem.* [2], **154,** 83 (1940).
23) a) G.A. Olah and J.J. Svoboda, *Synthesis,* 52 (1973).
b) G.A. Olah, J.A. Olah, and J.J. Svoboda, *ibid.,* 490 (1973).
24) a) G.A. Olah and J.J. Svoboda, *ibid.,* 203 (1973).
b) G.A. Olah and Y.K. Mo, *J. Am. Chem. Soc.,* **96,** 3560 (1974).
c) G.A. Olah, "Halonium Ions," Wiley-Interscience, New York, N.Y., 1975, and references cited therein.
25) G.A. Olah, G.K.S. Prakash, and M.R. Bruce, *J. Am. Chem. Soc.,* in press.
26) a) G.A. Olah, *Angew. Chem.,* **85,** 183 (1973).
b) G.A. Olah, *Aldrichimica Acta,* **6,** 7 (1973).
27) G.A. Olah, J.J. Svoboda, and A.T. Ku, *Synthesis,* 492 (1973).
28) G.A. Olah, B.G.B. Gupta, and S.C. Narang, *ibid.,* 274 (1979).
29) G.A. Olah, R. Malhotra, S.C. Narang, and J.A. Olah, *ibid.,* 672 (1978).
30) a) G.A. Olah and H.C. Lin, *ibid.,* 342 (1974).
b) G.A. Olah, H.C. Lin, and A. Germain, *ibid.,* 895 (1974).
31) a) See reference 16.
b) G.A. Olah and S.J. Kuhn, *J. Am. Chem. Soc.,* **82,** 2380 (1960).
32) G.A. Olah, Y.D. Vankar, M. Arvanaghi, and J. Sommer, *Angew. Chem.,* in press.
33) a) G.A. Olah and J. Welch, *Synthesis,* 809 (1976).
b) G.A. Olah, J. Welch, G.K.S. Prakash, and T.L. Ho, *ibid.,* 808 (1976).
c) G.A. Olah and J. Welch, *ibid.,* 419 (1971).
d) G.A. Olah, J. Welch, and M. Henninger, *ibid.,* 308 (1977).
34) G.A. Olah and J. Welch, *J. Org. Chem.,* **43,** 2830 (1978).
35) a) G.A. Olah, N. Yoneda, and D.G. Parker, *J. Am. Chem. Soc.,* **99,** 483 (1977).
b) G.A. Olah and N. Yoneda, *ibid.,* **99,** 3113 (1977).
c) G.A. Olah and R. Ohnishi, *J. Org. Chem.,* **43,** 865 (1978).
d) G.A. Olah, D.G. Parker, and N. Yoneda, *Angew. Chem., Int. Ed. Engl.,* **17,** 909 (1978).
e) G.A. Olah, T. Keumi, and A.P. Fung, *Synthesis,* in press.
36) a) G.A. Olah, N. Yoneda, and D.G. Parker, *J. Am. Chem. Soc.,* **98,** 2251 (1976).
b) *Idem, ibid.,* **98,** 5261 (1976).
c) G.A. Olah, N. Yoneda, and R. Ohnishi, *ibid.,* **98,** 7341 (1976).
37) a) G.A. Olah and T.L. Ho, *Synthesis,* 609 (1976).
b) *Idem, ibid.,* 610 (1976).
c) G.A. Olah and T.L. Ho, *J. Org. Chem.,* **42,** 3097 (1977).
d) T.L. Ho and G.A. Olah, *Synthesis,* 418 (1977).
e) G.A. Olah, S.C. Narang, G.F. Salem, and B.G.B. Gupta, *ibid.,* 273 (1979).
38) a) T.L. Ho and G.A. Olah, *Angew. Chem., Int. Ed. Engl.,* **15,** 774 (1976).
b) G.A. Olah and T.L. Ho, *Synthesis,* 417 (1977).
c) G.A. Olah and T.L. Ho, *Proc. Nat. Acad. Sci. U.S.A.,* **75,** 4 (1978).
d) G.A. Olah, B.G.B. Gupta, and S.C. Narang, *Synthesis,* 583 (1977).
e) G.A. Olah, S.C. Narang, B.G.B. Gupta, and R. Malhotra, *ibid.,* 61 (1979).
f) G.A. Olah, S.C. Narang, B.G.B. Gupta, and R. Malhotra, *J. Org. Chem.,* **44,** 1247 (1978).
g) *Idem, ibid.,* in press.
h) G.A. Olah, S.C. Narang, B.G.B. Gupta, and R. Malhotra, *Angew. Chem.,* in press.
39) a) M.E. Jung, W.A. Andrus, and P.L. Ornstein, *Tetrahedron Lett.,* 4175 (1977) and references cited therein.
b) M.E. Jung, M.A. Muzarek, and R.M. Lim, *Synthesis,* 588 (1978).
40) a) G.A. Olah and Y.D. Vankar, *ibid.,* 702 (1978).
b) G.A. Olah, Y.D. Vankar, and B.G.B. Gupta, *ibid.,* 36 (1979).
c) G.A. Olah, Y.D. Vankar, and A.P. Fung, *ibid.,* 59 (1979).

About the Author

George Olah is Professor of Chemistry at the University of Southern California, Los Angeles, and Co-director of the Hydrocarbon Research Institute. His work was honored by such previous recognitions as the American Chemical Society Award in Petroleum Chemistry, the Leo Hendrick Baekeland Award and the Morley Medal. He belongs to a number of scientific societies and is a member of the National Academy of Sciences.

Professor Olah's research interests range from basic studies in hydrocarbon and petroleum chemistry to the study of new synthetic methods and reactions including investigation of reaction mechanisms and intermediates, most notably carbocations. He pioneered, *inter alia*, the field of superacid chemistry, *i.e.*, acid systems millions of times stronger than sulfuric acid, allowing observation and even isolation of many previously considered unstable species such as carbocations, halonium ions, and various other onium and carboxonium ions. A new field of chemistry is rapidly evolving using both liquid and solid superacidic catalysts developed in his studies.

Lab Notes, *cont'd*

The agitating motion imparted to the paddle greatly increases its mixing efficiency and virtually eliminates the vortex encountered with rotary stirring which often results in the thermometer being left "high and dry" in the center of the reaction flask. If a hollow rod is used on the paddle stirrer the reaction solution can be sparged with gas, at the same time the reaction is being agitated, by simply connecting the hollow shaft of the stirring motor to a gas supply.

Dr. David E. Remy
Research Chemist, CEMEL
Naradcom, Natick, MA 01760

The *Aldrich Catalog-Handbook* and *Aldrich Libraries of Nmr and Ir Spectra* are central to an interactive computer simulation of qualitative organic analysis which we have written. Students are assigned an unknown and use the computer program to obtain information about it, *e.g.*, physical properties, results of characterization tests, melting points of derivatives, and spectral data (ir and nmr), using the logic that they would use to identify an unknown in the laboratory. For example, the student might request solubility data and receive from the program the information that the unknown is insoluble in water and sodium bicarbonate, but soluble in sodium hydroxide. This information suggests certain characterization tests which might be appropriate. The process of requesting information goes on until the compound can be identified. Unknowns were chosen which had spectra in the *Aldrich Libraries of Nmr and Ir Spectra*, use of which then becomes part of the identification process. To check for correct identification, the student enters the *Aldrich Catalog-Handbook* number of the compound, which is compared by the program with the correct answer.

A listing of QUALO, the main program, and LABTEC, a utility program for creating and editing files, plus documentation which describes how to create files for unknown compounds can be obtained by writing T.A. Evans. The programs are written in BASIC PLUS and run in 8K of memory on a PDP 11/45. A magnetic tape (9-track, 800bpi, 600ft) containing QUALO, LABTEC, and information for 50 unknown compounds can be obtained by sending a prepaid order ($35) to: Ms. Ann Dawson, Software Distribution Librarian, Denison Computer Center, Denison University, Granville, Ohio 43023.

Oi Ling Chang
James B. Summers
Thomas A. Evans
Department of Chemistry
Ebaugh Laboratories
Denison University
Granville, Ohio 43023

Any interesting shortcut or laboratory hint you'd like to share with Acta readers? Send it to Aldrich (attn:Lab Notes) and if we publish it, you will receive a handsome red-and-white ceramic Aldrich coffee mug as well as a copy of **Selections from the Bader Collection** *(see "About Our Cover"). We reserve the right to retain all entries for consideration for future publication.*

Choosing and Using Noble Metal Hydrogenation Catalysts

Paul N. Rylander
Engelhard Minerals and Chemicals Corporation
Engelhard Industries Division
Newark, NJ 07105

Catalytic hydrogenation at its best cannot be topped as a means of achieving controlled transformations of organic compounds. Yields are often very high and the products are obtained free of reagents by simply filtering off the catalyst. Appropriate conditions and catalysts usually can be chosen quickly, and satisfactory results obtained with very little experimentation.

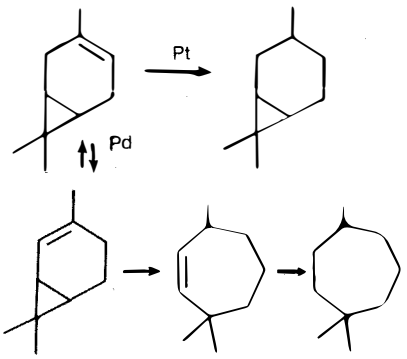
It is the aim of this paper to explore some of the factors that enter into the choice of catalysts and conditions and to set down general guidelines to facilitate suitable choices. Emphasis will be placed on noble-metal catalysts. These catalysts can be exceedingly active and can reduce most functions even at ambient conditions.

Choosing a Catalyst

The main catalytic properties of a catalyst are determined by the major metal present. In choosing a metal it is convenient to treat the metal as if it were a reagent with characteristic properties toward each type of function. This is done with the realization that these characteristic properties are modified by the reaction environment and by the overall electronic and steric structure of the molecule. All organic chemists are familiar with this type of thinking. Most noble metals will reduce most functions, but the activities vary tremendously. Metals can be chosen most easily by recourse to one of several books that list metals effective for hydrogenation of various functions.[1-4] A first-choice guide is appended herewith.

Suitable metals are chosen from these lists on two counts: they should be good for what one wants to do, and poor for what one does not want to do. For instance, palladium is excellent for the hydrogenation of aromatic nitro compounds and is widely used for this purpose, but it would not be the preferred catalyst for the hydrogenation of halonitroaromatics to chloroanilines, as palladium is also an excellent catalyst for dehydrohalogenation. Platinum is much better for halonitroaromatics, having excellent activity for nitro-group reduction, but relatively poor activity for dehydrohalogenation. This reduction can also be done quantitatively by use of a sulfided platinum-on-carbon catalyst; the sulfur present completely prevents dehalogenation.

Sometimes a combination of properties renders a metal unsuitable. The point is illustrated by hydrogenation of car-3-ene. This compound is reduced over platinum to *cis*-carane in very high yield, but over palladium the major product is trimethylcycloheptane. The latter compound results from three properties of palladium: it is excellent for double-bond migration, for hydrogenolysis of conjugated cyclopropyl systems, and for olefin saturation. Platinum, on the other hand, is relatively active only for olefin saturation, hence the excellent yield of carane.[5]



Choosing a Support

More effective use of a metal is made if it is supported. Hundreds of supports have been used, but for most purposes a good carbon or alumina support will be adequate for the majority of reactions. Indeed these supports account for most catalyst usage. Sometimes in reactions of the type A → B → C, a support such as calcium carbonate or barium sulfate may give slightly better yields of B, presumably because B is less strongly adsorbed. Hydrogenation of acetylenes to *cis*-olefins is an example.

Carbon seems more effective than alumina in promoting intermolecular reductions such as reductive alkylations and the formation of dicyclohexylamines in the reduction of anilines.[6] Alumina is a better support than carbon for the rhodium-catalyzed hydrogenation of acetophenone to cyclohexylethanol; in various solvents the yields with alumina are 15-25% higher than with carbon.[7]

Concentration of Metal on a Support

Metal concentration on commercial hydrogenation catalysts varies from a fraction of a percent to 30% or more. High

metal concentrations decrease the volume of catalyst to be handled, low metal concentrations increase the activity on a *weight of metal* basis. Some change in selectivity may also occur as concentration changes, as will be discussed later. In general, unless there are special demands, 5% metal-on-support is a convenient catalyst for most applications.

Concentration of Catalyst in the System

Commercial hydrogenations have been run with catalyst concentrations from a fraction of a percent of catalyst to equal weights of substrate and catalyst. In general, for easily hydrogenated functions a 0.5 to 2% catalyst on support loading is probably more than enough; more resistant functions and sterically impeded functions may require higher loadings for convenient rates. It is much less frustrating to use an unnecessarily large amount initially, than too little. The amount of catalyst can always be cut down once the reaction has been shown to go. Easily hydrogenated functions may produce marked exotherms and due allowance should be made for this.

Temperature and Pressure

Temperature and pressure ranges over which successful hydrogenations can be carried out are often very large, fortunately. In general, activity increases with increasing temperature and pressure, but obvious and not-so-obvious exceptions exist. In practice the conditions are often set by the equipment available, and lack of activity is compensated for by use of more catalyst and by patience.

Agitation

Heterogeneous liquid-phase hydrogenations are three-phase systems. For a reaction to proceed, hydrogen must leave the gas phase, cross a gas-liquid interface, cross a liquid-solid interface, and be adsorbed on the catalyst surface. There are surprisingly high resistances to these processes and the rates of many hydrogenations, especially over the very active noble metal catalysts, are controlled largely by these and other diffusional resistances. Vigorous agitation is important to achieve maximal activity of the catalyst.

Hydrogen Availability

When the rate is limited in large part by the rate of hydrogen transport to the catalyst surface, as it often is, the catalyst can be said to be operating in a "hydrogen-poor" condition. That is, the reduction would go faster if more hydrogen were available at the catalyst sites. On the other hand, when the rate is controlled largely by the intrinsic rate of the chemical reaction, the catalyst can be said to be operating in a "hydrogen-rich" mode. That is, the rate would not increase substantially if more hydrogen were available at the catalyst. It is easy to determine experimentally these different modes of operation.

Reactions operating in a "hydrogen-poor" mode increase in rate when the agitation is increased. Also, in reactions rate-limited by gas-liquid hydrogen transport, the rate will not increase linearly with an increase in the amount of catalyst. Reactions operating in a "hydrogen-poor" mode clearly are not using the catalyst efficiently, a consequence of some importance in industrial operations.

Effect of Hydrogen Availability on Selectivity

The concept of "hydrogen-poor" and "hydrogen-rich" catalysts can be used to predict the direction of change that changing pressure, temperature, metal concentration, catalyst loading and agitation will have on the selectivity of a reaction. Consider that hydrogenation of a substrate A can afford products B and C either by the parallel reactions A → B and C or the series reaction A → B → C. If the rate equations leading to B and to C contain hydrogen terms raised to different powers then the two reactions will be affected differently by changes in hydrogen availability at the catalyst surface.

Whether this condition exists can be easily determined experimentally. For instance, in going from a reaction with poor agitation to one with good agitation the ratio of B to C increases, then the assumption can be made that B is favored by a "hydrogen-rich" catalyst. Under this circumstance the product B is favored by a higher hydrogen pressure, a lower operating temperature (in that it decreases the rate of reaction relative to the rate of mass transport), a lower concentration of metal on the support, and less catalyst in the system. Deliberate deactivation of the catalyst may be in order. Solvents tend to increase hydrogen availability by lowering the surface tension and viscosity of the system. However, solvents have more complex effects as well, as will be discussed. On the other hand, if B is favored by a condition of low hydrogen availability, the reverse actions are taken.

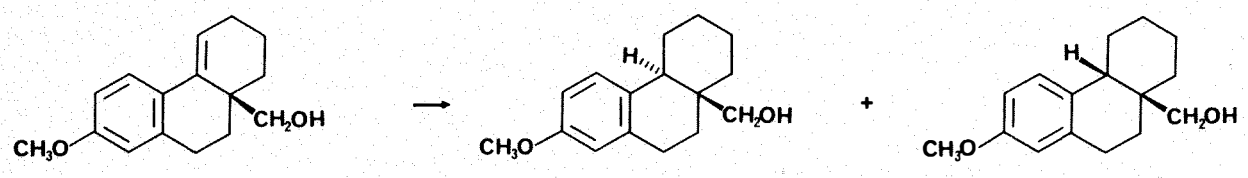
Two types of reactions that are favored by "hydrogen-poor" catalysts are the isomerization of a double bond relative to its hydrogenation and, in general, hydrogenolysis relative to hydrogenation.

Solvents

Solvents can have profound effects on both rate and selectivity of hydrogenation.[8] Rates can be influenced markedly both by an intrinsic property of the solvent and by its contained impurities. The number of active sites in a catalyst is usually only a small fraction of the catalyst present, and the amount of total catalyst used, a small fraction of the amount of solvent. Very small percentages of certain impurities can thus exert large influences on the rate. On the other hand, gross amounts of impurities can easily be tolerated if they happen not to affect the catalyst adversely. The best method for ascertaining suitability of a particular batch of solvent is by actual test. In general, impurities apart, more polar solvents tend to give faster rates than less polar ones.

Selectivity of hydrogenation sometimes can be drastically altered by the solvent and, fortunately, in ways that are largely predictable. Solvent is often a most important variable, but it is one whose potential for selectivity control is often overlooked. Some idea of the extent of influence by solvent is illustrated in the following examples concerning stereochemistry. From these data and others not presented here, some working generalities for choice of solvent will be given.

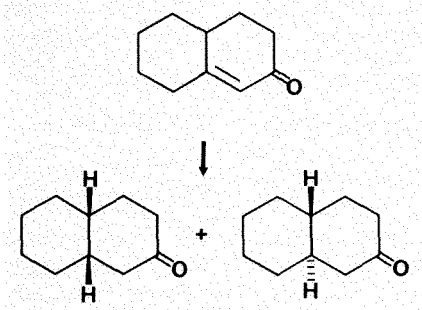
Stereochemistry: Solvents offer an important means of influencing stereochemistry, as illustrated by the following abstracted data:[9]



Solvent	Dielectric Constant	Relative Amounts in Product	
Hexane	1.9	39	61
DMF	36.7	94	6

In this case the influence of solvent was thought to arise from competition for catalyst sites by solvent and the hydroxymethyl function, which anchors the olefin in an orientation such that hydrogen adds from the same side of the molecule. Only extremes are shown here and the correlation between dielectric constant of the solvent and stereochemistry holds for a variety of solvents. From these data the generality was derived that to the extent this type of anchoring (haptophilic effect) is operative, the extremes of stereospecificity are likely to be found at the extremes of the dielectric constant of the solvent.

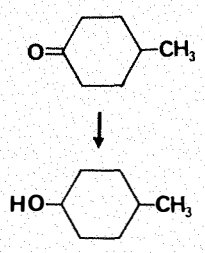
Augustine[10] found it necessary, in making a correlation between dielectric constant and stereospecificity, to group solvents as protic and aprotic. When this is done the extremes of stereospecificity are again found at the extremes of dielectric constant, but the direction of change is opposite in the two groups. The extremes of the two series are shown in the data below.



Solvent	Dielectric Constant	Percent *cis*-β-Decalone
MeOH	33.6	41
t-BuOH	10.9	91
DMF	38.0	79
n-Hexane	1.9	48

The data illustrate also how easily one can be misled in deriving generalities about solvents from limited experiments. If, for instance, only methanol and hexane had been compared, the conclusion would have been reached that large differences in dielectric constant cause only small changes in stereospecificity, whereas a comparison of methanol and dimethylformamide would suggest that relatively small differences in dielectric constant cause large differences in stereoselectivity. Perhaps the safest way of ascertaining whether a stereochemical (or other) sensitivity to dielectric constant exists, without extensive testing, is to compare two solvents of widely differing dielectric constant with both solvents being either protic or aprotic. Presumably the protic solvents should require separate treatment only with those substrates that would readily hydrogen-bond.

Stereochemistry of ketone hydrogenation also can be profoundly altered by solvent and catalyst. For example, hydrogenation of 5α-cholestan-3-one over platinum in *t*-butyl alcohol gives mainly the equatorial alcohol 5α-cholestan-3β-ol, whereas the axial alcohol 5α-cholestan-3α-ol is obtained in high yield over rhodium in isopropyl alcohol-hydrogen chloride.[11] The latter system, rhodium in isopropyl alcohol-hydrogen chloride or in tetrahydrofuran-hydrogen chloride, has been claimed to be one of the best means of producing axial alcohols from unhindered ketones by hydrogenation.[12]



Catalyst	Solvent	*cis*/*trans*
Platinum black	*t*-BuOH	3.5
Rhodium black	*i*-PrOH-HCl	11

Useful Working Generalities Regarding Solvents

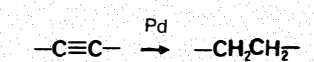
1) The extremes of selectivity of any kind will be found at the extremes of the dielectric constants of the solvents used, with the following provisos:
   a) protic and aprotic solvents may have to be considered separately as noted above
   b) the species actually undergoing hydrogenation must not change, as for example, a neutral species being changed by solvent into either an anionic or cationic one.
2) Hydrogenolysis relative to hydrogenation is favored by solvents of higher dielectric constant. The generality is applicable to a variety of competitive situations, and presumably holds because the transition state in the hydrogenolysis reaction always has the greatest charge separation.

GUIDE TO CATALYST SELECTION

Acetylenes → *cis*-Olefins

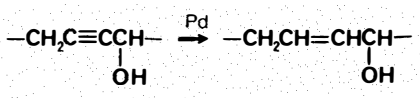
Palladium usually gives excellent results if the reduction is arrested at one mole of hydrogen absorption. Some *trans* olefin may form even in the earliest stages of reduction, but the amount increases rapidly as absorption of one mole of hydrogen is approached and exceeded. Subambient temperatures (-20° C) and/or inhibitors such as Pb or Cd may be used, if needed, to maximize the yield.

Acetylene → Paraffin



Palladium gives excellent results. Platinum is better, if isomerization of the intermediate olefin prior to its saturation is likely to affect selectivity.

Propargyl Alcohols → Allylic Alcohols

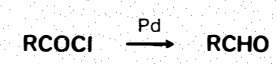


Hydrogenolysis of the allylic function is usually not a troublesome side reaction and palladium gives excellent results. Acetylenic glycols are more difficult. Rhodium, especially in the presence of alkali, may be suitable if palladium fails.

Acids → Alcohols

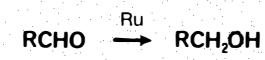
The reduction is difficult and requires high pressures. Ruthenium has been used at pressures of 15,000 psig. Rhenium heptoxide has given good results at 4,000 psig.

Acid Chlorides → Aldehydes



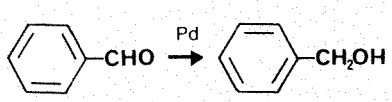
Palladium is the preferred catalyst. Reduction goes easily but the problem is to prevent reduction to the alcohol. Inhibitors are often used. Excellent yields have been obtained with one mole of added base or reduction at reduced pressures.

Aliphatic Aldehydes → Alcohols



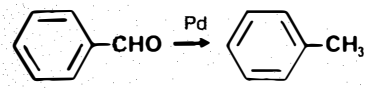
Ruthenium is excellent. Water acts as cocatalyst. Maximal yields are obtained at high pressures and low temperatures (which minimize noncatalytic condensations).

Aromatic Aldehydes → Alcohols



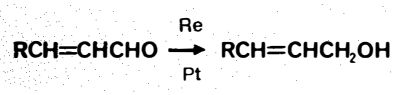
Palladium is excellent. If the yield of alcohol is less than quantitative, the problem can be corrected usually by the use of nonpolar, nonacidic solvents with perhaps a trace of base. Hydrogen absorption should be limited to one mole.

Aromatic Aldehydes → Hydrocarbons



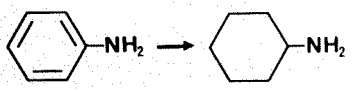
Palladium is excellent. Hydrogenolysis is promoted by traces of acids and by polar solvents. The reduction proceeds largely in a stepwise fashion through the benzyl alcohol.

Unsaturated Aldehydes → Unsaturated Alcohols



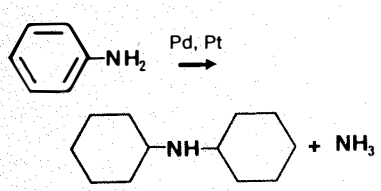
The reduction is difficult. Rhenium (modified), ruthenium (modified), and platinum (modified) have all been used successfully. The reaction depends critically on the metal, catalyst preparation and the presence of various modifiers. Most catalysts exhibit the reverse selectivity.

Anilines → Cyclohexylamines



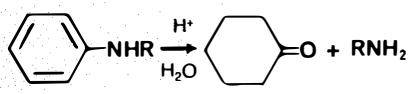
Rhodium and ruthenium are excellent. They are active and give little dicyclohexylamine. Slightly more coupling is obtained over carbon support than over alumina. Coupling may be decreased by the presence of ammonia, increased pressure, and decreased temperature.

Anilines → Dicyclohexylamines



Palladium and platinum give moderate yields which increase with increasing temperature. Coupling is decreased by increasing pressure.

Anilines → Cyclohexanones

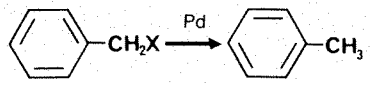


Palladium is quite effective, probably due to its excellence for double-bond migration in partially hydrogenated rings and relative ineffectiveness for imine saturation. Yields increase with increasing substitution on the nitrogen atom.

Aromatic (carbocyclic)→ Cycloparaffin

Rhodium, platinum, ruthenium and palladium are all used industrially. Choice depends on other functions present and on the operating conditions available. Palladium and ruthenium require more vigorous operating conditions than rhodium or platinum.

Benzyl Compounds → Aromatic Hydrocarbons

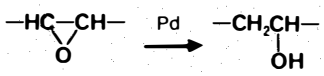


Palladium is excellent for hydrogenolysis of benzyl functions. The reaction is accelerated by polar solvents and by acids. Ring saturation is nil.

Dehydrohalogenation

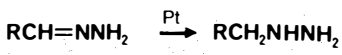
Palladium is excellent and is widely used. The reaction is frequently carried out in the presence of a mole of base. In complex molecules the base chosen may make a difference in yields. Polyhalo compounds can usually be dehalogenated in a stepwise manner.

Epoxides → Alcohols



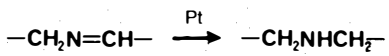
Palladium is usually used. It mainly opens the ring with inversion. Direction of the ring opening depends on the substrate and often on the pH. Deoxygenation is rarely a problem.

Hydrazones → Hydrazines



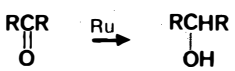
Platinum is usually used in this reduction. Hydrogenolysis of the nitrogen-nitrogen bond is rarely a problem.

Imines → Amines



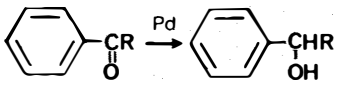
Platinum is widely used for this reaction and for reductive alkylation, which gives an imine intermediate. Palladium can be effectively used when there is little steric hindrance around the bond.

Ketones (aliphatic) → Alcohols



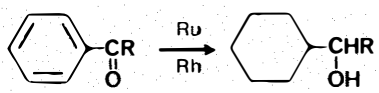
Ruthenium is excellent. Water functions as cocatalyst. Hydrogenolysis is nil, as is ketal formation in lower alcohols.

Aromatic Ketones → Aromatic Alcohols



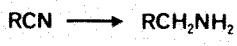
Palladium is excellent and yields approach 100%. Hydrogenolysis can be prevented by use of nonacidic, nonpolar solvents with traces of base if necessary.

Aromatic Ketones → Saturated Carbinols



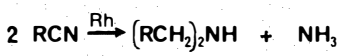
Rhodium and ruthenium have given excellent yields. Hydrogenolysis decreases as pressure is increased. Acidic solvents should be avoided although traces of acid have proved beneficial.

Aliphatic Nitriles → Primary Amines



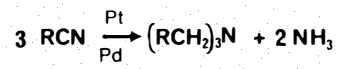
Palladium, platinum and rhodium have been used in this reduction, but little primary amine will result unless the nitrile is hindered or the reaction is carried out in a reactive solvent, such as ammonia, acid, or acetic anhydride.

Aliphatic Nitriles → Secondary Amines



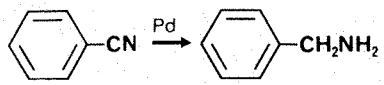
Rhodium is uniquely effective in this reduction and gives high yields of secondary amines. It is also useful in making unsymmetrical secondary amines by nitrile reduction in the presence of an amine.

Aliphatic Nitriles → Tertiary Amines



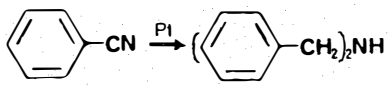
High yields of tertiary amines are obtained from low-molecular-weight nitriles in nonreactive solvents over either palladium or platinum.

Aromatic Nitriles → Benzylamines



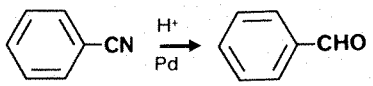
Using palladium, yields approach theoretical if small amounts of an aliphatic secondary amine are present. Otherwise a mixture of benzyl and dibenzylamine results. The yield is also solvent dependent.

Aromatic Nitriles → Dibenzylamines



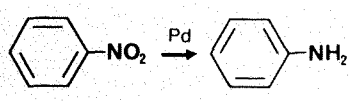
Nearly quantitative yields of dibenzylamines are obtained over platinum, preferably with one-half mole of water present to minimize catalyst inhibition.

Aromatic Nitriles → Aldehydes



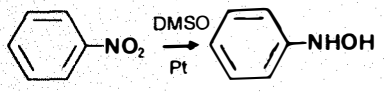
Good yields of aldehydes can be obtained over palladium in acidic media. Conditions should be arranged so that hydrolysis of the intermediate imine is faster than its hydrogenation. Hydrogen absorption should be limited.

Nitroaromatic Compounds → Anilines



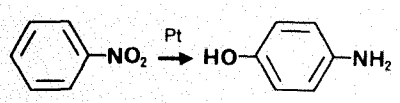
The reduction goes very easily over a number of catalysts. Palladium is usually preferred for economic reasons and for minimal ring reduction.

Nitroaromatic Compounds → Aromatic Hydroxylamines



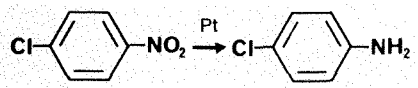
High yields of aromatic hydroxylamines can be obtained by hydrogenation over platinum in lower alcohols containing 1-2% of dimethyl sulfoxide.

Nitroaromatic Compounds → Aminophenols



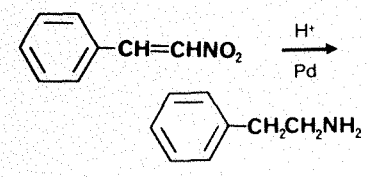
Production of aminophenol depends on successful competition between hydrogenation of the intermediate hydroxylamine and its acid-catalyzed rearrangement. Platinum is the preferred metal. The yield is sensitive to reaction variables.

Halonitroaromatics → Haloanilines



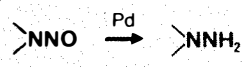
The product can be obtained in excellent yield over inhibited palladium or platinum, or over platinum or rhodium (sulfided).

Nitroolefins → Saturated Amines



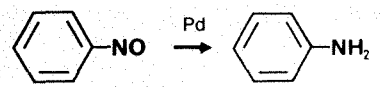
Good yields of saturated amine can be obtained over palladium in acidic media. In neutral media dimeric butane derivatives result.

***N*-Nitrosoamines → Hydrazines**



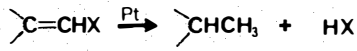
Over palladium, hydrogenolysis of the nitrogen-nitrogen bond can be kept to low levels. Excellent yields can be expected.

Nitrosoaromatic Compounds → Anilines



The reaction proceeds easily and in excellent yield over palladium.

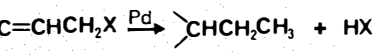
Hydrogenolysis of Vinyl Compounds



X = Cl, Br, OR, OCOR, etc.

The result is sensitive to structure. Hydrogenolysis should precede hydrogenation. Platinum seems generally preferred over palladium.

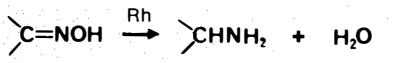
Hydrogenolysis of Allylic Compounds



X = Cl, Br, OR, OCOR, etc.

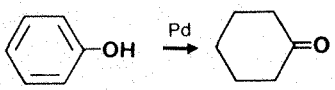
The result is sensitive to the steric requirements of the molecule. Palladium seems generally more effective than platinum. Hydrogenolysis should precede saturation.

Oximes → Primary Amines



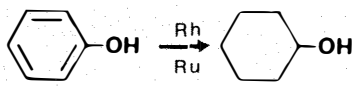
Excellent yields have been obtained by reduction over rhodium in alcoholic ammonia. Yields may be sensitive to substrate concentration due to hydrolysis of oxime by water formed in the reduction.

Phenols → Cyclohexanones



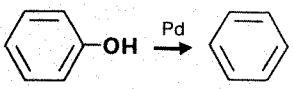
Palladium is excellent due to low activity for ketone reduction and high double-bond isomerization. Rhodium is perhaps better with polyhydric compounds. High yields can be expected.

Phenols → Cyclohexanols



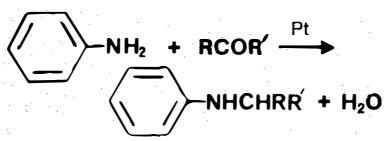
High yields are expected over rhodium or ruthenium. Hydrogenolysis is minimized by neutral, nonpolar solvents, low temperature, and high pressure.

Phenols → Benzenes



This reduction is easily achieved if the phenol is first converted to a suitable ether derivative as by reaction with 2-chlorobenzoxazole or 5-chloro-1-phenyltetrazole.

Reductive Alkylation



Platinum is used usually, affording high yields of alkylated product. Palladium is effective with aldehydes or low-molecular-weight ketones. Precursors of anilines such as nitrobenzenes or nitrosobenzenes may be used directly in the reductive alkylation without prior conversion to anilines.

References:

1) P.N. Rylander, "Catalytic Hydrogenation over Platinum Metals," Academic Press, New York, N.Y., 1967.
2) P.N. Rylander, "Catalytic Hydrogenation in Organic Syntheses," Academic Press, New York, N.Y., 1979.
3) M. Freifelder, "Practical Catalytic Hydrogenation," Wiley Interscience, New York, N.Y., 1971.
4) M. Freifelder, "Catalytic Hydrogenation in Organic Synthesis, Procedures and Commentary," Wiley Interscience, New York, N.Y., 1978.
5) W. Cocker, P.V.R. Shannon, and P.A. Staniland, *J. Chem. Soc.* (*C*), 41 (1966).
6) P.N. Rylander, L. Hasbrouck, and I. Karpenko, *Ann. N.Y. Acad. Sci.*, **214**, 100 (1973).
7) P.N. Rylander and L. Hasbrouck, *Engelhard Ind. Tech. Bull.*, **8**, 148 (1968).
8) P.N. Rylander in "Catalysis in Organic Syntheses, 1978," W.H. Jones, Ed., Academic Press, New York, N.Y., 1978.
9) H.W. Thompson, E. McPherson, and B.L. Lences, *J. Org. Chem.*, **41**, 2903 (1976).
10) R.L. Augustine, *Advan. Catalysis*, **25**, 63 (1976).
11) S. Nishimura, M. Katagiri, and Y. Kunikata, *Chem. Lett.*, 1235 (1975).
12) S. Nishimura, M. Ishige, and M. Shiota, *ibid.*, 963 (1977).

About the Author

Dr. Rylander received the B.Ch.E. degree from Johns Hopkins University in 1942 and his Ph.D. from Indiana University in 1948. After postdoctoral studies at the University of Rochester and at Harvard, he joined Standard Oil Co. of Indiana in 1951. For the past 23 years, Dr. Rylander has been associated with Engelhard Industries where he has pursued research in the field of his main interest: application of catalysis to organic syntheses.

Dr. Rylander is the author of three books and numerous papers on catalysis. He has edited two other books and holds quite a number of patents in the areas of hydrogenation, dehydrogenation, dehydration, oxidation, alkylation and polymerization.

Page intentially blank

Aldrichimica Acta

Volume 12, Number 4, 1979

Selective Oxygenation with *tert*-Butyl Hydroperoxide. **See page 63.**
Tilorone, Its Analogs, and Chemical Immunology. **See page 77.**

chemists helping chemists in research & industry
aldrich chemical co.

Aldrichimica Acta

Volume 12, Number 4, 1979
A publication of ALDRICH CHEMICAL COMPANY, INC.

Main Sales Office:
940 West Saint Paul Ave.
Milwaukee, Wisconsin 53233
Telephone: (414) 273-3850
Order Desk: (800) 558-9160 Toll-free
TWX: (910) 262-3052
Telex: 26 843

East Coast Service and Distribution Center:
159 Forrest Street
Metuchen, New Jersey 08840
Telephone: (201) 549-6300
TWX: (710) 998-0575

In Canada:
Aldrich Chemical Co. (Canada), Ltd.
1500 Stanley Street, Suite 405
Montreal, Quebec H3A 1R3
Telephone: (514) 845-9289
Eastern & Atlantic: (800) 361-6141 Toll-free
TWX: (610) 421-4608

In Great Britain:
Aldrich Chemical Company, Ltd.
The Old Brickyard, New Road
Gillingham, Dorset
SP8 4JL, England
Telephone: 074-76 2211
Telex: (851) 417238

In West Germany/Continental Europe:
EGA-Chemie KG
7924 Steinheim am Albuch
West Germany
Telephone: (07329) 6011
Telex: (841) 714838

In Belgium/Continental Europe:
Aldrich-Europe
B-2340 Beerse
Belgium
Telephone: 014/611431
Telex: (846) 32540

In Japan:
Aldrich Japan
c/o Tokyo Danchi Sohko Kanrito
4-1, 3-chome, Heiwajima, Ohta-ku
Tokyo, Japan
Telephone: 768-0555
TWX: (781) 246-6143

In Israel:
Sigma Israel Chemical Co.
P.O. Box 37673
Tel Aviv, Israel 61360
Telephone: 03-612315
Telex: (922) 35645

About Our Cover:

Our chemist-collector's favorite paintings are works by Rembrandt and his students. Hence we can understand his pleasure at acquiring a portrait of Rembrandt by Rembrandt's first student, Gerard Dou. Rembrandt loved fancy costumes, and here he himself is dressed as an oriental. This work (oil on panel, 16 x $13^1/_4$ inches) is so influenced by one of Rembrandt's famous works, the so-called "Noble Slav" now at the Metropolitan Museum, that we can conjecture the date of Dou's work. It must be close to that of Rembrandt's — 1632, when Rembrandt was 26.

Are you interested in our Acta covers? *Selections from the Bader Collection*, with 30 duotone reproductions, many of previous Acta covers, and an introduction by Professor Wolfgang Stechow is available to all chemist art-lovers.

Also, many paintings reproduced on our Acta covers were shown at the Milwaukee Art Center in an exhibition, "The Bible Through Dutch Eyes," arranged by Dr. Bader in 1976. The fully illustrated catalog with 66 black-and-white and 4 full-color reproductions contains many art historical and Biblical comments.

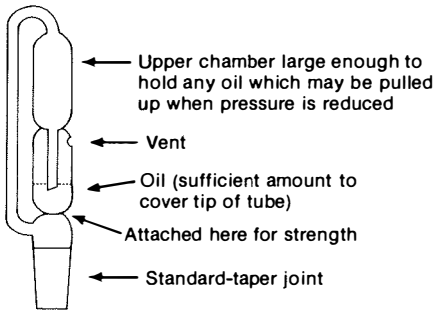
Many of the early issues of the *Aldrichimica Acta* have become very rare. Please do not throw your issues away. In time, we believe that complete sets will become valuable, and — if you do not want to keep them — there probably are chemists near you who would be interested.

Congratulations:

Just as we were about to go to press we received the wonderful news that Professors Herbert C. Brown and George Wittig are sharing this year's Nobel prize in chemistry. We do not believe that there can be many companies in the world that have benefited as much by the inventions of these two great scientists as has Aldrich. We have made many Wittig reagents, and have formed a company, Aldrich-Boranes, to utilize Professor Brown's inventions in the field of hydroboration. Thus, we are delighted to be able to share in their happiness.

Lab Notes

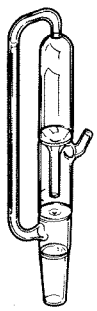
Oil bubblers are frequently used in the chemistry laboratory to monitor the evolution of a gas produced in a reaction, the rate of flow of an inert or reacting gas through a reaction vessel, or simply as a means of closing off a reaction vessel from the atmosphere. Because of problems associated with bubblers made from pipettes and test tubes connected to the reaction vessel with flexible tubing, I asked our glassblower to make a bubbler of the following design which can simply be fitted into the top of a condenser or addition funnel equipped with a standard-taper glass joint. The lower chamber is filled to



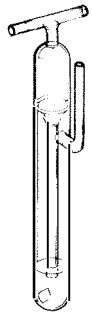
the proper level with an appropriate oil or other liquid through the vent. When not in use the bubbler can be stored by simply hanging it on a convenient hook. If desired, the bubbler could be fitted with a sidearm and stopcock for introduction of a gas.

Robert F. Boswell
Research Chemist
A.H. Robins Company
Research Laboratories
1211 Sherwood Ave.
Richmond, Virginia 23220

Editors note:
For the convenience of our customers, Aldrich offers the bubbler shown below.



Also available from Aldrich is the bubbler shown below whose use has been described in C.F. Lane, *Aldrichimica Acta*, **10**, 11 (1977).

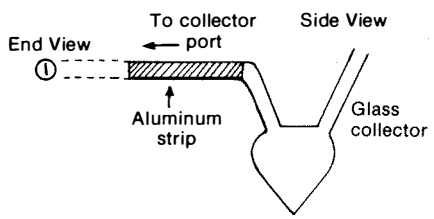


A recent note on the removal of small amounts of water and ethanol from chloroform [*Aldrichimica Acta*, **11**, 42 (1978)] prompts me to report a procedure, which is more rapid and easy.

Water and ethanol present in commercial chloroform or carbon tetrachloride can be eliminated simply by addition of zeolite NaA (pellets) just prior to use. After swirling for some minutes the amounts of water and ethanol are reduced to less than 5 ppm and less than 1 ppm, respectively (as determined by ^{1}H FT-NMR). Generally, 50g zeolite pellets/liter solvent is sufficient for effective elimination of water and ethanol. The zeolite can be recovered *via* filtration or after decantation of the solvent. As known, zeolite can be reused after drying in air at room temperature, at 120° (2 hrs) and at 400° (4 hrs).

J.A. Peters
Laboratory of Organic Chemistry
Delft University of Technology
Julianalaan 136
2628 BL Delft
The Netherlands

During preparative VPC collection, many high-boiling compounds often form troublesome aerosols instead of completely condensing in the collector. Aerosol (smoke) formation can be greatly reduced by decreasing the rate of cooling of the gaseous compound as it leaves the collector port. Accordingly, a thin strip of aluminum approximately 2.5-3cm long is cut with scissors from an aluminum can or the backing of a used, washed TLC plate. The width of the strip should equal the inside diameter of the collector tube. The strip is inserted into the collector as shown. The strip, being heated by the effluent gases at one end, provides a shallower cooling gradient for the compound to be collected.



When used with a cooling bath in the usual manner, collection efficiency of both high- and low-boiling compounds is improved.

K.L. Smouse
Chemistry Department
University of Utah
Salt Lake City, Utah 84112

A.G. Anderson
Central Research & Development Dept.
E.I. du Pont de Nemours & Company
Experimental Station
Wilmington, Delaware 19898

Any interesting shortcut or laboratory hint you'd like to share with Acta readers? Send it to Aldrich (attn: Lab Notes) and if we publish it, you will receive a handsome red-and-white ceramic Aldrich coffee mug as well as a copy of **Selections from the Bader Collection** *(see "About Our Cover"). We reserve the right to retain all entries for consideration for future publication.*

"Please Bother Us."

by Jerry Bader.

Professor Richard Bertrand's letter from the University of Michigan in Dearborn is typical of dozens of letters I have received recently:

"I am not sure how long you have been offering the Fieser Molecular Models for sale through your catalog, but I wish to thank you for doing so. They are about the best models available for classroom use and are a bargain at that.

"There is one other device Prof. Fieser came up with that I cannot find anywhere, and that is the "Fieser Triangle." This is a template which can be used to draw organic chemical structures. The scale of the drawings is just right for manuscript copy and classwork or examination copy. I would like to suggest you consider offering them for sale through your catalog. As with the models, making available the Triangle would be of great service to the chemical community."

We now offer the Fieser Triangle.

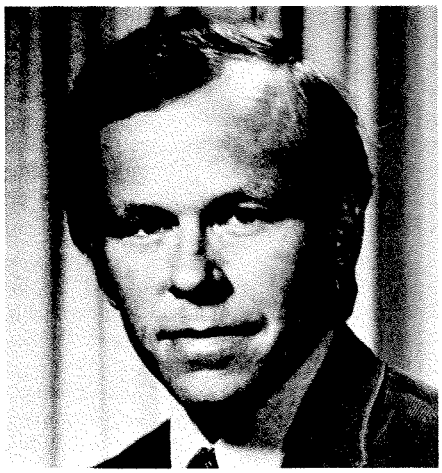
It was no bother at all, just a pleasure to be able to help.

Metal-Catalyzed, Highly Selective Oxygenations of Olefins and Acetylenes with *tert*-Butyl Hydroperoxide. Practical Considerations and Mechanisms.

K. Barry Sharpless
and Thomas R. Verhoeven
Department of Chemistry
Stanford University
Stanford, California 94305

I. Introduction

The purpose of this review is to call attention to recent advances in the use of *tert*-butyl hydroperoxide (TBHP) in organic synthesis. The emphasis here will be on the nonradical, metal-catalyzed oxygenations shown in Scheme I.

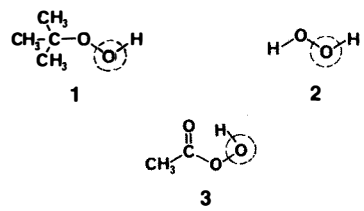


Professor K. Barry Sharpless

Dr. Thomas R. Verhoeven

When one considers the combined features of economics, selectivity, and safety, TBHP emerges as one of the best sources of oxygen atoms for a variety of organic oxygenations. Some of the factors which make TBHP (**1**) superior to better known sources of oxygen atoms such as hydrogen peroxide (**2**) and peracetic acid (**3**) are worth discussing. Perhaps the key advantage of TBHP is its selectivity. In contrast to hydrogen peroxide and peracetic acid, TBHP is unreactive toward most organic compounds in the absence of catalysts. TBHP is less sensitive to contamination by metals than either peracetic acid or H_2O_2, and on this basis is safer to handle. In dilute organic solution TBHP has high thermal stability (its half-life is 36 days at 115°C as a 0.2*M* solution in benzene).[1] Hydrogen peroxide is, in principle, also very stable thermally, but it is more sensitive to decomposition catalyzed by trace metallic impurities than is TBHP.[2]

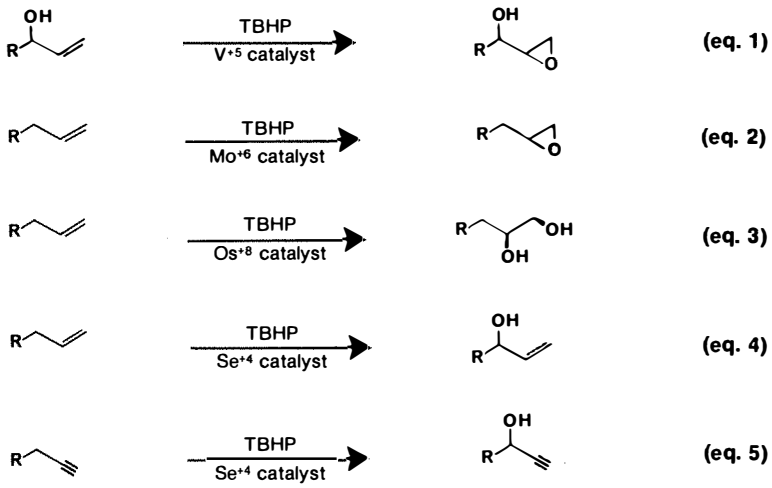
Scheme II. Oxygen Atom Sources



1 **2** **3**

Peracetic acid is on every count less stable than TBHP. The 40% solution of peracetic acid in acetic acid sold by FMC can only be shipped by truck, and even then only in minidrums or smaller containers, whereas solutions which are (by weight) 70% TBHP and 30% H_2O may be shipped in tank car quantities. This does not mean there are no hazards associated with using TBHP (potentially hazardous situations to be avoided in handling TBHP will be discuss-

Scheme I.



ed later). What it does mean is that peracetic acid is more dangerous in almost every situation than is TBHP. High-strength hydrogen peroxide solutions also tend to be less stable than TBHP solutions of comparable peroxide content.

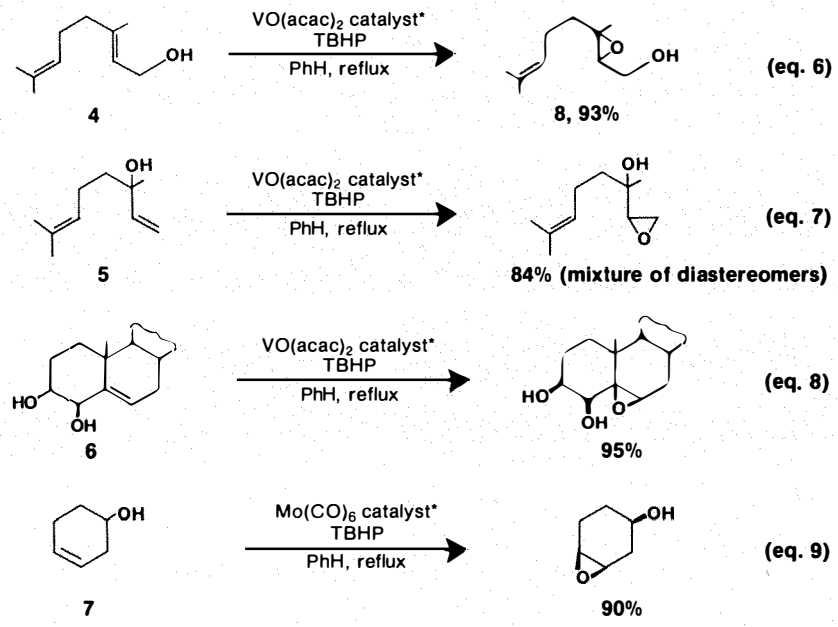
After six years of working on metal-catalyzed reactions of TBHP (somtimes as much as five moles in one reaction) we have not yet had a single explosion. On the other hand, we have had a few small explosions while working with small amounts of hydrogen peroxide and also with peracetic acid. The above mentioned explosions only occurred when some metal-catalyzed process was being attempted. In our opinion, these explosions were due to accelerated decomposition of H_2O_2 or of peracetic acid catalyzed by the metal.

We have made safety comparisons of TBHP with the two most common peroxidic oxidants, H_2O_2 and peracids, because it is our experience that most chemists regard these latter reagents as less dangerous than *tert*-butyl hydroperoxide (TBHP). The origin of this phobia toward organic peroxides (*e.g.*, TBHP) almost certainly is derived from two factors, the more important being that common organic ethers (diethyl ether, tetrahydrofuran and, especially, diisopropyl ether) form dangerously explosive hydroperoxides by autoxidation upon exposure to the atmosphere. Chemists are justifiably afraid of ether hydroperoxides, and tend to associate *tert*-butyl hydroperoxide with this deadly class of compounds. Thus, any substance whose name includes the word peroxide is regarded as very dangerous to work with. Some peroxides are indeed extremely unstable and can only be stored at low temperature; but the range of stability is wide, and TBHP is one of the most stable organic peroxides known.

The other important factor in the TBHP phobia is lack of familiarity. This is largely due to the fact that TBHP is a rather new compound, being first prepared in 1938 by Milas.[3] This has led to the curious situation where chemists, who have long been comfortable with the idea of using peracids[4] (*e.g.*, for epoxidation of olefins), have less respect for the explosive possibilities with peracids than they do with the tamer substance TBHP. All of this has begun to change due to the discovery, almost simultaneously (*ca.* 1965) in several industrial laboratories,[5-7] that propylene could be epoxidized by TBHP in the presence of a molybdenum catalyst. This process (Oxirane Process) is now yielding two billion pounds of propylene oxide each year. Our interest in metal-catalyzed reactions of TBHP began in 1972 and was aroused by the remarkable effectiveness of the industrial epoxidation process.[8]

II. Epoxidation of Olefins

1. Selective Epoxidation of Olefinic Alcohols (Scheme I, eq. 1)



From reports by Sheng and Zajacek[9] and by List and Kuhnen[10] one could see that simple allylic alcohols were especially reactive toward epoxidation by TBHP in the presence of vanadium catalysts. We decided to have a look at more complex allylic alcohols in order to determine the regioselectivity and/or stereoselectivity available with these systems. The results were unexpectedly dramatic in that the selectivities were much greater than those discovered by Henbest[11] for the epoxidation of olefinic alcohols by carboxylic peracids. As shown in equations 6 through 9, geraniol (**4**), linalool (**5**), 4β-hydroxycholesterol (**6**) and 3-cyclohexen-1-ol (**7**) all gave excellent yields of only one of the possible isomeric epoxy alcohols.[12a] Both allylic and homoallylic (*e.g.*, **7**) alcohols showed the effects. In the case of vanadium catalysis even a bishomoallylic alcohol [1-hydroxy-(*E*)-4-nonene] exhibited a substantial (13.4 times) rate acceleration over an analogous olefin [(*E*)-5-decene).[12a]

The different, and often superior, stereoselectivity of these metal-catalyzed epoxidations is also observed with acyclic olefinic alcohols (Table I). The examples in Table I are taken from our recent publication[13] in which we correct the errors in our earlier work[14,15] on this same subject.

The experimental details for these epoxidations are contained in our original publications[12a,14] although two important modifications of those procedures merit discussion: (1) Heating (reflux in benzene) was employed for both the vanadium- and molybdenum-catalyzed epoxidations (eq. 6-9). **Although heating is often necessary to achieve reasonable rates for the molybdenum-catalyzed process, most vanadium-catalyzed epoxidations of olefinic alcohols proceed readily at, or below, room temperature.**[12b] (2) We originally used aqueous bisulfite (HSO_3^-) to reduce excess TBHP. We have found that the use of bisulfite makes it difficult, and often impossible, to distill the products without extensive polymerization occurring. These problems became especially severe when large-scale (>1 mole) distillations were attempted (after bisulfite work-up) with simple epoxides as well as with epoxy alcohols and even allylic alcohol products. **The use of aqueous sulfite (*e.g.*, Na_2SO_3, pH of aqueous solution is *ca.* 9)[17] or dimethyl sulfide (with or without a catalytic amount of acetic acid)[18] provide preferable alternatives[19] for reduction of excess TBHP.**

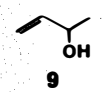
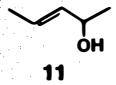
During the past five years these molybdenum- and vanadium-catalyzed epoxidations of olefinic alcohols have been utilized often in complex synthetic sequences. Space does not allow enumeration of all the applications. Consequently, only some of the more interesting examples are presented here (eq. 10→ eq. 31). The examples are arranged in the order of allylic alcohols, then homoallylic alcohols, and finally bishomoallylic alcohols.

Allylic alcohols have been the substrates most often epoxidized by these reagents (*e.g.*, eqs. 10-26). Although molybdenum catalysts are much (*ca.* 100 times) more reactive for epoxidation of isolated olefins, vanadium catalysts are usually preferred for allylic alcohols. With vanadium catalysts the rate acceleration for epoxidation of allylic alcohols is so great (on the order of 10^3 faster than the parent olefin) that the absolute rates, and usually also the selectivities, surpass those realized with molybdenum catalysis.[12b]

Reasonable selectivities are also achieved with some homoallylic (*e.g.*, eqs. 27-30) and bishomoallylic (eq. 31) alcohols. In

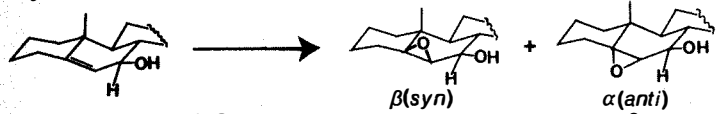
*We usually add the vanadium and molybdenum catalysts in these lower valent forms [*i.e.*, $VO(acac)_2$ and $Mo(CO)_6$]. However, these species are oxidized by TBHP to the catalytically active V^{+5} and Mo^{+6} complexes.

Table I. Stereochemistry of Epoxidation of Acyclic Allylic Alcohols.[a]

Allylic alcohol		*threo*	*erythro*
 9	V^{+5}, TBHP	20	80
	MCPBA	60	40
 10	V^{+5}, TBHP	5	95
	MCPBA	45	55
 11	V^{+5}, TBHP	29	71
	MCPBA	64	36
 12	V^{+5}, TBHP	71	29
	MCPBA	95	5

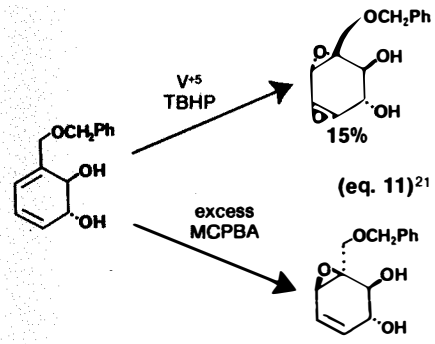
[a]For the reaction conditions and for additional examples see ref. 13.

(a) Allylic Alcohols



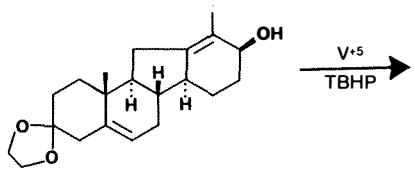
(eq. 10)[20]

	β(syn)		*α(anti)*
MCPBA	4	:	3
V^{+5}, TBHP	100	:	~0

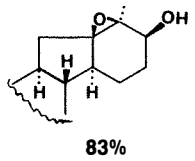


15%

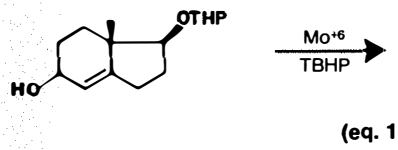
(eq. 11)[21]



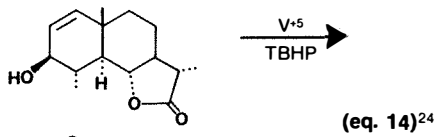
(eq. 12)[22]



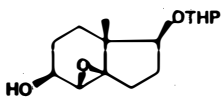
83%



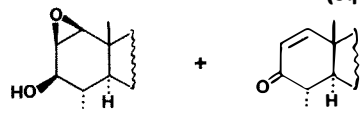
(eq. 13)[23]



(eq. 14)[24]

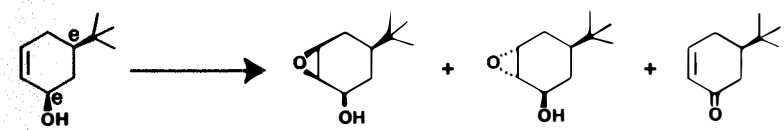


93% (MCPBA, 90%)



47%

39%



(eq. 15)[25]

V^{+5}, TBHP	18%	1%	74%
MCPBA	90%	2%	0.5%

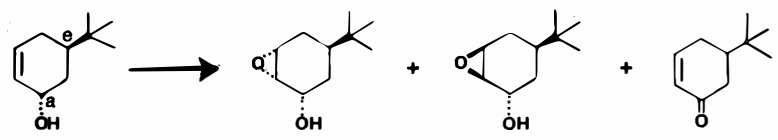
these cases peracids usually exhibit poor or no selectivity. Kishi's use of NaOAc as a buffer (eq. 31) to prevent premature cyclization of the epoxy alcohols to the tetrahydrofurans is a noteworthy modification[39] which should prove useful in other cases where acid-sensitive epoxides are produced.

In spite of the remarkable selectivity exhibited in these new metal-catalyzed epoxidations, they do have limitations. The most common problem occurs with certain rigid cyclic allylic alcohols (eqs. 14-16). In these cases there can be competition from a dehydrogenation process leading to the α,β-unsaturated ketone.[24,25] This side reaction seems to intrude principally in six-membered rings having an equatorial hydroxyl group. However, eqs. 10, 12 and 13 reveal that even this structural feature does not necessarily mean there will be trouble. From existing results,[24,25,40] the factors leading to unsaturated ketone formation are not altogether clear; however, this side reaction is likely if the face of the molecule *syn* to the equatorial hydroxyl is substantially hindered in the vicinity of the olefinic linkage. Severe steric shielding of the double bond can lead to unsaturated ketone formation even when the allylic hydroxyl moiety has an axial orientation.[85]

One of the more attractive features of these metal-catalyzed epoxidations is that they look appealing for the purpose of accomplishing asymmetric epoxidations. The first successes in this area were achieved independently by Yamada's group[41] and by our group.[42] Yamada used a molybdenum catalyst with chiral ligands derived from ephedrine. We employed vanadium catalysts bearing chiral hydroxamic acids as ligands. Since our initial publication we have found[43] more effective chiral hydroxamate ligands. The best asymmetric induction we ever achieved is shown in eq. 32.

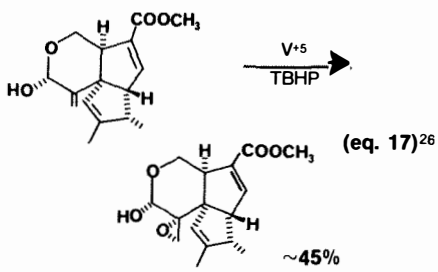
Breslow and Maresca have reported that these metal-catalyzed epoxidations can be directed over a remarkably long distance using their template-directed strategies (eq. 33).[44]

There has been recent interest in assigning optimum O—C—C=C dihedral angles for epoxidation of allylic alcohols by both peroxy acids[45,46] and by vanadium catalysts.[25,40] The conclusions reached in earlier studies were based on epoxidation of cyclohexenols and suggested optimum dihedral angles of *ca.* 150° (peroxy-acid epoxidations)[25,40,45] and *ca.* 90° (V^{+5}-catalyzed epoxidations).[25] We feel that the different steric environments between equatorial and axial positions in cyclohexenols as well as the rapid half-chair/ half-boat interconversion could cloud the interpretation of epoxidation results based on such models. We feel a careful consideration of the stereoelectronic requirements of the epoxidation process might provide a more fruitful approach.

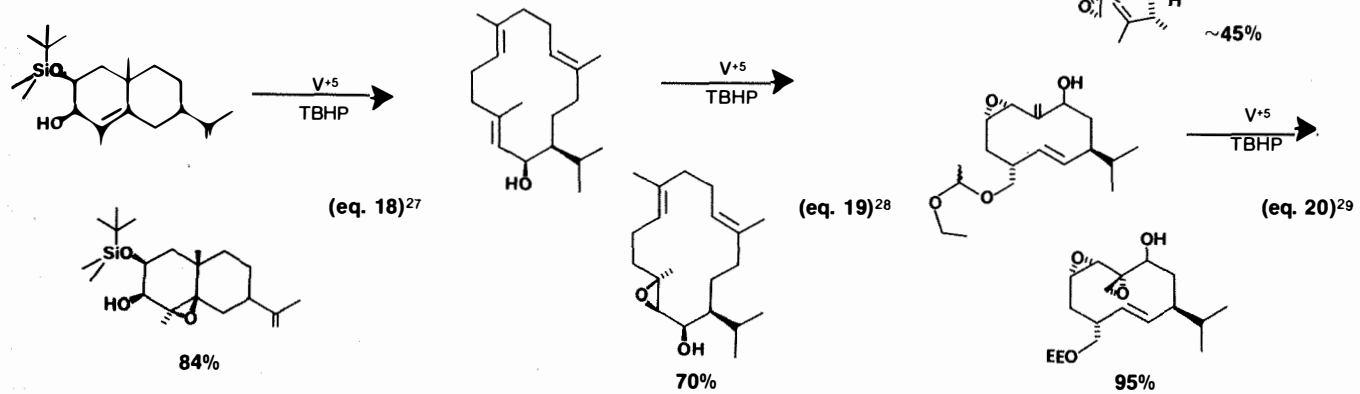


V^{+5}, TBHP	83%	0.08%	15%
MCPBA	80%	9%	3%

(eq. 16)[25]



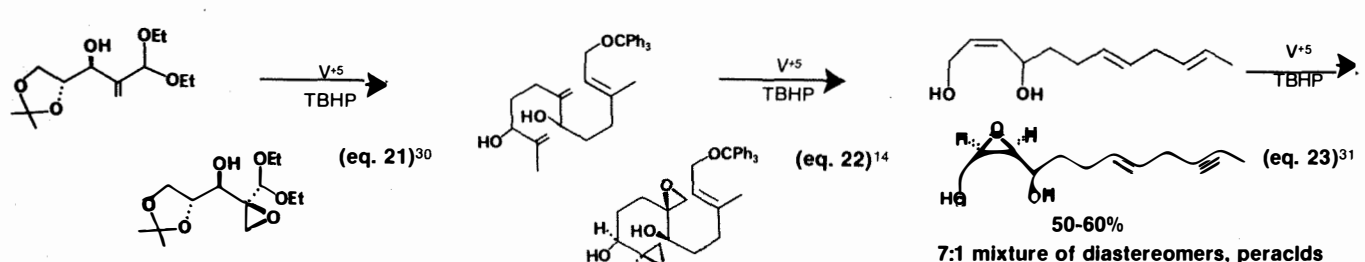
(eq. 17)[26]



(eq. 18)[27]

(eq. 19)[28]

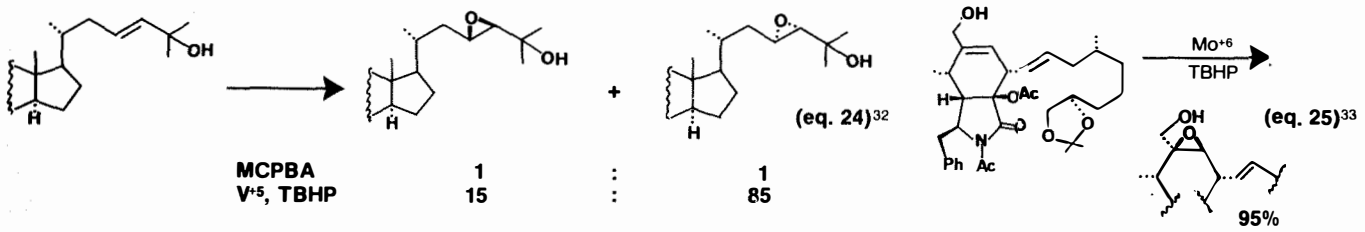
(eq. 20)[29]



(eq. 21)[30]

(eq. 22)[14]

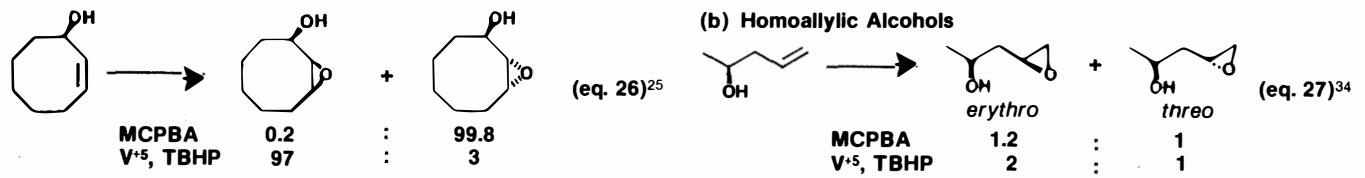
(eq. 23)[31]



(eq. 24)[32]

(eq. 25)[33]

MCPBA	1	:	1
V^{+5}, TBHP	15	:	85

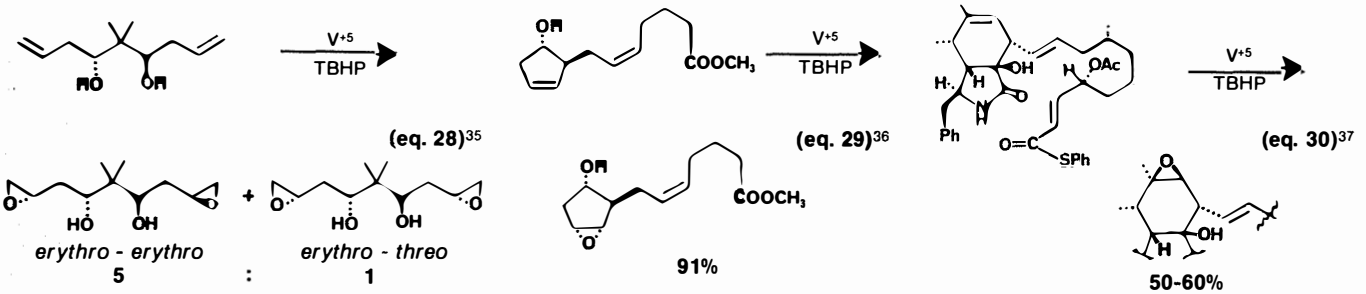


(eq. 26)[25]

(eq. 27)[34]

MCPBA	0.2	:	99.8
V^{+5}, TBHP	97	:	3

	erythro		*threo*
MCPBA	1.2	:	1
V^{+5}, TBHP	2	:	1

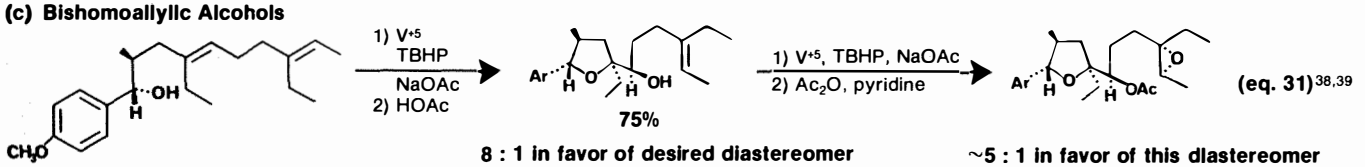


(eq. 28)[35]

(eq. 29)[36]

(eq. 30)[37]

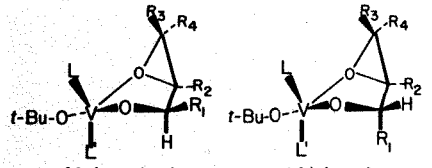
erythro - erythro	:	*erythro - threo*
5	:	1



(eq. 31)[38,39]

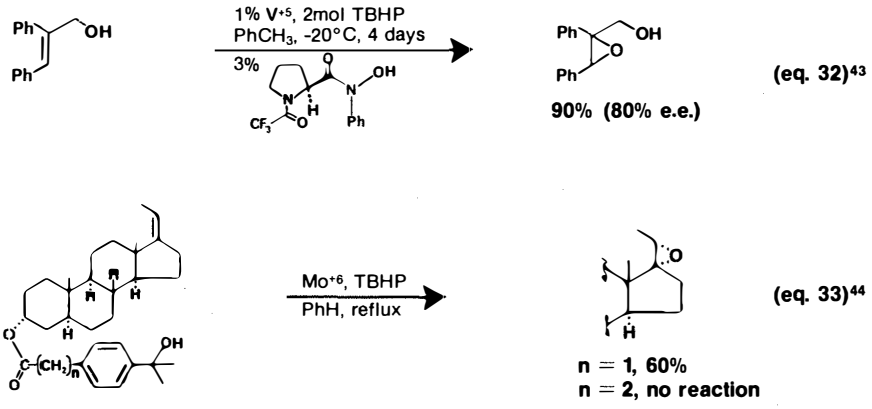
Our detailed mechanistic picture for the vanadium-catalyzed epoxidations is shown in Scheme III. The exchange reactions depicted are well precedented for similar vanadium(+5) alkoxide complexes.[47] The key intermediates are **13** and **14**, both being neutral, roughly trigonal bipyramidal complexes. The slow step in the catalytic cycle is thought to be the oxygen-transfer step (*i.e.*, **13**→**14** in Scheme III). Of course, this is also the step in which the stereoselectivity is determined. A crucial variable associated with the transformation of **13** to **14** is the orientation of the olefinic linkage with respect to the peroxide bond being broken in the oxygen-atom-transfer process. It is our opinion that all epoxidation processes involving attack of olefins on peroxide reagents will be subject to fairly rigid stereoelectronic requirements. (Surprisingly, this point has often been ignored even in the well studied epoxidations of olefins by organic peroxy acids.) In particular, displacement on the peroxide bond should occur from the backside and along the axis of the O—O bond being broken.[48] Thus, in **13** the conformation of the allyloxy group which best allows linear backside displacement on the O^1—O^2 bond produces a boat-like folding resulting in an O—C—C=C angle near 50°. The predicted conformations for the vanadium(+5)-catalyzed epoxidation are illustrated in Scheme IV (**15** and **16**). Thus, the stereoselectivities for the vanadium-catalyzed epoxidations of alcohols **10** (R_1 and R_2=alkyl) and **12** (R_1 and R_3= alkyl) are readily rationalized in terms of the stereoelectronically predicted conformations (either **15** or **16**) of the allyoxy moiety.

To adequately deal with allylic alcohols **9** and **11** however, the interactions between substituents on the allylic alcohol and the ligands on vanadium need to be considered (these interactions are ignored in the simplified analysis of Scheme IV). To the extent that the coordinated epoxy alcohol product **14** resembles the transition state, one can rationalize the stereoselectivity by analyzing the interactions for various substitution patterns in **14**. When R_1 is α (*threo*

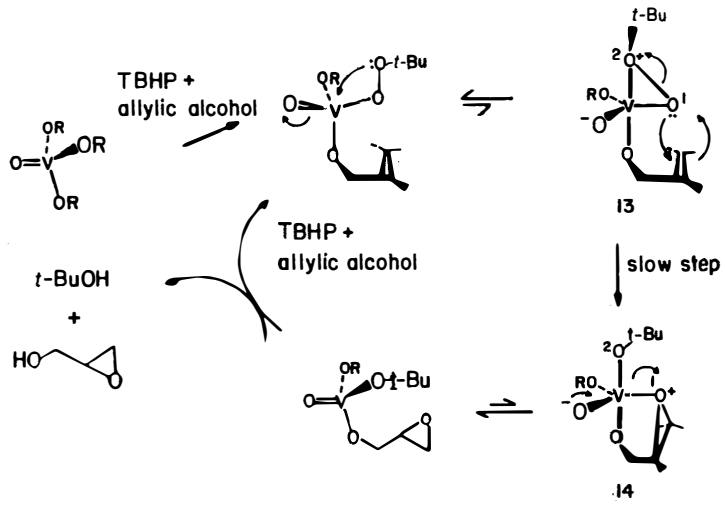


14 (*erythro*) **14**(*threo*)

product) it experiences a 1,3-diaxial-like interaction with the L′ ligand (L′ is either O or OR). At present we have no way of predicting the relative positions of the O and OR ligands in **14**. When R_1 is β (*erythro* product) there is no obvious interaction with the metal ligands. R_3 experiences a weak 1,3-diaxial-like interaction with the L ligand in **14** (L is either O or OR) in both the *erythro* and *threo* cases; therefore its effect on the product ratios should be negligible. R_2 and R_4 are not in a position to interact with the vanadium



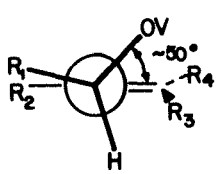
Scheme III. Possible Mechanism for the Vanadium-Catalyzed Epoxidations.



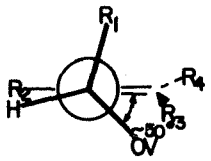
Scheme IV. Predicted O-C-C=C Dihedral Angles

for V^{+5}, TBHP epoxidations:

~50°



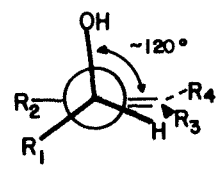
15, leads to *threo* product



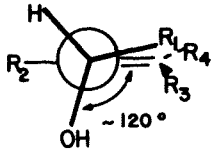
16, leads to *erythro* product

for peroxy acid (MCPBA) epoxidations:

~120°



17, leads to *threo* product

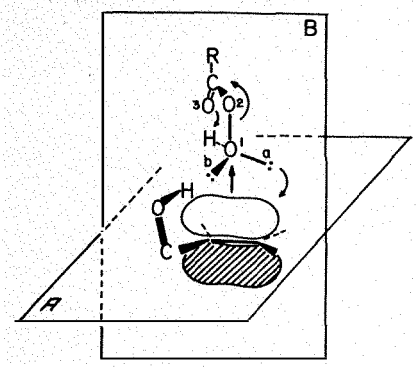


18, leads to *erythro* product

ligands. Thus, it appears that other things being equal these interactions add up to a slight disadvantage for the *threo* transition state. This effect provides an appealing rationale for the weak *erythro* selectivity with substrates **9** and **11** (Table I).

The application of similar stereoelectronic considerations to the peroxy-acid epoxidations leads us to propose the orientation of the reactants illustrated in Scheme V. The plane defined by the peracid molecule is oriented (about 60° to plane B) so that one of the nonbonding pairs on oxygen (pair a) lies in plane B and is nicely oriented to begin bonding with the olefinic carbon; it may also be able to interact favorably with the antibonding π orbital of the olefin. The nonbonding pair b is favorably oriented (in front of plane B) to hydrogen-bond with an allylic hydroxyl group. It should be noted that the selectivity effects seen in the peracid epoxidations of allylic alcohols have previously been explained by hydrogen bonding to either oxygen-2 or oxygen-3 of the peracid,[45] never to oxygen-1 as is suggested in Scheme V. However, if one invokes

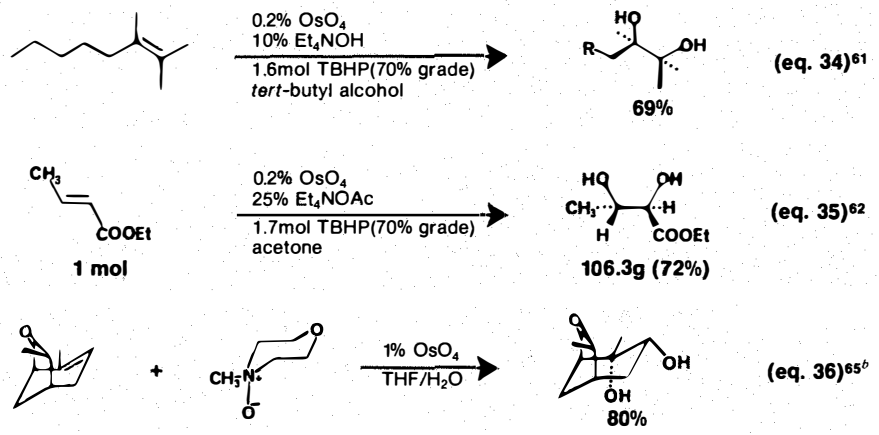
Scheme V. Consideration of Stereoelectronic Effects in Peracid Epoxidations of Allylic Alcohols.



backside displacement on the peroxide bond,[48] it is impossible to form a hydrogen bond between the allylic hydroxyl and either oxygen-2 or oxygen-3. A hydrogen bond to oxygen-1 in Scheme V appears feasible for O—C—C=C dihedral angles ranging from ~50° to ~130°. The observed stereoselectivities in Table I seem best accommodated by a dihedral angle near 120° (see **17** and **18** in Scheme IV).[49]

2. Epoxidation of Isolated Olefins (Scheme I, eq. 2)

If one wishes to epoxidize an isolated olefin, peracids are the first reagents which come to mind. Several years ago we wondered whether the industrially important Oxirane Process (TBHP and Mo^{+6} catalyst) could be adapted to laboratory-scale (*e.g.*, 1-5 mole) epoxidations. We immediately encountered two problems. The commercially available forms of TBHP contained varying amounts of water. Water is deleterious to the reaction, for it not only inhibits the epoxidations, but also gives rise to epoxide opening which produces diols as byproducts.[50,51] We have since found that the epoxidation of isolated



olefins can be carried out efficiently by operating in nonreactive solvents (*e.g.*, benzene, dichloromethane, dichloroethane) under moderately anhydrous conditions. The use of small amounts of anhydrous disodium hydrogen phosphate (Na_2HPO_4) powder as an additive in these reactions further reduces the formation of byproducts.[52] Since this work has not been published yet[51] the complete experimental details for the epoxidation of 1-decene are presented below. Monosubstituted olefins such as 1-decene are among the most difficult to epoxidize. Therefore, the conditions now given for 1-decene will epoxidize all simple di-, tri- and tetrasubstituted olefins much more rapidly[51] than the *ca.* 10 hrs at reflux required for complete conversion of 1-decene. With more reactive olefins we recommend that the course of oxidation be followed so that it can be stopped soon after completion. The more reactive olefins also give rise to more reactive epoxides, and there is no sense in heating such epoxides in the presence of Mo^{+6} (a weak Lewis acid) any longer than necessary.

Epoxidation of 1-Decene (1-mole scale)

a) General procedure for azeotropic drying of "Aqueous TBHP-70" (or the equivalent Aldrich 18,471-3): "Aqueous TBHP-70" (500ml, 3.6 mol) and 850ml of reagent-grade 1,2-dichloroethane [53] are combined in a 2-liter separatory funnel, which is then swirled (vigorous shaking can lead to emulsions) for about one minute. Two phases form, and the upper, aqueous layer (*ca.* 125ml) contains only about 2.7% (0.10mol) of the TBHP originally added. The lower organic layer (1225ml, containing *ca.* 2.35mmol of TBHP per ml and, therefore a total of 3.5mol of TBHP) is drained into a 2-liter, one-necked, round-bottomed flask. **[Thus, by simple phase separation one obtains this TBHP solution which is similar in water content to solutions which we used[12,14,54] to prepare by adding commercial Lucidol-90 or Aldrich's 21,312-8 to the appropriate organic solvent (*e.g.*, CH_2Cl_2, benzene or $ClCH_2CH_2Cl$). We now recommend TBHP solutions prepared in this way for the SeO_2-catalyzed oxidations[54,55] (CH_2Cl_2 or $ClCH_2CH_2Cl$ as solvent) and for the vanadium-catalyzed epoxidation of allylic alcohols (benzene or CH_2Cl_2 as solvent). However, for the molybdenum-catalyzed epoxidations of isolated olefins removal of even this last bit (estimated to be *ca.* 5-7%) of water is important, and is easily accomplished as described below.]** A few boiling stones are added and the flask is fitted with a distillation head. Distillation ($ClCH_2CH_2Cl/H_2O$ azeotrope, bp 72°C) commences a few minutes after heat is applied with a steam bath. The distillate is cloudy and separates in the collection vessel into organic and aqueous layers. After *ca.* 450ml of solvent is removed the distillate becomes clear and homogeneous. A total of *ca.* 575ml of distillate[56] is collected, and this leaves about 650ml of an anhydrous,[57] *ca.* 4.1*M* solution of TBHP (*ca.* 2.67moles) in dichloroethane.* [The precise TBHP concentration can be very easily determined by iodometric titration; the exact details for these titrations are given in Note 58a below. The TBHP concentration can also be estimated (± 10%) by NMR integration; a convenient equation for calculating the molarity of such solutions when using dichloroethane as solvent is given in Note 58b below.] The anhydrous TBHP solution is allowed to cool and can be stored[59] or used immediately.

b) Molybdenum-catalyzed epoxidation: A 2-liter, 3-necked round-bottomed flask is equipped with a Teflon-coated magnetic stirring bar, a reflux condenser, a 500-ml dropping funnel, and a nitrogen inlet. All glassware was dried in an oven, and the system flushed with nitrogen. The flask is charged with 1 liter of reagent-grade 1,2-dichloroethane, 146.14g (1.00mol, corrected for purity) of Aldrich 1-decene (95% purity), 0.668g (0.0025mol, 0.25mol %) of $Mo(CO)_6$, and 1.0g (0.007mol) of anhydrous disodium hydrogen phosphate (Na_2HPO_4, AR grade, freshly ground into a powder). The dropping funnel is charged with 490ml (*ca.* 2mol) of the previously prepared solution of anhydrous TBHP in dichloroethane. The stirrer is started, and the reaction mixture is brought to a gentle reflux. Dropwise addition of the TBHP solution is started and then the source of heat is removed from the reaction vessel.[60] The TBHP solution is added to the stirred mixture at a rate which is sufficient to maintain reflux. The addition requires ~0.5hr. (With unreactive olefins such as 1-decene it may be necessary to reapply the heat source before the addition is complete in order to sustain reflux.) When the addition is complete heat is reapplied and refluxing is continued until the olefin is completely consumed (monitor by GLC, TLC or other appropriate method). In the present experiment with 1-decene this required *ca.* 10 hours at reflux (GLC revealed <1% olefin). If for some reason olefin still remains, one can simply add more of the anhydrous TBHP solution to the refluxing reaction mixture.

The reaction vessel is then cooled in an ice bath and 300ml (*ca.* 0.24mol) of a freshly prepared 10% solution of sodium sulfite (Na_2SO_3) is added dropwise with stirring. When addition is complete the ice bath is removed and stirring is continued for 3 hours at autogenous temperature. At this point the organic phase should give a negative peroxide test using acidified starch-iodide test paper.[80] If the test is positive additional aqueous sulfite solution should be added and stirring continued until the test is negative. The aqueous and organic phases are separated, and the milky white organic layer is washed twice with 250-ml portions of water, once with 250ml of brine, dried ($MgSO_4$) and concentrated to afford a colorless but somewhat cloudy oil. Distillation of this oil afforded 137.4g (center cut, bp 52-4°C/1mm) of 1-decene oxide which was 98% pure by GLC analysis (therefore 86% yield).

Other isolated olefins which have been epoxidized following the above procedure in 85-95% distilled yield include cyclohex-

***Warning:** It is important not to allow the distillation to proceed too long, for this would eventually produce high-strength TBHP solutions.

ene, methyl oleate, 1-methylcyclohexene, 1-phenylcyclohexene, (*E*)-2-decene and methyl 10-undecenoate. Other solvents (*e.g.*, benzene,[53] CH_2Cl_2 and CCl_4) also work well in this epoxidation procedure (*i.e.*, in both the azeotropic drying and epoxidation stages of the process). The use of methylene chloride, due to the less favorable composition of its azeotrope with water, requires about twice the initial volume of solvent needed for the other solvents mentioned above. Furthermore, the epoxidation step takes longer in methylene chloride due to its lower boiling point. In fact, 1-decene cannot be epoxidized in CH_2Cl_2, but more reactive olefins can be epoxidized in excellent yield in 5-24 hours at reflux.[51]

In summary, we feel that even with isolated olefins these metal-catalyzed epoxidations may sometimes have advantages over the more traditional peracid methods. This would seem especially true for larger-scale (1-5mol) epoxidations where cost and safety become important considerations.

III. Vicinal Dihydroxylation of Olefins (Scheme I, eq. 3)

Our experience with vanadium- and molybdenum-catalyzed epoxidations encouraged us to think of TBHP as a possible oxygen-atom source for other metal-catalyzed oxidations of olefins. This has led to the discovery of very effective procedures[61,62] for the osmium-catalyzed vicinal hydroxylation of olefins (eq. 3, Scheme I), and for selenium-catalyzed allylic oxygenations of olefins[54] and acetylenes[55] (eqs. 4 and 5, Scheme I).

These new TBHP-based osmium-catalyzed procedures for *cis*-vicinal dihydroxylation of olefins are much more reliable than the earlier ClO_3^- (Hofmann[63])- and H_2O_2 (Milas[64])- based osmium-catalyzed procedures for this transformation. The key to the success of the new methods appears to be the presence of a nucleophile (either Et_4N^+OH[61] or Et_4N^+OAc[62]). It seems likely that the role of the nucleophile is to increase the turnover rate of the catalytic cycle by facilitating removal of the glycol product from the coordination sphere of the osmium. Thus, it has been possible to hydroxylate even some tetrasubstituted olefins using the Et_4NOH modification (eq. 34). The Et_4NOAc modification fails with tetrasubstituted olefins, but, being much less basic than the Et_4NOH method, it can be used with base-sensitive olefinic substrates (eq. 35).

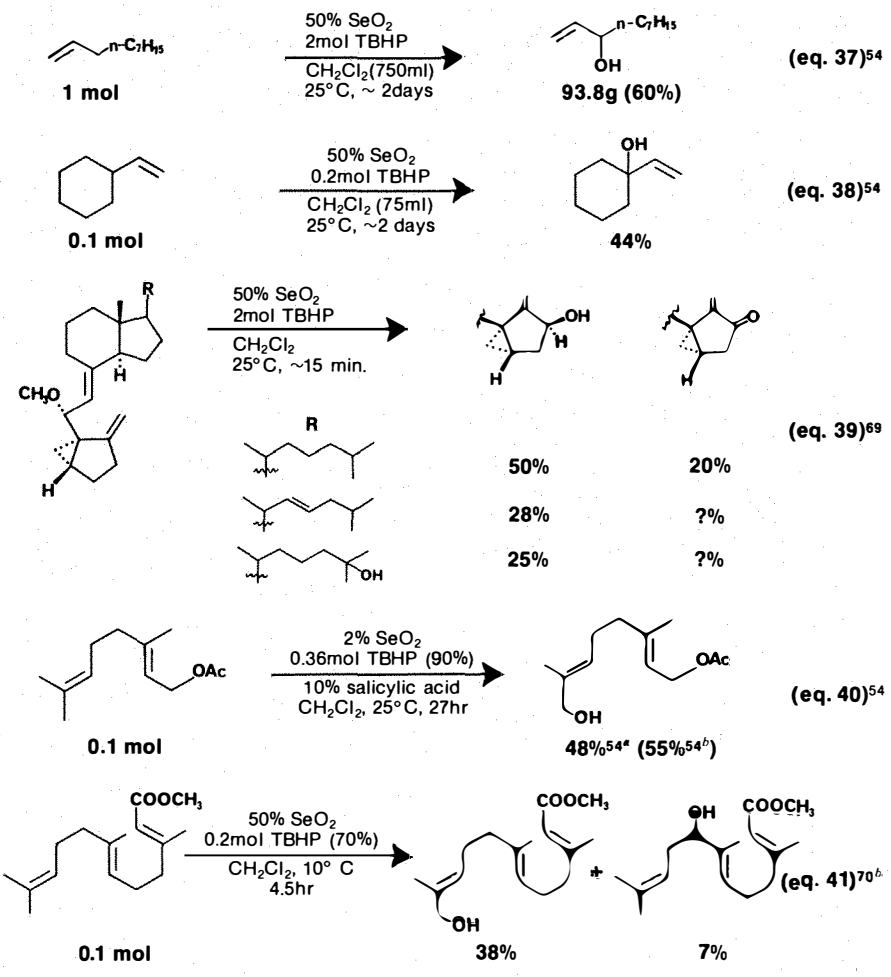
Upjohn chemists have also recently reported a very effective new osmium-catalyzed procedure for *cis*-vicinal dihydroxylation of olefins.[65a] The oxidant in their process is *N*-methylmorpholine-*N*-oxide. In the short time since its discovery it has been used many times with great success (*e.g.*, eq. 36). In comparing this method with our TBHP-based procedures we noted that the Upjohn procedure failed in our hands with the tetrasubstituted olefin shown in eq. 34. We also suggested that it might not be very useful with trisubstituted olefins. **We now wish to retract and apologize for that inference, because enough examples are now known to make it clear that the *N*-methylmorpholine-*N*-oxide method is marvelously effective with many trisubstituted olefins (*e.g.*, eq. 36).**

There have been only two applications[66,67] of our method so it has not really been adequately tested. At present it would appear to have only two possible advantages over the Upjohn procedure. Our procedure does work with some tetrasubstituted olefins, and TBHP is about 20 times less expensive than *N*-methylmorpholine-*N*-oxide (NMO) even at fine chemical prices (and TBHP is available at much lower prices in bulk quantities). Another minor point is that we always use 0.2% OsO_4 catalyst, whereas the NMO procedure has been reported with from 0.2 to 5% OsO_4 catalyst. If the TBHP and NMO routes gave comparable yields of diol in a given case, considerations of cost would favor the TBHP process, especially on larger-than-mmole scales.

In summary, these two new catalytic methods (TBHP-based[61,62] and NMO-based[65a]) have greatly increased the reliability of the olefin to *cis*-vicinal diol transformation. Of equal importance, the reaction can now be carried out on a one-mole scale at a reasonable cost; this should allow the use of such a step early in a synthetic sequence.

IV. Allylic Oxidation of Olefins and Acetylenes (Scheme I, eqs. 4 and 5)

Selenium dioxide is the most reliable and predictable reagent for direct insertion of oxygen into an allylic carbon-hydrogen bond.[68] A serious complication in this reaction is the inevitable production of reduced forms of selenium. The frequent difficulty of removing colloidal selenium from the products is well known. Another drawback of these oxidations is the formation of organoselenium by-products. We reasoned that an oxidant which would rapidly and selectively reoxidize the reduced selenium species to SeO_2 would circumvent these problems, and furthermore might enable the reaction to proceed with catalytic amounts of SeO_2. Indeed, we found that TBHP is an excellent oxidant for this purpose.[54] Allylic oxidation proceeds in CH_2Cl_2 at room temperature with catalytic (2-50%) amounts of SeO_2. Examples from our work[54] (eqs. 37, 38, 40) and from other laboratories (eqs. 39, 41, 42) are shown below. The transformation shown in eq. 42 by Cook and Campos[70a] is interesting in that the substrate contains both indole and

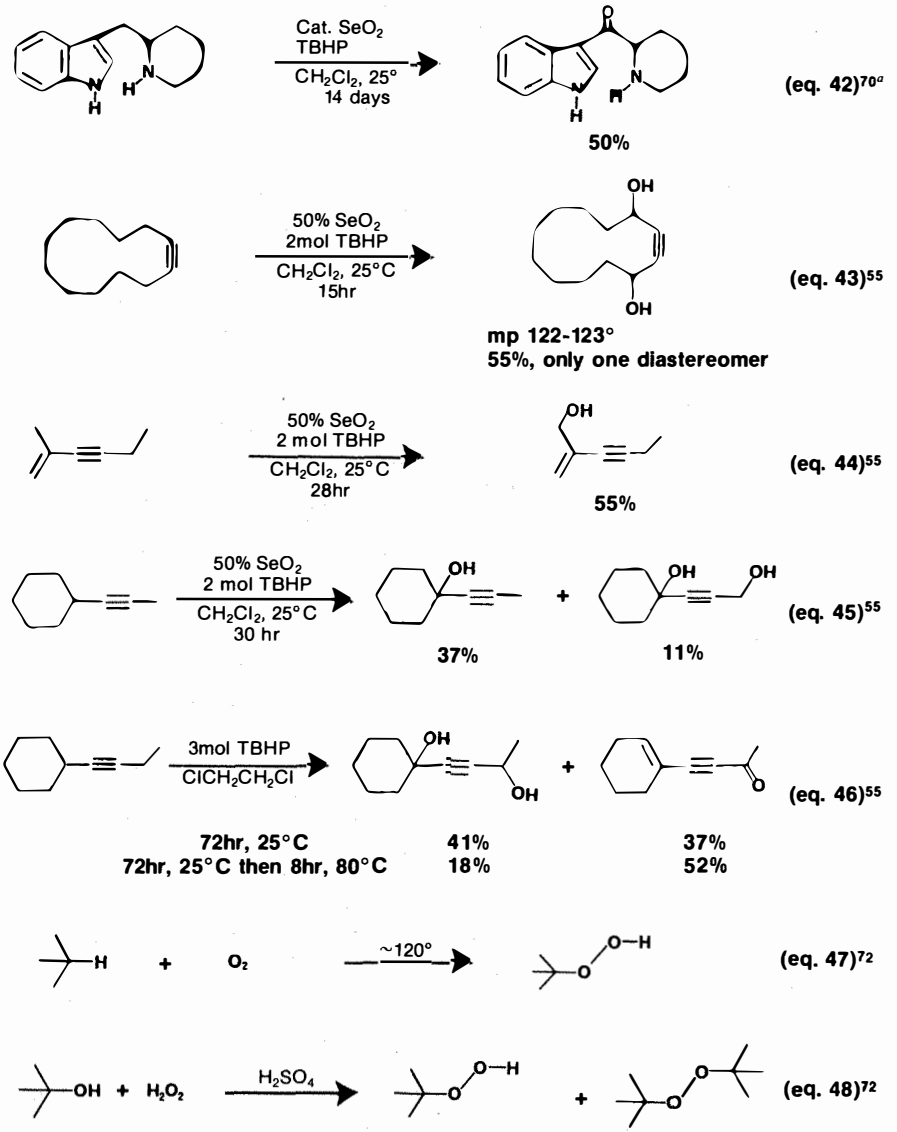


piperidine moieties. Stoichiometric SeO_2 oxidation of the same substrate required more vigorous conditions, and gave only the product of complete dehydrogenation (*i.e.*, piperidine ring → pyridine ring).[70a]

In our first publication on this subject,[54] we mentioned that cyclohexene was a poor substrate for the SeO_2/TBHP allylic oxidation procedure. The allylic alcohol is a minor product and the two major products are the allylic *tert*-butyl ether and the allylic *tert*-butyl perether. We have since found that this is a general problem when the olefinic linkage is in a ring (*i.e.*, endocyclic).[71] Smaller-ring olefins (*e.g.*, 5- and 6-membered) are worse than larger-ring olefins (*e.g.*, 8- and 12-membered), but even in the case of cyclododecene the ether and perether by-products are still apparent. For cyclododecene the ratio of allylic alcohol to by-products (*i.e.*, allylic ether and perether) is 7:3; the ratio for cyclohexene is 1:4. **Thus, it is important that one be wary of applying our procedure to endocyclic olefins which are in small- and medium-sized rings,** especially if the C—H bond to be oxidized lies within the same ring. However, exocyclic olefins work well (eq. 39), and it also appears that the reaction proceeds normally with endocyclic olefins if the allylic C—H bond which is oxidized lies outside the ring.[71]

We have recently found that, unlike olefins, acetylenes show a strong tendency to undergo α,α'-dioxygenation upon reaction with the SeO_2/TBHP system (eq. 43).[55] The oxidation of ten different acetylenes allowed assignment of the relative reactivity sequence as $CH_2 \cong CH > CH_3$, thus allowing selective monooxygenation in the case of CH_2 *vs.* CH_3 or of CH *vs.* CH_3 (eq. 45). Alkynes bearing one methylene and one methine substituent afford the enynone as the major product (eq. 46).

Both the olefin[54] and the acetylene[55] **SeO_2/TBHP** α-oxygenation procedures have been performed on a one-mole scale with no difficulty. One advantage of these procedures is that they can be run quite concentrated (at least 1 *M* in olefin or acetylene), and hence are conveniently scaled-up. **However, the key advantage of the SeO_2/TBHP/CH_2Cl_2 system is that it is more reactive and also more selective than any known[68] stoichiometric SeO_2 oxidation procedures.** With the exception of the endocyclic olefins mentioned above, it is clearly the method of choice for obtaining synthetically useful yields of unrearranged allylic alcohols from a greatly broadened spectrum of olefins. The positional selectivity, which has been the chief attraction of SeO_2 oxidations, is retained. The milder conditions avoid the rearrangements and dehydrations which can occur under the standard stoichiometric conditions. Finally, the dramatic reduction in the amount of colored, malodorous organoselenium by-products formed, and the elimination of precipitated selenium metal should help to overcome the selenophobia which currently afflicts many synthetic organic chemists.



V. Practical Considerations in Handling TBHP

1. Commercial Sources. There are two commercial routes to TBHP. The most important is the autoxidation[72] of isobutane (eq. 47). The older route involves acid-catalyzed alkylation[72] of hydrogen peroxide with *tert*-butyl alcohol (eq. 48). This latter route leads to coproduction of di-*tert*-butyl peroxide (DTBP). Lucidol offers two grades of TBHP: (1) Lucidol-TBHP-70 contains (by wt.) 70% TBHP, ~19% DTBP, and 11% of TBA and water;[73] (2) Lucidol-TBHP-90 contains 90% TBHP, ~6% TBA, ~4% H_2O, and <1% DTBP.

The 90% grade of TBHP is also available from Aldrich, but it must now be sent by truck according to a recent ruling of the DOT.

Oxirane Corporation produces TBHP by the autoxidation route. Almost all of this TBHP is used on-site for the molybdenum-catalyzed epoxidation of propylene. However, they do sell some of it for use outside their plant. This material is almost pure TBHP except for 30% water which is added as a stabilizer to permit shipment in tankcar and tanktruck quantities. Oxirane calls this material "Aqueous TBHP-70".[74] The vital statistics for the Oxirane "Aqueous TBHP-70", Lucidol TBHP-90 and pure TBHP are given in Table II. Please note that the data for pure TBHP are given only for the sake of comparison with the commercial grades. Pure TBHP is not commercially available nor should it, in our opinion, ever be prepared and used except on a very small scale. The 70% TBHP is available from Aldrich and can be shipped by UPS making it an ideal form in which to receive TBHP for laboratory-scale operations.

2. Purification. Of the three[75] commercial grades of TBHP only the two shown in Table II are suitable for use in the metal-catalyzed oxidations described here. Since the 90% grade is inherently more expensive, and is made even more so because it must travel by truck, we have adapted to

using the 70% grade (70% TBHP/30% H_2O) for all our needs. This approach is actually much more attractive than one might at first think.

The aqueous 70% TBHP is ideal for direct use in the osmium-catalyzed vicinal dihydroxylation of olefins (eq. 3, Scheme I).[61,62] This process requires the presence of water and there is absolutely no virtue in using drier grades of TBHP. In fact, anhydrous solutions of TBHP do **not** work for this application.

The vanadium- and selenium-catalyzed oxidations (eq. 1,4 and 5, Scheme I) were all initially developed[12,14,54,55] using the commercial 90% grade (~4-5% H_2O) of TBHP. The vanadium-catalyzed processes are definitely slowed by the presence of water, but the 90% grade is dry enough to give reasonable rates and good yields. However, the rates and sometimes the yields can be increased if one prepares anhydrous solutions of TBHP in organic solvents. The selenium-catalyzed processes show a more complicated dependence on the water content of the TBHP. When using 50% SeO_2 catalyst the reactions are rather insensitive to water content. Thus, Sum and Weiler were able to use 70% TBHP directly for oxidation of methyl farnesoate (eq. 41),[70b] whereas we have found that 90% TBHP was optimum when using only 2% SeO_2 catalyst for oxidation of the similar olefin, geranyl acetate (eq. 40).[54] Both less water (anhydrous TBHP) and more water (70% TBHP or phase-separated TBHP in CH_2Cl_2) resulted in substantially slower oxidations under otherwise identical conditions.[76a] However, even in this case the phase-separated TBHP/CH_2Cl_2 solutions were adequate for use.

The only process in Scheme I which actually requires anhydrous conditions for good yields is the molybdenum-catalyzed epoxidation of isolated olefins (eq. 2). Fortunately, we have found that it is relatively easy to obtain anhydrous solutions of TBHP in organic solvents, even when starting with the wettest grade of TBHP, namely "Aqueous TBHP-70" (70% TBHP/30% H_2O, w/w) by employing the phase-separation and azeotropic-distillation techniques which are described above for the epoxidation of 1-decene.

Note that the easy phase-separation procedure for removing most of the water from the 70% TBHP means that the less convenient (more expensive and less stable) 90% commercial grade of TBHP is no longer really essential. Recall that 90% TBHP was the grade we used to recommend for the vanadium- and selenium-catalyzed oxidations (eqs. 1, 4 and 5, Scheme I). **We have also found that the TBHP solutions one gets by the simple phase-separation procedure have nearly the same reactivity as solutions generated by dissolving commercial 90% TBHP in the same solvent.**[76] This is as it should be since both methods yield TBHP solutions which contain similar (based on TBHP content) amounts of water (*i.e.*, 4-5% H_2O for Lucidol TBHP-90 and 6-7% H_2O for the TBHP solutions we prepare by phase separation).

3. Dangers. We have so far emphasized the relative safety of working with TBHP as compared to working with other peroxidic substances. **Now we must point out that TBHP, like almost all substances having O—O bonds, has to be regarded with respect. However, provided one avoids certain situations, this state of respect need not degenerate into a state of fear.**

There are three main situations to avoid. The first rule is never add a strong acid (even just a drop) to high-strength TBHP solutions. The second rule is never add transition metal salts known to be good autoxidation catalysts (*e.g.* Mn, Fe and Co are particularly bad) to high-strength TBHP solutions. Alkyl hydroperoxides are sensitive to metal-catalyzed radical-chain decomposition.[8,72,77] Among other things this produces a lot of oxygen gas. **The third rule** (which, if followed, will ameliorate any problems arising from violations of the first two rules) **is never work with pure TBHP and avoid using high-strength solutions of it whenever possible.**

The literature contains a number of examples of violations of this last rule.[78] Most of these involve distillation of TBHP to purities of 98% or greater. These are performed at reduced pressure and, if done carefully in clean glassware, are probably quite safe. However, many people use heating mantles for distillations and one wonders what would happen if the flask broke or had a crack in it. But the real problem here is that one might produce really pure (>99%) TBHP which has to be regarded as too dangerous to work with, especially on a preparative scale. In the past, perhaps the main reason for distilling TBHP was the desire to obtain anhydrous material for further reactions (*e.g.*, to form *tert*-butyl peresters from the corresponding acid chlorides[78]). **Our new azeotropic procedure for generating anhydrous solutions of pure TBHP in aprotic organic solvents should in many cases obviate the need to distill pure TBHP.**

Since much of this review is concerned with removing water from TBHP, one might naturally wonder about the effectiveness of molecular sieves for this purpose. For this reason we quote the following account of a small accident which occurred at Shell Development Company in Houston: "We had been routinely drying 90% TBHP (typically containing 6% H_2O, 3% TBA and 1% Di-*t*-butyl peroxide) on a small scale using 4A molecular sieves. A technician inadvertently used Linde 13X mol sieves. After pouring one or two liters on the packed bed the technician was sufficiently alarmed at the unusual exothermic reaction taking place that he quickly closed the fume hood. Within one or two minutes the hydroperoxide ignited. The ensuing fire was contained within the fume hood. We surmise that the heat of adsorption of TBHP on 13X sieves (pore size ~9Å) was sufficient to raise the temperature to the autoignition point. Note that, in contrast, penetration of TBHP into the pores of a 4A sieve is not possible)."[79]

Perhaps this behavior is specific for the 13X sieves, but at present we would not be too sanguine about pouring high-strength (*e.g.*, 90%) TBHP over molecular sieves of any kind.

One can remove some of the remaining (~6-7%) water from the organic solutions of TBHP (obtained from 70% TBHP by the phase-separation technique) by swirling them with anhydrous $MgSO_4$. The $MgSO_4$ should be removed by filtration through a plug of glasswool placed in the stem of a regular funnel; a sintered-glass funnel should not be used for it may be contaminated with metals. However, TBHP solutions dried in this way are less effective (presumably because they are wetter) in the molybdenum-catalyzed epoxidations of isolated olefins than are TBHP solutions dried by the azeotropic technique.[51]

If one contemplates larger-scale (0.1 mole and greater) reactions of the type shown in Scheme I, then the following advice is of special importance. **Whenever possible add the TBHP slowly to the reaction mixture under conditions where it is being consumed as it is added.** We have run the molybdenum-catalyzed epoxidation of isolated olefins (eq. 2, Scheme I) on a 2.5-mole scale; this involves at least 5 moles of TBHP. However, the TBHP is added at a rate which maintains a gentle reflux and therefore does not build up in the reaction mixture. The larger-scale reactions also tend to need less catalyst. We have used as

Table II. Properties of Commercial Grades of TBHP

Properties	Aqueous TBHP-70	Lucidol TBHP-90	Pure TBHP*
diluents	30% H_2O	~6% TBA ~4% H_2O <1% DTBP	
bp(°C/mm)	96/760		133/760
mp(°C)	-2.8	-10	4.2
density (25°C)	0.935	0.90	0.8960
ca. mmol TBHP/ml	7.2	9.0	9.94
shipping	UPS	Truck only	

*Not commercially available, only included in table for comparison with the two commercial grades.

little as 0.1% $Mo(CO)_6$ catalyst in the 2.5-mole scale epoxidations. **A situation to be avoided at all costs is that where one places large quantities of TBHP and the substrate (olefin or acetylene) together and then adds the catalyst.** This can sometimes be done, but only after one has very carefully established that the substrate is so unreactive that the reaction cannot get out of control. Finally, if you really must risk mixing everything together at once it is always safer to be in a lower boiling solvent than a higher boiling one.

Dr. E.S. Shanley has pointed out that there is a common ambiguity in the use of the term "stability". We have used it in this review to mean low decomposition rate during storage. Another meaning of "stability" is lack of potential for spontaneous change. TBHP is certainly not stable in this latter sense. **It is therefore important to be sure that most all peroxidic substances are reduced before engaging in distillation of reaction mixtures in which TBHP was used as oxidant.** The Na_2SO_3[17] and dimethyl sulfide[18] procedures for reducing excess TBHP are reliable, and the absence of TBHP can, and should, be established with acidified starch-iodide test paper.[80] **However, of greater concern is the possibility that the TBHP has become bound into the molecule in some more-stable form.** This is especially true in those reactions in Scheme I which involve mildly acidic conditions (*viz.*, eqs. 1, 2, 4 and 5). **If the molecule contains a ketone or aldehyde function in addition to the olefinic unit one should be aware of the possibility of peroxyketal or peroxyacetal formation.**[81] An NMR spectrum of the crude reaction mixture should reveal contamination by *tert*-butyl peroxyacetals or ketals.

Above all, we prefer steam baths for heating TBHP reaction mixtures (especially on a large scale). Oil baths are also acceptable, but messy on a large scale, and heating mantles involve obvious dangers. We have used heating mantles for heating TBHP solutions, but are **careful to use low power settings, and to see that the level of solvent in the flask is always above the top of the mantle.**

A lot more information about safety and handling of TBHP as well as other peroxides is available in various bulletins from the companies which sell it (*e.g.*, Lucidol,[82] Oxirane,[83] and Witco[1]). E.S. Shanley has written a chapter on "Organic Peroxides: Evaluation and Management of Hazards" in Swern's series on "Organic Peroxides".[84]

4. Storage. The maximum recommended storage temperature for TBHP is 38°C (100°F).[82] It is stable essentially indefinitely at room temperature (25°C) and, thus, does not need refrigeration. In fact, it is important that the "aqueous 70% TBHP" not be stored much below room temperature. It is essentially saturated with water at 25°C, and at lower temperatures an aqueous phase separates which is visible on the bottom of the storage container. This circumstance would cause the concentration of the supernatant TBHP solution to vary. TBHP containers should best be stored in the dark or at least out of bright light, and should be kept in an area free of accelerators, corrosives and other inherently hazardous materials. **To avoid contamination while sampling always pour TBHP out of the container, never stick sampling devices into the container, and never return unused TBHP to the container.**

Like all strong oxidants TBHP is an eye and skin irritant. It is especially bad in the eyes. Should it get in your eyes flush them immediately with copious amounts of water and contact a physician. Eye protection and rubber gloves should be worn when handling these materials.

"Aqueous 70% TBHP" will burn vigorously if ignited but will not explode unless it is contained. This is one of the advantages of shipping peroxides in plastic containers. Should things get hot the containers melt down and prevent containment. Should a fire arise copious amounts of water, coolants and foam extinguishers should be employed.

VI. Conclusion

Because TBHP is a **selective,** inexpensive, and relatively safe oxidant, its applications in organic synthesis should continue to increase. Few reactions have caught on as rapidly among synthetic chemists as the vanadium-catalyzed epoxidation of olefinic alcohols (eq. 1, Scheme I). This gives some insight into the importance of being able to stereoselectively introduce new asymmetric centers into a molecule under the direct control of a preexisting chiral center. The fact that this particular reaction also exhibits good stereoselectivity on acyclic molecules, and even over fair distances, makes it all the more valuable. As synthetic chemists become more familiar with TBHP, they may find that some of the other metal-catalyzed oxygenations discussed here (Scheme I) are also useful for the construction of complex molecules.

Acknowledgement

We are grateful to Lucidol, Oxirane and Witco Chemical Companies for having provided us with generous samples of various hydroperoxides and peroxides. We especially wish to thank Dr. Chester Sheppard of Lucidol for many helpful discussions over the past six years in which he taught us a lot about peroxide chemistry. Most of our TBHP-related research described here was carried out in the Chemistry Department of the Massachusetts Institute of Technology. This research was, and still is, supported by grants from the National Science Foundation and from the National Institutes of Health. We are also very grateful to Bryant E. Rossiter, Doris J. Scheffel and Dr. Per H.J. Carlsen for their help with many last-minute details needed to get this manuscript ready. Finally, we are indebted to Drs. Orville L. Mageli, Edward S. Shanley, Chester S. Sheppard and Jeff White for reading and providing important criticisms of the manuscript, and to Prof. Julius Rebek for many insightful discussions on the mechanism of peracid epoxidations (see his student's Ph.D. thesis[48d]).

References and Notes

1) Technical bulletin on 70% TBHP/30% H_2O (their USP-800 grade) from Witco Chemical, a U.S. Peroxygen Division.
2) The catalytic decomposition of H_2O_2 by a variety of transition metals is well known [see J.A. Connor and E.A.V. Ebsworth, *Adv. Inorg. Chem. Radiochem.*, **6**, 359-360 (1964), and S.B. Brown, P. Jones, and A. Suggett, *Prog. Inorg. Chem.*, **13**, 159-204 (1970)].
3) N.A. Milas and S.A. Harris, *J. Am. Chem. Soc.*, **60**, 2434 (1938).
4) a) N. Prileschajew, German Patent 230,723 (1908); b) N. Prileschajew, *Ber.*, **42**, 4811 (1909).
5) N. Indictor and W.F. Brill, *J. Org. Chem.*, **30**, 2074 (1965).
6) J. Kollar, U.S. Patents 3,350,422 and 3,351,635 (1967).
7) M.N. Sheng and J.G. Zajacek, *J. Org. Chem.*, **33**, 588 (1968).
8) For a very recent and excellent review on "Metal Catalyzed Epoxidations of Olefins with Hydroperoxides" by R.A. Sheldon, see Vol. IV. of "Aspects of Homogeneous Catalysis," C. Manfred, Ed., Monotipia Rossi-Santi-Milano, Italy, in press.
9) M.N. Sheng and J.G. Zajacek, *J. Org. Chem.*, **35**, 1839 (1970).
10) F. List and L. Kuhnen, *Erdoel. Kohle*, **20**, 192 (1967).
11) a) H.B. Henbest and R.A.L. Wilson, *J. Chem. Soc.*, 1958 (1957); b) for a review on the stereochemical aspects of the synthesis of epoxides, see G. Berti, *Top. Stereochem.*, **7**, 93-251 (1973).
12) a) K.B. Sharpless and R.C. Michaelson, *J. Am. Chem. Soc.*, **95**, 6136 (1973); b) epoxidations of allylic alcohols proceed approximately ten times faster with vanadium than with molybdenum catalysts.
13) B.E. Rossiter, T.R. Verhoeven, and K.B. Sharpless, *Tetrahedron Lett.*, in press.
14) S. Tanaka, H. Yamamoto, H. Nozaki, K.B. Sharpless, R.C. Michaelson, and J.D. Cutting, *J. Am. Chem. Soc.*, **96**, 5254 (1974).
15) Although this work was done in collaboration with the Yamamoto/Nozaki group, we wish to emphasize that the errors were exclusively due to our group and have nothing to do with that portion (*i.e.*, the juvenile hormone synthesis and the trisubstituted olefin synthesis)[16] of the publication contributed by our Japanese colleagues.
16) A. Yasuda, S. Tanaka, H. Yamamoto, and H. Nozaki, *Bull. Chem. Soc. Jpn.*, **52**, 1701 (1979).
17) A.G. Davies, "Organic Peroxides," Butterworths, London, 1961, pp 189-90. Peroxide chemists apparently have known for a long time that sulfite (SO_3^{-2}) is a much better reagent for reducing hydroperoxides than is bisulfite (HSO_3^-).
18) a) J.J. Pappas, W.P. Keaveney, E. Gancher, and M. Berger, *Tetrahedron Lett.*, 4273 (1966); b) M.A.P. Dankleff, R. Curci, J.O. Edwards, and H.-Y. Pyun, *J. Am. Chem. Soc.*, **90**, 3209 (1968); c) other reduction methods are available (see R. Hiatt in "Organic Peroxides," Vol. II, D. Swern, Ed., Wiley, New York, N.Y., 1971, p 49).
19) We still occasionally experience polymerization upon distillation especially with higher-boiling epoxides. This may be due to the presence of small amounts of the Mo^{+6} catalyst. The pot residues always give a weak spot test for molybdenum, but analyses of the residues for molybdenum indicate that >95% of the molybdenum is removed by the extractions during the work-up.
20) D. Baldwin and J.R. Hanson, *J. Chem. Soc., Perkin Trans. I*, 1941 (1975).
21) M.R. Demuth, P.E. Garrett, and J.D. White, *J. Am. Chem. Soc.*, **98**, 634 (1976).
22) a) A. Murai, N. Iwasa, and T. Masamune, *Chem. Lett.*, 235 (1977); b) A. Murai, N. Iwasa, M.

Takeda, H. Sasamori, and T. Masamune, *Bull. Chem. Soc. Jpn.*, **50,** 429 (1977); c) A. Murai, H. Sasamori, and T. Masamune, *ibid.*, **51,** 234 (1978).
23) B.M. Trost, M.J. Bogdanowicz, W.J. Frazee, and T.N. Salzmann, *J. Am. Chem. Soc.*, **100,** 5512 (1978).
24) K. Yamakawa, K. Nishitani, and T. Tominaga, *Tetrahedron Lett.*, 2829 (1975).
25) T. Itoh, K. Jitsukawa, K. Kaneda, and S. Teranishi, *J. Am. Chem. Soc.*, **101,** 159 (1979).
26) S. Danishefsky, M. Hirama, K. Gombatz, T. Harayama, E. Berman, and P. Shuda, *ibid.*, **100,** 6536 (1978).
27) A. Murai, M. Ono, A. Abiko, and T. Masamune, *ibid.*, **100,** 7751 (1978).
28) T. Kato, M. Suzuki, M. Takahashi, and Y. Kitahara, *Chem. Lett.*, 465 (1977).
29) W.C. Still, *J. Am. Chem. Soc.*, **101,** 2493 (1979).
30) J.-C. Depezay and A. Durêault, *Tetrahedron Lett.*, 2869 (1978).
31) R.K. Boeckman, Jr. and E.W. Thomas, *J. Am. Chem. Soc.*, **101,** 987 (1979).
32) J.J. Partridge, V. Toome, and M.R. Uskokoviċ, *ibid.*, **98,** 3739 (1976).
33) G. Stork, Y. Nakahara, Y. Nakahara, and W.J. Greenlee, *ibid.*, **100,** 7775 (1978).
34) P.A. Bartlett and K.K. Jernstedt, *ibid.*, **99,** 4829 (1977).
35) K. Tsuzuki, Y. Nakajima, T. Watanabe, M. Yanagiya, and T. Matsumoto, *Tetrahedron Lett.*, 989 (1978).
36) M. Kobayashi, S. Kurozumi, T. Toru, and S. Ishimoto, *Chem. Lett.*, 1341 (1976).
37) S. Masamune, Y. Hayase, W. Schilling, W.K. Chan, and G.S. Bates, *J. Am. Chem. Soc.*, **99,** 6756 (1977).
38) T. Nakata, G. Schmid, B. Vranesic, M. Okigawa, T. Smith-Palmer, and Y. Kishi, *ibid.*, **100,** 2933 (1978).
39) T. Fukuyama, B. Vranesic, D.P. Negri, and Y. Kishi, *Tetrahedron Lett.*, 2741 (1978).
40) R.B. Dehnel and G.H. Whitham, *J. Chem. Soc., Perkin Trans. 1,* 953 (1979).
41) S. Yamada, T. Mashiko, and S. Terashima, *J. Am. Chem. Soc.*, **99,** 1988 (1977).
42) R.C. Michaelson, R.E. Palermo, and K.B. Sharpless, *ibid.*, **99,** 1990 (1977).
43) K. Oshima and K. B. Sharpless, unpublished results.
44) R. Breslow and L.M. Maresca, *Tetrahedron Lett.*, 623 (1977).
45) P. Chamberlain, M.L. Roberts, and G.H. Whitham, *J. Chem. Soc. (B),* 1374 (1970).
46) P. Chautemps and J.-L. Pierre, *Tetrahedron*, **32,** 549 (1976).
47) P.J. White, M.J. Kaus, J.O. Edwards, and P.H. Rieger, *Chem. Commun.*, 429 (1976).
48) Nucleophiles have long been thought to attack peroxidic reagents in this manner (*i.e.*, S_N2 process): a) J.O. Edwards in "Peroxide Reaction Mechanisms," J.O. Edwards, Ed., Wiley, New York, N.Y., 1962, pp 67-106; b) A.O. Chong and K.B. Sharpless, *J. Org. Chem.*, **42,** 1587 (1977). For the particular case of peracid epoxidations, a number of authors have favored this backside attack by the olefin along the axis of the O—O bond, for example, see: c) T. Yonezawa, H. Kato, and O. Yamamoto, *Bull. Chem. Soc. Jpn.*, **40,** 307 (1967); d) S.F. Wolf, Ph.D. thesis, University of California, Los Angeles, 1977; e) R.D. Bach, C.L. Willis, and J.M. Domagla, "Applications of MO Theory in Organic Chemistry," Vol. II, I.G. Csizmadia, Elsevier, 1977; f) B. Plesničar, M. Tasevski, and A. Ažman, *J. Am. Chem. Soc.*, **100,** 743 (1978); g) E.J. Corey, H. Niwa, and J.R. Falck, *ibid.*, **101,** 1586 (1976).
49) We had originally preferred a dihedral angle near 90° for these peracid epoxidations. We would like to thank Professor Satoru Masamune for pointing out to us that the data (Table I) appears to better fit a dihedral angle near 120°. Pierre had earlier proposed 120° as a possible preferred dihedral angle.[46]
50) R. Hiatt, "Oxidation," Vol. 2, R.L. Augustine, Ed., Marcel Dekker, New York, N.Y., 1971, Chap. 3.
51) B.E. Rossiter, R.C. Michaelson, L.E. Khoo, and K.B. Sharpless, unpublished results.
52) We are at present uncertain of the reason(s) for the beneficial effect of anhydrous disodium hydrogen phosphate. Dr. Jeff White of Oxirane has pointed out that the effect of Na_2HPO_4 is probably related to the already known beneficial effect of basic additives on these reactions. See Ref. 6 for details.
53) Most of our early development work on this problem was done using benzene as the solvent. Benzene is an ideal solvent for these epoxidations, but for obvious reasons we decided to move away from it. We have found that dichloroethane, with its similar boiling point and its similar ability to remove water azeotropically, is a good alternative to benzene. However, it must be pointed out that benzene is the best solvent we have ever found for these epoxidations. Anhydrous solutions of TBHP in benzene are more stable than those in dichloroethane, and the Mo^{+6}-catalyzed radical decomposition of TBHP is more serious competition for the desired epoxidation pathway in dichloroethane than it is in benzene. However, given the toxicity problem with benzene, dichloroethane is the best alternative solvent we have found to date.
54) a) M.A. Umbreit and K.B. Sharpless, *J. Am. Chem. Soc.*, **99,** 5526 (1977); b) when the reaction was performed on a 1-mol scale and followed by BH_4^- reduction (to reduce the α,β-unsaturated aldehyde by-product), a 55% distilled yield was realized: D.J. Scheffel and K.B. Sharpless, to be submitted to *Org. Syn.*
55) B. Chabaud and K.B. Sharpless, *J. Org. Chem.*, **44** 4202 (1979).
56) This distillate (aqueous phase = 20ml, organic phase = 555ml) contains *ca.* 0.9 mole of TBHP which co-distills along with the dichloroethane and the water (90% of this TBHP is in the organic phase of the distillate). Co-distillation of TBHP also occurs when benzene is used as the azeotropic solvent, but occurs only to a very slight extent when CH_2Cl_2 is the azeotropic solvent.
57) We have no proof that these solutions are truly anhydrous. The important fact is that they are highly effective for the Mo^{+6}-catalyzed epoxidations of isolated olefins.
58) a) This procedure was adapted from that described in the October, 1971 technical bulletin available from the Oxirane Corporation. Place 2ml of glacial acetic acid and 25ml of isopropanol in a 250ml Erlenmeyer flask. Mix the contents and add 10ml of a freshly prepared sodium iodide-isopropanol solution prepared by refluxing a mixture of 22g of NaI in 100ml of isopropanol, followed by cooling to room temperature and filtering. Add an accurately measured sample of the TBHP solution (containing no more than 2.5mmoles of active oxygen) and gently reflux for 30 sec. After dilution with 100ml of distilled water, immediately titrate the solution with 0.1*N* sodium thiosulfate (E.M., "Titrasol") to the disappearance of the yellow iodine color. Starch indicator solution may be used toward the end of the titration to enhance the endpoint. The concentration is calculated according to the equation: [S x N]/[2 x (ml of sample)] = molarity of TBHP solution, where S = ml of thiosulfate for titration and N = normality of thiosulfate. b) Molarity $\cong$ A/[(0.10A) + (0.18B)] where A = integration of *tert*-butyl resonance ($\sim$ 1.25 δ) and B = integration of dichloroethane resonance ($\sim$ 3.70 δ).
59) We have prepared, by this azeotropic technique, anhydrous solutions of TBHP in a variety of organic solvents. We have stored these solutions for at least 6 months at room temperature with no significant loss of titer. However, such solutions prepared from chlorinated solvents (*e.g.*, CH_2Cl_2, $ClCH_2CH_2Cl$, $CHCl_3$, and CCl_4) all seem to very gradually release a gas (presumably oxygen); if the container is opened every few weeks, one notices a hissing sound. This has never caused us any trouble, but we would not recommend that large quantities of such solutions be stored in sealed vessels for long periods of time. In contrast to this behavior, we have found that azeotropically dried solutions of TBHP in benzene, toluene, cyclohexane, ethyl acetate and *tert*-butyl alcohol seem to be completely stable (no out-gassing) when stored in sealed containers at room temperature.
60) **It is especially important to remove the heat source, during TBHP addition, in large-scale epoxidations. The reaction is exothermic and refluxing will be sustained by gradual addition of the TBHP solution.** In small-scale epoxidations, especially with less reactive olefins (*e.g.*, 1-decene), it may be necessary to maintain heating to sustain reflux.
61) K.B. Sharpless and K. Akashi, *J. Am. Chem. Soc.*, **98,** 1986 (1976).
62) K. Akashi, R.E. Palermo, and K.B. Sharpless, *J. Org. Chem.*, **43,** 2063 (1978).
63) K.A. Hofmann, *Ber.*, **45,** 3329 (1912).
64) N.A. Milas and S. Sussman, *J. Am. Chem. Soc.*, **58,** 1302 (1936).
65) a) V. VanRheenen, R.C. Kelly, and D.Y. Cha, *Tetrahedron Lett.*, 1973 (1976); b) S.D. Larsen and S.A. Monti, *J. Am. Chem. Soc.*, **99,** 8015 (1977).
66) S.G. Levine and B. Gopalakrishnan, *Tetrahedron Lett.*, 699 (1979).
67) S. Current and K.B. Sharpless, *ibid.*, 5075 (1978).
68) N. Rabjohn, *Org. React.*, **24,** 261 (1976).
69) H.E. Paaren, D.E. Hamer, H.K. Schnoes, and H.F. DeLuca, *Proc. Nat. Acad. Sci. U.S.A.*, **75,** 2080 (1978).
70) a) O. Campos and J.M. Cook, *Tetrahedron Lett.*, 1025 (1979); b) F.W. Sum and L. Weiler, *J. Am. Chem. Soc.*, **101,** 4401 (1979).
71) B. Chabaud and K.B. Sharpless, unpublished results.
72) R. Hiatt in "Organic Peroxides," Vol. II, D.Swern, Ed., Wiley, New York, N.Y., 1971, pp 1-151.
73) **This (Lucidol-TBHP-70) is the one commercial grade of TBHP which should not be used for the metal-catalyzed oxidations discussed in this review.** The problem is that it contains 19% di-*tert*-butyl peroxide (DTBP). DTBP will largely survive the reactions and then will present problems during work-up and distillation. The presence of DTBP also greatly lowers the thermal stability of TBHP. Lucidol-TBHP-70 should not be confused with Lucidol-TBHP-70X. The latter is equivalent to Oxirane's "Aqueous TBHP-70."
74) This is equivalent to Aldrich's 18,471-3, Lucidol-TBHP-70X, and Witco Chemical's USP-800.
75) Oxirane Aqueous TBHP-70, Lucidol-TBHP-90, and Lucidol-TBHP-70.
76) a) B. Chabaud, L.E. Khoo, B.E. Rossiter, D.J. Scheffel, and K.B. Sharpless, unpublished results. b) The TBHP solutions generated by phase separation are slightly less reactive, presumably because they contain a little more (*ca.* 1-3% more) water than the solutions made from commercial 90% TBHP.
77) G. Sosnovsky and D.J. Rawlinson in "Organic Peroxides," Vol. II, D. Swern, Ed., Wiley, New York, N.Y., 1971, pp 153-268.
78) L.F. Fieser and M. Fieser, "Reagents for Organic Synthesis," Vol. I, Wiley, New York, N.Y., 1967, pp 88-89.
79) Shell Development Company, private communication.
80) TBHP reacts very slowly with starch-iodide test paper. Therefore, commercially available starch iodide test paper is acidified with a few drops of 1-3*N* hydrochloric acid solution. Then a few drops of the solution to be tested are placed on the wet, acidified test paper.
81) We have observed peroxyketal and peroxyacetal formation with TBHP and ketones and aldehydes in CH_2Cl_2 in the presence of catalytic amounts of SeO_2: I. Takagi, B. Chabaud, and K.B. Sharpless, unpublished results,
82) A looseleaf folder entitled "Organic Peroxides" is available from the Lucidol Division of the Pennwalt Corporation. It contains numerous, very useful bulletins on all aspects of the commercially available organic peroxides.
83) A number of very informative technical data sheets on TBHP are available from Oxirane Corporation.
84) E.S. Shanley in "Organic Peroxides," Vol. III, D. Swern, Ed., Wiley, New York, N.Y., 1972, Chap. V.
85) Y. Kishi, private communication.

About the Authors

Dr. Sharpless received a B.A. degree from Dartmouth College in 1963 and his Ph.D. from Stanford University in 1968. He was a professor at the Massachusetts Institute of Technology from 1970-1977 and has been Professor of Chemistry at Stanford University since 1977. He received an A.P. Sloan Fellowship and a Dreyfus Teacher-Scholar Award in 1973.

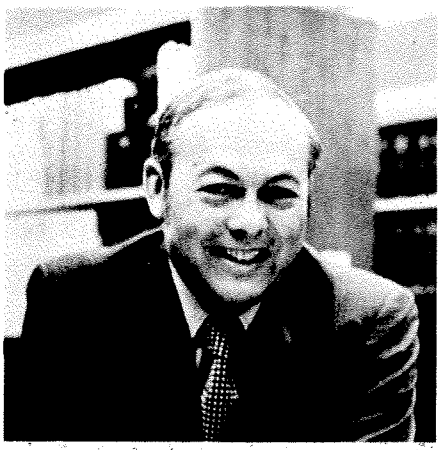
His present research interests include the

development of new homogeneous catalysts for the oxidation of organic compounds, utilization of inorganic reagents to effect new synthetic transformations in organic chemistry, and the asymmetric oxidation of organic compounds.

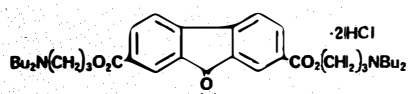
Dr. Verhoeven obtained his Ph.D. from the University of Wisconsin in 1979 and is currently a postdoctoral fellow with Dr. Sharpless at Stanford.

Tilorone, Its Analogs, and Developments in Chemical Immunology *

Robert H. Levin, Ph.D.
Research/Management Consultant
906 Oregon Trail
Cincinnati, Ohio 45215



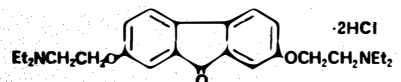
Slightly more than ten years ago an *in vivo* screen for antiviral activity developed by researchers R.F. Krueger and G.D. Mayer at the Cincinnati Research Center of Richardson-Merrell, showed that bis(3-dibutylaminopropyl)-9-oxofluorene-2,7-dicarboxylate dihydrochloride (I) was



(I)

effective in protecting mice against lethal encephalomyocarditis.

Intensive classical "molecular modification" of this compound resulted in the development of Tilorone (II) and its



(II)

analogs as a new class of orally active, small-molecule immunomodulating agents.

*A bibliography containing over 250 literature references on Tilorone and analogs is available on request.

Starting with the demonstration of broad-spectrum oral antiviral activity, further studies revealed that Tilorone is an inducer of interferon, a stimulator of the reticuloendothelial system and of cell-mediated immunity, and, paradoxically, can also function as an immunosuppressant.

Today, after almost a decade of studies as reported in more than 250 international publications and countless meetings, new and selective biochemical, pharmacologic, and immunologic effects of Tilorone are still being discovered.

The immune system is an enormously complicated mechanism, with hundreds of interacting components that together protect the body from infective microorganisms and other foreign substances. It now appears to have some involvement in almost every disease state.

The whole concept of immunology has changed in the last ten years. In addition to the use of vaccines to stimulate the production of antibodies, now there is also a much broader approach — intervention in the intricate chemistry of the immune processes themselves.

Immunology has thus emerged as an entirely new field with tremendous opportunities for rapidly expanding basic biomedical knowledge. We are beginning to understand many of the chemical connections between abnormal immune processes and specific disease. Scientists of diverse disciplines are using this information to search for drugs that will correct the abnormal mechanisms, and thereby either control or cure many diseases. Tilorone is a prime example of this new group of immunoactive compounds which can demonstrate a broad range of biological activities related to the whole subject of host defense.

In the laboratory the study of immunoactive molecules is providing new insights into the complexities of the immune process, at the enzyme/biochemical, molecular, cellular, tissue, organ, and whole-animal levels.

Advantageously, these studies can now be conducted with pure chemical substances rather than with less well defined natural-product isolates. By comparison, even today, after decades of study, materials such as BCG, C-parvum and ALG may give different results in different laboratories.

Further, at the clinical level, it is generally agreed that these newly recognized substances (Tilorone, Levamisole, thymic hormone fractions, muramyl dipeptide analogs, etc.) represent, collectively, exciting leads to the treatment of disease by modulation of host defense mechanisms. The elucidation of these biological activities will certainly prove intellectually satisfying, and must ultimately prove to be of great importance in human therapeutics.

Tilorone: What Does It Do?

The new immunology has resulted in the blurring of the boundaries of the classical scientific disciplines. Nevertheless, laboratory studies with Tilorone may be listed (somewhat arbitrarily) under the following areas and subjects:

A) Immunology/immunobiology/-cellular immunology
B) Immunopharmacology and immunopathology
C) Virology/viral chemotherapy
D) Interferon/interferon induction
E) Cancer
F) Enzyme and molecular biochemistry
G) Microbiology and immunogenetics.

A. IMMUNOLOGY

Table I summarizes the effect of Tilorone hydrochloride on antibody response. Tilorone increases IgM and IgG antibody production in the Jerne Plaque assay in mice and the IgE antibody production in rats using the passive cutaneous anaphylaxis (PCA) model in rats. Tilorone enhances hemagglutination antibody (HA) titer to sheep red blood cell (SRBC) in mice. It also enhances thymus-dependent (sheep red blood cells) as well as thymus-independent (*E-coli* lipopolysaccharide) antibody production. Finally, Tilorone serves as an adjuvant for influenza vaccine when given simultaneously at the same site with the vaccine, or when given at a different site from the vaccine in guinea pigs.

Table 2 summarizes Tilorone's effects on cell-mediated immune responses. Tilorone prevents the paralysis associated with experimental allergic encephalomyelitis (EAE) in Lewis rats. When administered to rats, Tilorone completely inhibits the paw edema associated with adjuvant polyarthritis prophylactically, and it suppresses, to a lesser degree, the inflammation when given therapeutically. Tilorone completely inhibits the tuberculin skin reaction in rats and guinea pigs when administered at the same time as the antigen, or after a tuberculin skin reaction has been established. Tilorone completely inhibits the local graft-*versus*-host reaction in the F_1 hybrid Lewis x Brown Norway recipient rat when administered to the donor parent Lewis rat prior to the transfer of the spleen cells to the recipient. Lastly, Tilorone significantly delays the rejection of skin and heart transplants in rats and kidney transplants in dogs.

In addition to the results summarized in Tables 1 and 2, Tilorone appears to have the paradoxical property of stimulating antibody production by way of the B-lymphocyte, while simultaneously suppressing T-lymphocyte function. The reason for this paradoxical action was clarified in part by Merrell scientists and others who showed that after an initial lymphopenia and depletion of lymphocytes from the T-lymphocyte areas in spleen, lymph node and Peyer's patches, a rebound phenomenon took place in which the T-lymphocytes in the peripheral blood were replaced by B-lymphocytes. Furthermore, there were significant increases in the numbers of B-cells in the spleen. Therefore, it was concluded that Tilorone selectively suppressed the T-cell and its function, and increased the B-cell and its function, namely, antibody production. Thus, from an immunologic point of view, Tilorone represents a unique compound.

B. IMMUNOPHARMACOLOGY

In the broad area of inflammation, Tilorone again presents a paradox in that it shows broad-spectrum anti-inflammatory action using classical (pharmacologic) as well as immune-mediated anti-inflammatory animal test systems.

Table 1

Effect of Tilorone Hydrochloride on Antibody Responses

1. Increases IgM and IgG antibody production
2. Increases IgE antibody titers
3. Increases HA antibody to SRBC
4. Enhances T-cell- and B-cell-dependent antibodies
5. Acts as adjuvant for influenza vaccine

P.F. Hoffman, *et al.,* Advances in Antimicrobial and Antineoplastic Chemotherapy, **1,** Urban and Schwarzenberg, Munich, 1972, p 217.
A.E. Munson, *et al., Cancer Research,* **32,** 1397 (1972).
H. Megel, *et al., Proc. Soc. Exp. Biol. Med.,* **145,** 513 (1974).

Table 2

Effect of Tilorone on Cell-Mediated Immune Responses

1. Prevents paralysis in EAE model
2. Suppresses paw edema in adjuvant-arthritis
3. Inhibits tuberculin skin reactions
4. Inhibits local GVH response
5. Delays rejection of skin and heart transplants

H. Megel, *et al., Proc. Soc. Exp. Biol. Med.,* **145,** 513 (1974).
A. Wildstein, *et al., Transplantation,* **21,** 129 (1976).

Table 3 presents comparative antiarthritic profiles of Tilorone and other representative antiarthritic compounds. In the complement-dependent Arthus screen in which an inflammation of the rat paw is induced, Tilorone and several other analogs markedly inhibited the paw edema. Of the non-steroidal anti-inflammatory compounds, only large doses of aspirin suppressed the Arthus reaction. Phenylbutazone and indomethacin suppressed the response slightly, if at all. In addition, Tilorone was active in the classical anti-inflammatory test. It inhibited the carrageenan-induced abscess and carrageenan-induced paw edema in rats. This anti-inflammatory activity of Tilorone was also observed in adrenalectomized rats.

It is evident from these pharmacologic and immunologic studies that the biologic properties of Tilorone hydrochloride meets new, more "rational" criteria for selecting a chemical compound for clinical trial in the treatment of rheumatoid arthritis; more specifically, Tilorone has been shown to inhibit an immunologically-induced inflammatory reaction and to selectively inhibit a variety of cell-mediated immune responses.

The immunologic properties of Tilorone further suggest additional possible medical applications — in the prevention of homograft rejection and in the treatment of cancer. It is well documented that the initial rejection phenomenon of transplants is a result of a cell-mediated immune process, where the T-lymphocytes of the graft recipient recognize the antigenic determinants on the graft itself as foreign and cause its rejection. The use of general immunosuppressants, prednisolone, cyclophosphamide and the like, and more recently, antilymphocytic globulin (ALG), that selectively suppresses T-lymphocyte function, has been shown to delay significantly homograft rejection. However, a major problem in the clinical evaluation of ALG is associated with the need to establish specifications for the "biological preparation" which would enable different investigators to work with standardized material having reproducible biological end points.

Tilorone has also been reported to prevent the rejection of skin transplants in mice, heart transplants in rats, and kidney transplants in dogs. As summarized in Table 4, Tilorone shares many of the reported attributes of ALG. It also has antiviral activity in various animal species. Further, Tilorone would appear to have a potential advantage over ALG in that it is a well defined, synthetic organic substance, which is also orally active.

C. ANTIVIRAL ACTIVITY

The antiviral activity of Tilorone has been demonstrated in mice, rats, rabbits, and primates, as evidenced by an increased number of survivors, increased length of survival times, prevention of viremia, prevention of antibody response to live virus, and attenuation of eye and skin lesions. Activities are primarily observed with prophylactic regimens and can be obtained with oral, topical, or parenteral treatment, depending on the type of infection. Viruses against which Tilorone or its analogs were found to be effective in laboratory animal experimentation include: Semliki Forest (SF) virus, encephalomyocarditis viruses, Venezuelan equine encephalomyelitis (VEE) virus, influenza viruses, herpes virus, vaccinia virus, vesicular stomatitis (VS) virus, tick-borne encephalitis (TBE) virus, foot-and mouth disease (FMD) virus, Friend leukemia virus, scrapie virus, Spring-Summer meningoencephalitis virus, and flaviviruses.

Table 3

Comparison of Tilorone's Actions With Representative Anti-arthritic Compounds

Compound (mg/kg)	Carrageenan Paw Edema	Arthus Paw Edema	Adjuvant Arthritis			EAE	PFC Antibody
			Prophyl.R_x Paw Edema	Therap. R_x Paw Edema	TB Skin Reaction		
Tilorone 25-100 p.o.	↓	↓	↓	↕	↓	↓	↑
Phenylbutazone 50-100 p.o.	↓	—	↓	↓	—	—	—
Hydrocortisone 10-25 s.c.	↓	—	↓	↓	↓	↓	↓
Cyclophosphamide 5-25 p.o.	—	—	↓	—		↓	↓

↓ Suppresses, ↕ Slightly Suppresses, ↑ Enhances, — No Effect

Composite table from H. Megel, *et al., Proc. Soc. Exp. Biol. Med.*, **149**, 39 (1975). M.E. Rosenthale, *Anti-inflammatory Agents*, **11**, 123 (1974).

Although generally less active than amantadine, Tilorone was more active than this anti-influenza compound if the virus was given by aerosolization instead of by nasal instillation.

Tilorone was also an effective antiviral agent in many tissue culture systems.

D. INTERFERON

Interferon was discovered in 1957 by Isaacs and Lindermann. The concept of a natural substance produced by cells and effective against a wide range of viruses excited the imagination of chemotherapists. Interferon is formed by immune stimulation involving sensitized lymphocytes. Gradually over the years, it has come to be recognized that there is a family of interferons. Initially interferons were found to be species-specific. More recently, even within a single species, interferons are being differentiated. Tilorone has played a role in this research, starting with its characterization as a small-molecule, orally active inducer of interferon.

INTERFERON INDUCERS

Interferon is produced (induced) when the body's natural defenses are called upon in response to various stimuli. The first interferon inducers known were the viruses themselves. It was possible to show that viruses, when injected into animals, needed an intact genome to induce interferon. In this respect, the most active viruses are those whose replicative form is a double-stranded RNA (DS-RNA), or those like reoviruses whose nucleic acid is of the double-stranded type throughout their replication.

Such observations led the *Merck group* to show that a synthetic homopolymer pair of polyriboinosinic and polyribocytidylic acids (in short, poly-I:C) may be regarded as a model of inducers of the double-stranded RNA type. As with most immunopharmacological agents, poly-I:C and other natural and synthetic DS-RNA's exert quite diverse and sometimes opposite effects on immune reactions, depending on dosage, time, and route of administration.

Table 4

Effect of Tilorone and ALG on Cell-Mediated and Other Immune Responses

Immune Response	Tilorone	ALG
EAE	↓	↓
Adjuvant arthritis	↓	↓
Tuberculin skin reactions	↓	↓
GVH	↓	↓
Transplant rejection	↓	↓
Antibody responses	*Increases*	*Increase or no effect*
Spleen and lymph node	*Transient T-cell depletion*	*T-cell depletion*
WBC	*Transient lymphopenia*	*Lymphopenia*

↓ suppresses

H. Megel, *et al.*, personal data; editorial, *Brit. Med. J.*, **1**, 644 (1975).

Immunostimulating substances like poly-I:C and other synthetic and natural DS-RNA's cause abnormalities in the lymphoid system of adult mice, concomitant thymic atrophy, and splenic hypoplasia.

In the search for effective and safe interferon inducers many natural sources have been found from which double-stranded polyribonucleotides could be extracted, in most cases in a relatively low yield. In general, these natural products have behaved, *in vivo* and *in vitro*, like the synthetic polynucleotides described above. Two antiviral agents isolated very early, helenine and statolon, were later found to be identical with the DS-RNA from the mycophages latently infecting the fungi producing these agents. In most experimental systems the minimal effective antiviral doses of the two natural inducers were of the same order of magnitude as those of poly-I:C. Data about many other interferon inducers and immunostimulating substances of natural origin are scanty since few of these were isolated in sufficient quantity for systematic testing.

An important discovery was reported in 1970 (from the Merrell National Laboratories). It was found that a synthetic compound of relatively simple structure possessed an *in vivo* broad-spectrum antiviral activity in mice and was capable of inducing the production of significant levels of serum interferon following oral or parenteral administration to rodents.

One must remember that interferon-inducing double-stranded polynucleotides are totally devoid of activity when given orally. This synthetic compound, named Tilorone, was extensively studied in many laboratories, and its immunopotentiating activities, of which interferon induction is but one aspect, were soon recognized.

INTERFERON AND THE LYMPHOKINE/CYTOKINE SYSTEM

It has become increasingly clear over the past few years that interferons are not wholly unique biological substances, but must be included among a group of so-called lymphokines or cytokines, all formed concurrently. Literally dozens of these factors have been reported, and the nature of the experimental process has made

replication of many of these results difficult from laboratory to laboratory. Figure I illustrates some of the more commonly accepted factors such as interferon, migration inhibition factor (MIF), transfer factor, cytotoxic factors, and mitogenic factors.

E. CANCER

In common with other immunomodulators, Tilorone shows a wide spectrum of activity against a variety of experimental (and human) tumors including:

A) the ascitic Walker 256 carcinosarcoma (R. Adamson, 1971)
B) leukemia L 5178Y, Novikoff hepatoma (R. Adamson, 1971)
C) Ehrlich carcinoma solid tumor, Friend leukemia virus (Munson, 1972)
D) a syngeneic murine lymphoid leukemia MCAS-10 (Pearson, 1974)
E) malignant hepatomas 3924A, 7777, 5123A, and 7794A (Rhoads, 1973)
F) an acute lymphocytic leukemia arising in a BALB/cX DBA/$2F_1$ mouse that is morphologically and pathologically similar to human acute lymphocytic leukemia and is generally resistant to alkylating agents and somewhat less resistant to vincristine and prednisolone (Yancey, 1974)
G) In a Phase I study of Tilorone with metastatic melanoma previously untreated by chemotherapy, partial responses were obtained without marrow depression (G.L. Wampler, 1973).
H) When administered to C57BL mice with drinking water in a daily dose of about 50mg/kg for a year, Tilorone significantly retarded the appearance of tumors induced by a single subcutaneous dose of 120μg methylcholanthrene (MC) dissolved in olive oil. Several signs of chronic toxicity were observed. No co-oncogenic effect of Tilorone was found (Glaz, 1974).
I) Tilorone, given orally at weekly intervals to rats, was effective against Walker 256 carcinosarcoma and Morris hepatoma 7777 and 3924A. This inhibition did not relate to interferon levels (Walker, 1974).

F. ENZYME AND MOLECULAR BIOCHEMISTRY

Tilorone is a specific inhibitor of DNA polymerases from RNA tumor viruses (Chandra, 1972). Product analysis of the DNA-polymerase reaction (Friend leukemia virus) in the absence and in the presence of Tilorone ($1 \times 10^{-4} M$) showed that it specifically blocked the formation of double-stranded DNA (Chandra, 1974). Tilorone and its analogs appear to render polynucleotides ineffective as template/primers by physically binding to them by intercalation (Smith, 1974).

The mechanism of action for Tilorone's stimulation of interferon is believed to be inhibition of protein synthesis (Cahn, 1973).

On drug distribution studies, Tilorone is subcellularly concentrated in the nucleus. The highest levels are found in the liver and spleen, and the brain receives an equal share of drug as compared to the spleen at 16 hours (Gaur and Chandra, 1973; Walker, 1972).

Although various interferon inducers (*e.g.*, pyran) are thrombocytopenic agents both *in vivo* and *in vitro*, Tilorone may actually increase blood platelet levels. *In vitro* Tilorone exerts antiplatelet effect through a photoactivation process (Matyasova, *et al.*, 1974).

Tilorone activates plant phenylalanine ammonia lyase (Hadwiger, 1972). Administration of Tilorone to rodents results in an increase in serum complement levels (Raychaudhuri, 1977).

Another interesting feature of Tilorone is the depression of the cytochrome P450 monooxygenase system (Leeson, 1976; Renton, 1976).

G. MICROBIOLOGY AND IMMUNOGENETICS

Tilorone and its analogs can stimulate phagocytic function in liver and spleen (Munson, 1972; Regelson, 1970). As with other immunoregulators and/or interferon inducers, the route of administration is critical. Tilorone can abort foot-and-mouth disease in mice when it is given in drinking water (Richmond, 1973), and is a potent stimulator of phagocytosis when given by mouth (Regelson, 1974). When Tilorone is given subcutaneously it is not as effective in the same experiment.

The effect of Tilorone on bacterial infections varies with the organism, route and timing of treatment, and other factors not yet elucidated, thus, some Tilorone analogs increased the resistance of mice to *S. aureus* providing the drug was injected 24 hours before challenge. No protection was afforded against *D. pneumonia* (Wampler, 1972; Munson, 1972).

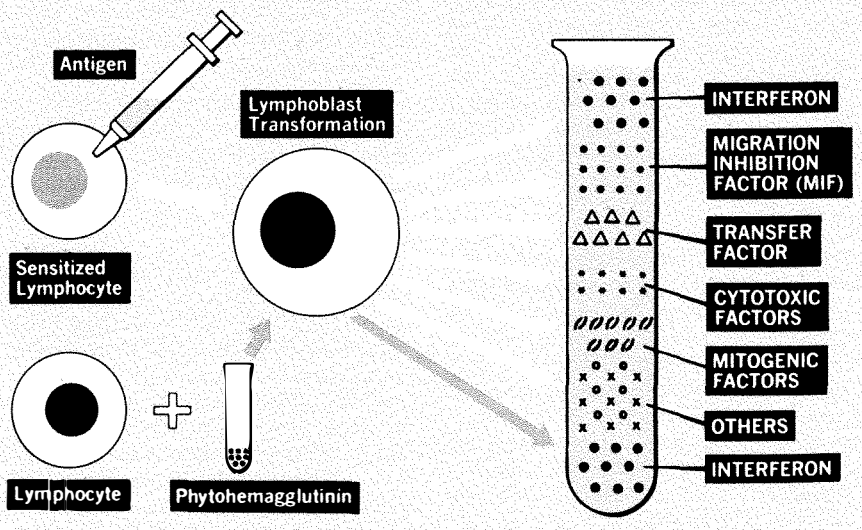
Tilorone Analogs Provide New Opportunities in the Laboratory

The opportunities for new research with Tilorone analogs lie in two directions. One is to sort out and further dissect the paradoxical activities exhibited by Tilorone in various biological systems. A second, and perhaps more attractive prospect, is to seek among these bis-basic substituted polycyclic molecules, those showing the greater specificities of biological action required for immunotherapy.

In limited studies reported to date, in the areas of antiviral activity, immune-regulation, inflammation, enzyme inhibition, etc., **Tilorone analogs** have demonstrated a range and spectrum of activities. This fact is best illustrated by Table 5 which summarizes the biological responses of eight of the analogs now being offered to the research community by Sigma-Aldrich in comparison with Tilorone. It is evident, and not unexpected, that no two compounds provide the identical spectrum of biological responses.

When we examine in greater detail, in

Figure I
Lymphokine/Cytokine Formation by Immune Stimulation



Sensitized lymphocytes in the presence of specific antigen and phytohemagglutinin are known to undergo blast transformation and to release many biologically active substances thought to be important in specific cellular immunity.

Reprinted with author's and publisher's permission from M. Ho, *Resident and Staff Physician*, October 1973, p 52.

Table 5

Summary of the Biological Responses of Tilorone Hydrochloride and Related Compounds[a]

Compound (RMI number)	Acute LD_{50} (mg/kg. mouse) oral	sc[b]	Interferon oral	sc[b]	Antiviral: *in vitro* Herpes	VSV[c]	vaccinia mouse	EMC mouse	SFV mouse	VEE mouse	VEE monkey	Flu mouse	Herpes mouse oral top.[b]	Herpes rabbit oral top.[b]	Immunological: Cell-mediated response EAE rat	adjuvant arthritis rat pro.[d]	adjuvant arthritis rat ther.[d]	Tuberculin skin response guinea pig pro.[d]	Tuberculin skin response guinea pig ther.[d]	MMIT *in vitro*	Humoral antibody mouse IgM	Humoral antibody mouse IgG	Anti-inflammatory: carrageen rat edema	carrageen rat abscess	Passive Arthus reaction rat	Anticancer: rat/mouse	*in vitro*	R.T.[e]
Tilorone	1520	111	+	+	+	0	+	+	+	+		+	0 +	+	↓	↓	↓	↓	↓	0	↑	↑	↓	↓	↓	+		+
9563 DA	>4000	684	0	+	0	+	0	+	+			0			↓					0	↑	0	↓	0	↓	+	+	+
10,024 DA	1560	110	+	+	+	0	+	+	+			0			0					0	0	↑		0		+	+	+
10,874 DA	1780	353	+	+	+		+	+	+	+		0			↓					+	↑	↑	↓	0		+	+	+
11,002 DA	5000	353	+	+	0	0	0	+	+	+	+	0	0 +	0 0	↓	↓	↓	↓	↓	+	↑	↑	↓	↓	↓	+	0	+
11,513 DA	1410	304	+	+	+	0	0	+	+			+			0					+	0	↑		0		+	+	
11,567 DA	2700	1000	+	+	0	0	+	+	+	+	+	0	0 +	0 0	↓	↓	0	↓	↓	+	↑	↑	↓	+	↓	+	+	0
11,645 DA	2590	930	+	+		+	0	+	+			0			↓					+	↑	↑	0		0	0	+	
11,877 DA	2930	820	+	+	+	0	+	+	+	+	+	+	0 +	+ +	↓	↓	0	↓	↓	+	↑	↑	↓	0	↓	+	+	

[a]Symbols: + - active, 0 - inactive, no entry - not tested, ↓ - suppression, ↑ - enhancement.
[b]sc - subcutaneous, top. - topical administration.
[c]photoinactivation.
[d]pro. - prophylactic, ther. - therapeutic treatment.
[e]Reverse Transcriptase.

Table 6, the more precise activities of a group of Tilorone analogs (selected as candidates for clinical trial), we find an even greater range of quantitative differences in such biologic properties as interferon induction, antiviral activity, anti-inflammatory action, and even LD_{50} values.

In a recent study of the enzymatic activities of a group of Tilorone analogs DiCloccio (1978) commented that "although some or all of these compounds have been shown to induce interferon, stimulate the immune system, and inhibit the DNA polymerase activity of several RNA tumor viruses, none of these effects completely explains the antitumor action of these compounds."

Fine Tuning the T-Lymphocyte System

The immunoregulatory properties of Tilorone are probably related to its initial ability to deplete thymus-derived (T) lymphocytes. This is followed by an increase in B-cells, macrophages and probably new subpopulations of T-cells which cell biologists can now characterize using more sophisticated methodology.

Some T-cells can function as helper T-cells, so named because their presence helps B-cells to produce antibodies. Other T-cells can become killer cells, *i.e.*, lymphocytes that attack foreign tissues or foreign organisms directly. A third type of T-cell functions as suppressor lymphocytes, retarding the production of antibodies. This function may be important in regulating immunity.

In one series of studies mice were challenged with allogeneic leukemia L1210 cells. Tilorone administered without antigen proved capable of creating "killer" lymphocytes. However, Tilorone in this experiment did not exert a truly adjuvant effect as it did not increase the response to concomitant antigen. Thus, Tilorone resembled BCG and C-parvum in their action. However, in other tumor and viral systems, Tilorone and its analogs cause ad-

Table 6

Biologic Properties of Selected Tilorone Analogs

ACTIVITIES	Tilorone	RMI 11,002 DA	RMI 11,567 DA	RMI 11,877 DA	RMI 9,563 DA
LD_{50}, mg/kg, p.o.	1530	5000	2700	2930	>4000
s.c.	111	353	1000	820	684
Anti-inflammatory percent reduction (100 mg/kg, rat, p.o.)					
Carrageen paw	47	35	19	17	53 (s.c.)
Carrageen abscess	40	40	0	21	45 (s.c.)
Adjuvant arthritis	39	41	25	41	
Arthus	90	49	43	42	92 (s.c.)
Complement (*in vitro*) percent inhibition, $10^{-4}M$	0	0	0	0	80
Antiviral Activity					
EMC (percent increase mean survival time, 250 mg/kg, p.o., -22 hr.)	137	123	145	129	116 (s.c.)
Vaccinia (percent decrease tail lesion score, 250 mg/kg, s.c.)	89	28	66	79	26 (100mg/kg, s.c.)
SFV (percent survivors, 250 mg/kg, p.o., -24 hr.)	100	100	100	100	40 (100mg/kg, s.c.)
Interferon Induction					
Reciprocal of interferon titer (peak time hr.) 250 mg/kg, p.o.	6,400 (24)	3,200 (12)	25,600 (24)	6,400 (12)	800 (24) (500mg/kg, s.c.)

juvant effects in addition to selective changes in the T-lymphocyte subpopulation.

Tilorone is believed to augment cell-mediated immunity (CMI) in this experimental model by a direct effect upon T-lymphocytes (Friedlander, 1974).

Finally, the current interest in Natural Killer (NK) cells and their enhancement by interferon and interferon inducers, particularly Tilorone, again raises the question of mechanism of action. Here again a study of Tilorone analogs could serve to help clarify this point and perhaps accelerate the opportunity of establishing a role in cancer therapy for this exciting development.

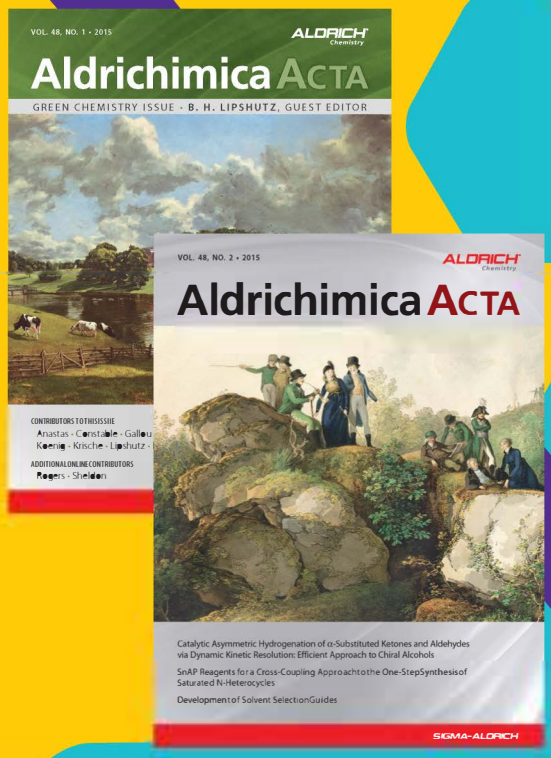
Chemical Immunology has a bright future.

About the Author

Dr. Levin earned a Bachelor's Degree in 1937 from the University of Illinois and the Ph.D. from the University of Wisconsin in 1941. He spent the next 27 years with the research staff of the Upjohn Company, closely involved with steroid, cortical hormone, and antibiotic developments. His name appears on 26 publications and 90 U.S. patents.

In 1968 Dr. Levin was elected Corporate Vice President for Research for Richardson-Merrell, Inc. with line responsibility for worldwide ethical pharmaceutical research. In 1978 he retired from Richardson-Merrell to establish his Research/Management consulting service for government and industry.

Acta Archive Indexes



The Acta Archive Indexes document provides easy access to all of the Acta content; 1968 to the present.

The volumes, issues, and content are sorted as follows:

- Chronological
- Authors
- Titles
- Affiliations
- Painting Clues (by volume)

From this index, you can jump directly to a particular volume. Using the sorted sections, you can locate reviews by various authors or author affiliation. Additionally, the content is fully searchable, allowing you to look for a particular key word from the various data available.

To access the index, **click here**.

2017-02521
02/17