Aldrichimica Acta

Volume 7, Number 1, 1974

PUBLISHED BY THE ALDRICH CHEMICAL COMPANY, INC.

Distributed by: Ralph N. Emanuel Ltd., 264 Water Road, Wembley, Middx. HA0 1PY

ALDRICHIMICA ACTA

Volume 7, Number 1
1974

Published by
ALDRICH CHEMICAL COMPANY, INC.
Milwaukee, Wisconsin

Editorial Staff: Deanna R. Cruz
David W. Griffiths
Ramona H. Jules

ALDRICH CHEMICAL COMPANY, INC.
CRAFTSMEN IN CHEMISTRY

Main Office:
940 W. St. Paul Avenue
Milwaukee, Wisconsin 53233
Telephone: (414) 273-3850

East Coast Service and Distribution Center:
10 Ridgedale Avenue
P.O. Box AA
Cedar Knolls, New Jersey 07927
Telephone: (201) 539-9494

West Coast Service and Distribution Center:
2098 Pike Street
San Leandro, California 94577
Telephone: (415) 352-1186

Southern Service and Distribution Center:
3355 Lenox Road N.E.
Suite 750
Atlanta, Georgia 30326
Telephone: (404) 233-1678

In Great Britain:
Ralph N. Emanuel Ltd.
264 Water Rd.
Wembley, Middlesex
HAO IPY, England
Telephone: 01-998 4414

In Germany:
EGA-Chemie KG
7924 Steinheim am Albuch
Kreis Heidenheim, Germany
Telephone: (07329) 302

In Continental Europe:
Aldrich-Europe
B-2340 Beerse
Belgium
Telephone: 014/61431

ABOUT THE COVER

Our chemist - collector is convinced that there are still some old masters whose ability is unappreciated, and that one of these is Leonard Bramer, the painter of this *Esther before Ahasuerus* (oil on wood, 28 ½ x 22 inches). Bramer had studied in Italy and was greatly influenced by the Venetians and Rembrandt. In fact, he provides a link between Rembrandt and the great 18th century Italian, Magnasco.

We have never greatly liked the story of Esther, and are not surprised that there was a good deal of argument by the compilers of the Bible as to whether or not this book should be included. It is not so much that we dislike stories of court intrigue as that we cringe at the all-too-kind treatment accorded King Ahasuerus, The Fool. Here is the most dangerous fool of all, the fool with power. He is not a killer himself, but a man who votes a Haman into office and then says: "Auschwitz? My Lai? Why, I never even heard of these places." Yet this fool of a king is never even criticized in the story.

Still, when we look at this beautifully balanced study of darkness and light, our admiration for its beauty overcomes our disgust for the king.

TABLE OF CONTENTS

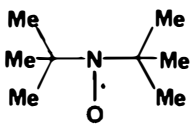
THE APPLICATION OF ELECTRON SPIN RESONANCE AND SPIN-LABELING IN BIOCHEMISTRY AND PHARMACOLOGY

Colin F. Chignell
Section on Molecular Pharmacology
Pulmonary Branch
National Heart and Lung Institute
Bethesda, Maryland 20014

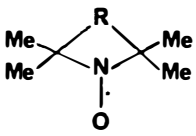
Spin-labeling is a spectroscopic technique that employs stable organic radicals as probes or reporter groups for biological macromolecules.[1-5] The first free radical to be used as a spin label was the cation radical of the phenothiazine drug chlorpromazine (I). Ohnishi and McConnell studied the binding of

I

this radical to shear-oriented DNA and found that the aromatic plane of the drug was perpendicular to the helix axis of the nucleic acid.[6] Since the chlorpromazine free radical was stable over a rather limited pH range, McConnell and coworkers sought other spin labels. In 1961, Hoffmann and Henderson had reported the synthesis of di-*t*-butyl nitroxide (DTBN) (II), a free radical that was stable in aqueous solution over a wide range of temperatures and pH values.[7] Subsequently, Rozantsev[8] in Russia and Rassat[9] in France had synthesized a large number of free radicals in which the nitroxide group was part of a heterocyclic ring system (III).



II



III

These nitroxides provided McConnell and his coworkers with the starting materials from which they prepared more specific spin labels. A wide variety of compounds containing the nitroxide free radical have now been synthesized.[1-5, 8, 9]

THE ELECTRON SPIN RESONANCE SPECTROSCOPY OF THE NITROXIDE RADICAL

When an unpaired electron is placed in a magnetic field, it may exist in one of two energy states in which its magnetic moment is aligned either parallel or antiparallel to the direction of the applied field. Transitions between these two energy states can be induced by the application of electromagnetic radiation of the appropriate energy. The relationship between the magnetic field strength *(H)* and the required frequency (ν) is given by

$$h\nu = g\beta H \qquad (1)$$

where h is Planck's constant, g is the so-called g-value for the electron, and β is the Bohr magneton, a fundamental constant for the electron. Equation (1) indicates that at resonance, the applied frequency (ν) is directly proportional to the magnetic field *(H)*, so that electron spin resonance (ESR) can be observed when either H or ν is varied. For experimental convenience, it is usual to keep ν constant while H is changed. Most commercial ESR spectrometers operate in the microwave frequency range of 9 x 10^9 Hz (or 9 GHz) so that H is approximately 3300 gauss (G).

When the nitroxide radical is present at low concentration in a non-viscous solvent, its ESR spectrum consists of three equally spaced lines of about the same height (Fig. 1). This

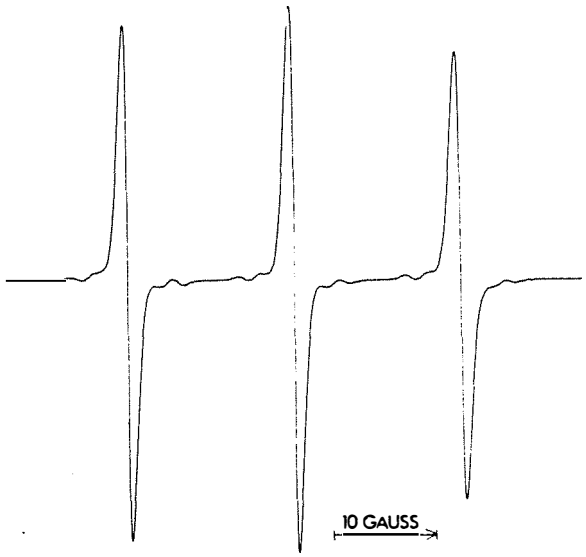


Fig. 1. The ESR spectrum of a nitroxide radical in aqueous solution.

triplet results from an interaction between the magnetic moment of the unpaired electron and the magnetic moment of the ^{14}N nucleus. In qualitative terms, the magnetic moment of the nitrogen nucleus can be aligned parallel, anti-parallel or perpendicular to the applied magnetic field. Since the magnetic field experienced by the electron is the sum of the external magnetic field and the local contribution provided by the ^{14}N nucleus, it follows that the electron experiences three different magnetic field values each of which gives rise to an absorption line in the spectrum (Fig. 1). For technical reasons, the commercially available ESR instruments display the spectrum as its first derivative instead of the simple absorption spectrum familiar to optical spectroscopists. The spectrum is characterized by three parameters: (1) the hyperfine splitting (A_o), *i.e.*, the distance (G) between adjacent lines, (2) the so-called g-factor (g_o), *i.e.*, the position of the center line in the magnetic field and (3) the peak-to-peak linewidth (G).

When a nitroxide spin label is incorporated into a host crystal, the ESR spectrum of the free radical is dependent upon its orientation with respect to the magnetic field (Fig. 2). The largest hyperfine splitting (A_{zz}) is observed when the magnetic field is parallel to the nitrogen π-orbital (z-axis) (Fig. 3). The g-values are also dependent on the orientation of

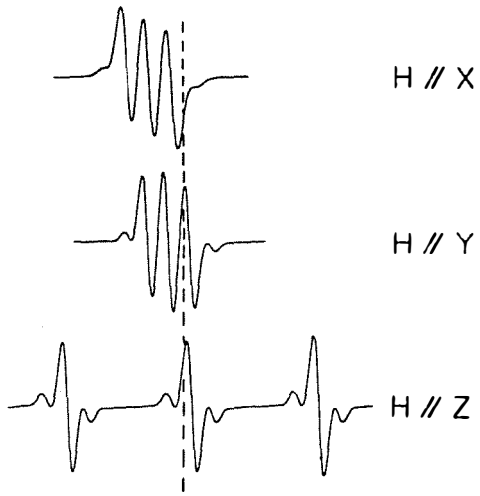


Fig. 2. The ESR spectra of 4',4'-dimethyloxazolidine-*N*-oxyl derivative of acetone oriented in the crystal 2.2.4.4-tetramethyl-1.3-cyclobutanedione (adapted from reference 26).

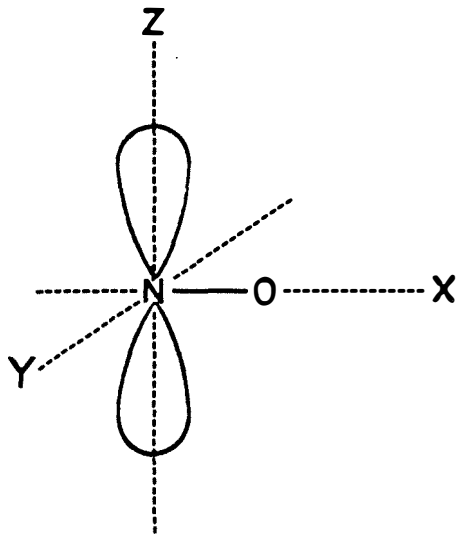


Fig. 3. The molecular coordinate system of the nitroxide group.

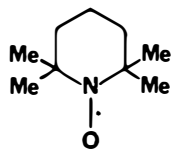
the nitroxide group (Fig. 2). At angles that lie between the three principal axes, the ESR spectra are intermediate between those shown in Fig. 2. When the crystal of nitroxide is dissolved in a solvent of low viscosity, the motion of the free radical is so rapid that its ESR spectrum appears as a triplet (Fig. 1) in which the hyperfine splitting (A_o) and g-value (g_o) are the average of the values seen in Fig. 2.

The ESR spectrum of the nitroxide radical is sensitive to changes in (1) the **polarity** of the environment of the radical, (2) the **molecular motion** of the radical and (3) the **orientation** of the radical with respect to the applied magnetic field. The ESR spectrum of the nitroxide group is modified by the presence of other paramagnetic species. Furthermore, the nitroxide group can be chemically reduced by a variety of agents with the concomitant loss of its ESR signal. While these properties make the nitroxide radical an almost ideal reporter group, it should be borne in mind that the bulkiness of the nitroxide radical may cause a large steric perturbation of its local environment.

THE NITROXIDE GROUP AS A PROBE FOR BINDING SITE POLARITY

Solvent effects on the ESR spectrum of the nitroxide radical are characterized by changes in both A_o and g_o parameters. DTBN in water yields A_o = 16.7 G and g_o = 2.0056 while DTBN in hexane is characterized by A_o = 14.8 G and g_o = 2.0061. An extensive study by Dodd *et al.* has shown that A_o decreases while g_o increases as the solvent polarity is decreased.[10] In line shape studies of moderately immobilized spin labels, the solvent dependence can be troublesome because it is difficult to estimate the effects on the principal values of A and g. However, when small, rapidly tumbling spin labels are used, the solvent effects can be useful.

Hubbell and McConnell have reported that when IV is dif-



IV

fused into an aqueous phospholipid dispersion or a rabbit vagus nerve in Ringer solution, the high field line is replaced by two lines.[11] Similar observations have been made by Jost and Griffith with the DTBN-myelin system.[12] The relative intensities of the two high field lines provide a measure of the amount of spin label in hydrocarbon and aqueous environments. McConnell and coworkers have made use of this fact to develop a method for the estimation of the fraction of lipid in a biological membrane that is in a fluid state.[13]

THE NITROXIDE GROUP AS AN INDICATOR OF MOLECULAR MOTION

When the molecular motion of a nitroxide radical in dilute solution is decreased by increasing solvent viscosity, the ESR lines of the free radical appear to broaden and the spectrum becomes asymmetric (Fig. 4). The limiting line shape is known as the rigid glass, powder or polycrystalline spectrum of the nitroxide radical. This spectrum can be thought of as a simple sum of all the spectra shown in Fig. 2 together with the spectra of all possible intermediate orientations. As a result, the splitting between the outermost peaks of the rigid glass spectrum is $2A_{zz}$, corresponding to the bottom spectrum of Fig. 2. The rigid glass spectrum is encountered whenever the spin label is randomly oriented and molecular motion is either absent or very slow on the ESR time scale, *i. e.*, when $\tau^{-1} << |A_{zz} - A_{xx}| \sim 7 \times 10^7$ sec^{-1} and $\tau^{-1} << |g_{xx} - g_{zz}| \beta Hh^{-1} \sim 3 \times 10^7$ sec^{-1} (at 9.5 GHz), where τ is the rotational correlation time.

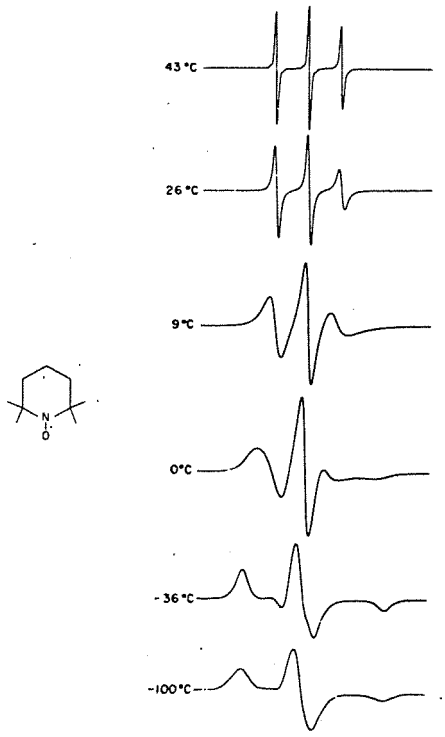
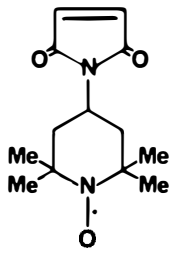


Fig. 4. The effect of solvent viscosity on the ESR spectrum of 2.2.6.6-tetramethylpiperidine-1-oxyl (5×10^{-4}M) dissolved in glycerol (adapted from reference 26).

The ESR spectrum of the nitroxide group can often provide useful information on the mobility of the spin label probe. For example, the ESR spectrum of human erythrocyte ghost membranes labeled with V reveals the presence of at least two



V

populations of spin labels that differ in their relative mobilities. The spectrum of one group resembles the rigid glass spectrum of the nitroxide group (*cf.* Fig. 4) with a splitting of 59 G between the low and high field extrema (Fig. 5, lines a and e). These spin labels are highly immobilized. In contrast, a second group has a fairly sharp three line spectrum (Fig. 5, lines b and d) that is characteristic of mobile nitroxide groups. The center line in Fig. 5 (line c) contains contributions from all of the spin labels. Holmes and Piette[14] have suggested that the highly immobilized spin labels are attached to sulfhydryl groups which are buried deep within the membrane where their motion is restricted. The more mobile spin labels are probably attached to surface sulfhydryl groups. In contrast to the maleimide spin label (V), the iodoacetamide analog (VI) labels only the surface sulfhydryl groups.[14]

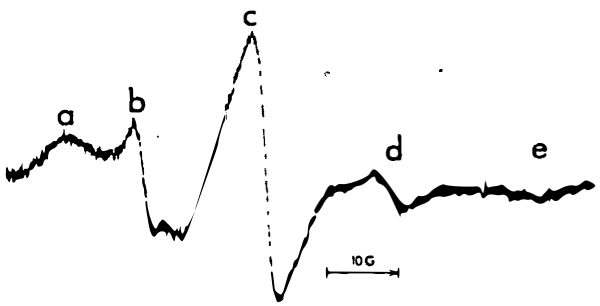
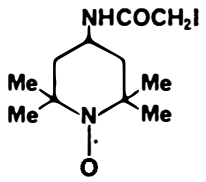


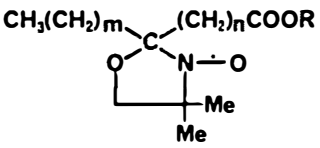
Fig. 5. The ESR spectrum of human erythrocyte ghost membranes spin-labeled with V.



VI

Holmes and Piette have found that when erythrocyte ghosts labeled with VI are treated with chlorpromazine, a highly immobilized population of spin labels appears in the spectrum. They have suggested that the drug induces a change in the conformation of the erythrocyte membranes so that spin labels which are on the outside of the membrane are moved into the interior.[14]

Spin-labeled analogs of stearic acid (VII) have proved to be very useful probes for both natural and artificial membranes.



VII

For example, when VII (m=12, n=3, R=H) is incorporated into erythrocyte ghost membranes, its ESR spectrum resembles the rigid glass spectrum of the nitroxide group with a splitting of 57 G between the low and high field extrema (Fig. 6). In contrast, when VII (m=1, n=14, R=H) is incorporated into the ghost membranes, its ESR spectrum (Fig. 6) indicates a high degree of motional freedom. Since it seems most likely that both labels are oriented with their ionized

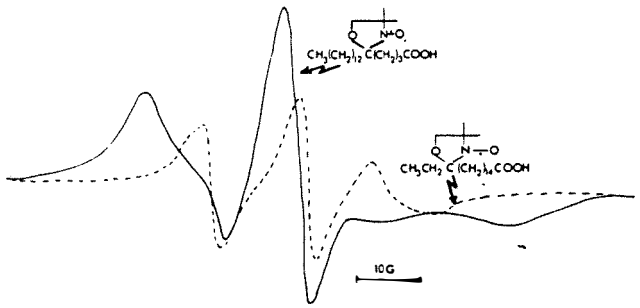


Fig. 6. The ESR spectra of two stearic acid spin labels bound to human erythrocyte ghost membranes.

carboxyl groups at the membrane interface, these observations suggest that near its surface, the membrane has a highly ordered rigid structure, whereas the interior of the membrane is fairly fluid in nature. Similar results have been observed for other membrane systems both natural and artificial.[15–17]

Spin labels have been employed to study the effect of various perturbants on membrane systems. For example, Hubbell and coworkers have made use of nitroxide analogs of methyl stearate (VII, m=5, n=10, R=CH_3) and 17β-hydroxy-5α-androstane to study the interaction of the local anesthetics benzyl alcohol and lidocaine with erythrocyte ghost membranes.[18] ESR measurements indicated that at low concentrations, benzyl alcohol produced a fluidizing effect on the membrane. However, at high (lytic) benzyl alcohol concentrations, the spin labels became highly immobilized. Hubbell and coworkers have suggested that at lytic concentrations, benzyl alcohol uncovered protein spin label binding sites that were covert in the unperturbed membrane.[18] These results were in good agreement with the previously reported nuclear magnetic resonance studies of Metcalfe and coworkers.[19]

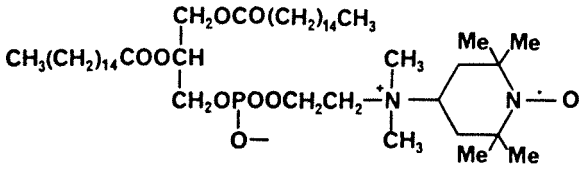
THE NITROXIDE GROUP AS A PROBE FOR MOLECULAR ORIENTATION

The ESR spectrum of the nitroxide radical is sensitive to the orientation of the radical with respect to the applied magnetic field (Fig. 2). The z-axis of the stearic acid spin label VII (m=5, n=10, R=H) is parallel to the long hydrocarbon chain. Hubbell and McConnell have shown that when this spin label is incorporated into shear-oriented canine erythrocytes, there is a larger splitting when the magnetic field is oriented perpendicular to the surface of the red cells.[11] This suggests that the preferred orientation of VII (m=5, n=10, R=H) is one in which its long hydrocarbon chain is perpendicular to the membrane surface. Similar observations have been made with artificial membrane systems such as oriented phospholipid multilayers. In their experiments with phosphatidylcholine multilayers, Griffith and coworkers [20] have reported that as the nitroxide group is moved farther and farther away from the carboxyl head group of stearic acid, the difference between spectra recorded with the field parallel and perpendicular to the plane of the multilayers decreases until with VII (m=1, n=14, R=H), there is little difference between the two orientations. These observations indicate that while an ordered multilamellar arrangement of hydrocarbon chains exists at the surface, the interior of the multilayer is quite fluid. Other experiments by Hsia and coworkers [21–23] employing both a cholestane spin label and VII (m=10, n=5, R=H) have shown that cholesterol causes an increase in the rigidity of egg lecithin multilayers. Similar results have been reported by Kroes *et al.* for erythrocyte membranes isolated from cholesterol-fed guinea pigs.[24] In contrast to cholesterol, general anesthetics such as chloroform and butane decrease the organization of lecithin or brain lipid multilayers at very low concentrations.[25] Local anesthetics such as procaine or tetracaine increase order at low concentrations but decrease order at high concentrations.[25]

OTHER APPLICATIONS INVOLVING NITROXIDE SPIN LABELS

Membranes

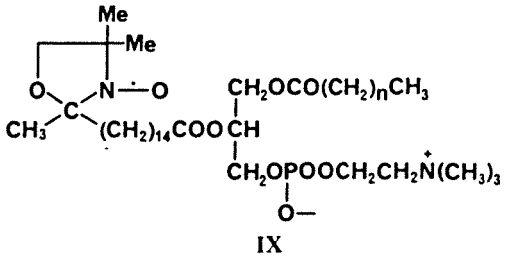
It is obvious from the foregoing discussion that spin labels have played an important role in determining the structure of membranes (see also refs. 26 and 27). More recently, McConnell and coworkers have used spin-labeled phosphatidylcholine analogs to measure some of the dynamic properties of membranes. For example, Kornberg and McConnell have estimated the rate of inside-outside transitions occurring in egg lecithin vesicles with the aid of spin label VIII.[28] In their



VIII

experiments, vesicles labeled with VIII were treated with ascorbic acid at 0°. The ascorbic acid quickly reduced the spin labels present in the external monolayer thereby abolishing their paramagnetism. Since ascorbic acid is a highly polar molecule, it cannot penetrate the vesicles and reduce the spin labels present in the internal monolayer. However, when the internally oriented labels reoriented toward the outside, they were reduced with a half time of 6.5 hrs. From this experiment, Kornberg and McConnell were able to measure the rate of phospholipid flip-flop across the artificial membrane.

Scandella and coworkers have estimated the rate of phospholipid lateral diffusion in rabbit sarcoplasmic reticulum using spin labels VIII and IX.[29] When vesicles were prepared from

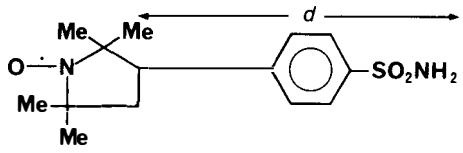


IX

either VIII or IX, nitroxide-nitroxide interactions reduced the ESR spectrum to a single line.[5] When such vesicles were added to a sarcoplasmic reticulum preparation, patches of the spin label were incorporated into the membrane. As the spin labels diffused into the membrane, their ESR spectra changed until eventually the three-line pattern reappeared. From an analysis of the line shapes and their rate of change with time, Scandella and coworkers were able to estimate that the diffusion constant D of the spin labels was 6×10^{-8} cm^2/sec at 37°.[29] Grant and McConnell have used this same approach to examine phospholipid diffusion in the membrane of *Acholeplasma laidlawii*.[30]

Topographical Studies of Binding Sites

Chignell and coworkers have studied the topographies of the active sites of several mammalian erythrocyte carbonic anhydrases by means of a series of spin-labeled aromatic sulfonamide (X) inhibitors.[31–34] The active site of carbonic anhydrase is a deep crevice at the bottom of which is a single zinc

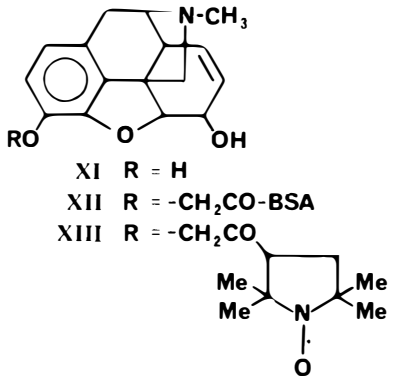


X

atom. When an aromatic sulfonamide inhibitor binds to the active site, the sulfonamide group is directly coordinated to the zinc atom. Chignell and coworkers prepared a series of spin-labeled sulfonamides in which the distance *d*, between the sulfonamide group and the pyrrolidine ring of the spin label, was varied. It was found that when *d* was small, the spin label was highly immobilized when the inhibitor bound to the enzyme active site. As *d* increased, the mobility of the spin label also increased until eventually the free radical demonstrated little or no interaction with the active site. Using this technique, it was possible to determine that the active site of human erythrocyte carbonic anhydrase C was funnel-shaped and about 14 Å deep. Similar studies with the human B isozyme and bovine carbonic anhydrase B suggested that the active sites of these enzymes were the same shape as human carbonic anhydrase C but somewhat deeper. This "molecular dipstick" approach was originally devised by Hsia and Piette who used the technique to study the topography of hapten binding sites on rabbit anti-2,4-dinitrophenyl immunoglobulins.[35]

Free Radical Assay Technique

Leute and coworkers have used spin labeling in conjunction with the immunoassay technique for the rapid determination of morphine (XI) and other drugs in urine, saliva and other



XI R = H
XII R = -CH2CO-BSA
XIII R = -CH2CO

biological fluids.[36] These workers prepared an antigen (XII) by coupling morphine to bovine serum albumin (BSA). Antibodies were then raised against the antigen in rabbits. When the spin-labeled morphine analog XIII bound to the antibodies, the ESR spectrum of the nitroxide group became broad and asymmetric, indicating a high degree of immobilization at the immunoglobulin binding site. When morphine was added to the spin label-immunoglobulin complex, the spin label was displaced and its ESR spectrum reverted to the sharp three-line pattern. Leute and coworkers were able to estimate the concentration of free spin label by measuring the amplitude of the low field peak. When this amplitude was plotted as a function of added morphine, a calibration curve was obtained from which it was possible to estimate the concentration of morphine in any biological sample. Morphine substitutes such as methadone and propoxyphene and unrelated drugs such as barbiturates and amphetamines were not recognized by the antibody. Thus, the technique is well suited for use in heroin treatment programs. Chignell and Starkweather[37] have recently shown that this same approach can also be used when other drug-binding proteins such as enzymes are available.

PROGNOSIS

Spin-labeling is a versatile spectroscopic technique that can be used to probe the structure of biologically important macromolecules. The future should see increasing application of spin-labeling to biological problems, particularly those that involve the various receptor proteins. Finally, when used in conjunction with immunoassay procedures, spin labels provide a rapid method for the detection and quantitation of drugs and other small molecules present in biological fluids.

Dr. Colin F. Chignell

REFERENCES

1) H.M. McConnell and B.G. McFarland, *Quart. Rev. Biophys.*, 3, 91 (1970).
2) C.L. Hamilton and H.M. McConnell in "Structural Chemistry and Molecular Biology," A. Rich and N. Davidson, Eds., W.H. Freeman, San Francisco, 1968, p 115.
3) O.H. Griffith and A.S. Waggoner, *Accounts Chem. Res.*, 2, 17 (1969).
4) I.C.P. Smith in "Biological Applications of Electron Spin Resonance Spectroscopy," H.M. Swartz, J.R. Bolton, and D.C. Borg, Eds., Wiley/Interscience, New York, N.Y., 1972, p 483.

5) P. Jost and O.H. Griffith in "Methods in Pharmacology," Vol II, C.F. Chignell, Ed., Appleton-Century-Crofts, New York, N.Y., 1972, p 223.
6) S. Ohnishi and H.M. McConnell, *J. Amer. Chem. Soc.*, **87**, 2293 (1965).
7) A.K. Hoffman and A.T. Henderson, *ibid.*, **83**, 4671 (1961).
8) E.G. Rozantsev, "Free Nitroxyl Radicals," Plenum Press, New York/London, 1970.
9) A. Rassat, *Bull. Soc. Chim. Fr.*, 3273 (1965).
10) G.H. Dodd, M.D. Barratt and L. Rayner, *FEBS Letters*, **8**, 286 (1970).
11) W.L. Hubbell and H.M. McConnell, *Proc. Nat. Acad. Sci. U.S.*, **61**, 12 (1968).
12) O.H. Griffith, L.J. Libertini and G.B. Birrel, *J. Phys. Chem.*, **75**, 3417 (1971).
13) H.M. McConnell, K.L. Wright and B.G. McFarland, *Biochem. Biophys. Res. Commun.*, **47**, 273 (1972).
14) D.E. Holmes and L.H. Piette, *J. Pharmacol. Exp. Ther.*, **173**, 78 (1970).
15) W.L. Hubbell and H.M. McConnell, *Proc. Nat. Acad. Sci. U.S.*, **63**, 20 (1969).
16) D. Chapman, M.D. Barratt and V.B. Kamat, *Biochim. Biophys. Acta*, **173**, 154 (1969).
17) H. Simpkins, E. Panko and S. Tay, *J. Membrane Biol.*, **5**, 334 (1971).
18) W.L. Hubbell, J.C. Metcalfe, S.M. Metcalfe and H.M. McConnell, *Biochim. Biophys. Acta*, **219**, 415 (1970).
19) J.C. Metcalfe, P. Seeman and A.S.V. Burgen, *Mol. Pharmacol.*, **4**, 87 (1968).
20) P. Jost, L.J. Libertini, V.C. Herbert and O.H. Griffith, *J. Mol. Biol.*, **59**, 77 (1971).
21) J.C. Hsia, H. Schneider and I.C.P. Smith, *Biochim. Biophys. Acta*, **202**, 399 (1970).
22) J.C. Hsia and J.M. Boggs, *ibid.*, **266**, 18 (1972).
23) J.C. Hsia, R.A. Long, E.E. Hruska and H.D. Gesser, *ibid.*, **290**, 22 (1972).
24) J.C. Kroes, R. Ostwald and A. Keith, *ibid.*, **274**, 71 (1972).
25) I.C.P. Smith, *Chimia*, **25**, 350 (1971).
26) P. Jost, A.S. Waggoner and O.H. Griffith in "Structure and Function of Biological Membranes," L. Rothfield, Ed., Academic Press, New York, N.Y., 1971, p 83.
27) R.J. Melhorn and A.D. Keith in "Membrane Molecular Biology," C.F. Fox and A.D. Keith, Eds., Sinauer Associates, Stanford, 1972, p 192.
28) R.D. Kornberg and H.M. McConnell, *Biochemistry*, **10**, 1111 (1971).
29) C.J. Scandella, P. DeVaux and H.M. McConnell, *Proc. Nat. Acad. Sci. U.S.*, **69**, 2056 (1972).
30) C.W. Grant and H.M. McConnell, *ibid.*, **70**, 1238 (1972).
31) C.F. Chignell, *Life Sci.*, **10**, 699 (1971).
32) R.H. Erlich, D.K. Starkweather and C.F. Chignell, *Mol. Pharmacol.*, **9**, 61 (1973).
33) C.F. Chignell, D.K. Starkweather and R.H. Erlich, *Biochim. Biophys. Acta*, **271**, 6 (1972).
34) C.F. Chignell and D.K. Starkweather, *Comp. Biochem. Pharmacol.*, **46B**, 813 (1973).
35) J.C. Hsia and L.H. Piette, *Arch. Biochem. Biophys.*, **129**, 296 (1969).
36) R.K. Leute, E.F. Ullman, A. Goldstein and L.A. Herzenberg, *Nature New Biol.*, **236**, 93 (1972).
37) C.F. Chignell and D.K. Starkweather, *Pharmacology*, **8**, 368 (1972).

Organic Synthesis *via* Organoboranes II[1]

Selective Reductions Using Borane·tetrahydrofuran Complex

Clinton F. Lane
Aldrich-Boranes, Inc.

Borane·tetrahydrofuran complex (BH_3·THF) in tetrahydrofuran is a convenient laboratory hydroboration reagent and its utility as a selective reducing agent has been described in detail by Brown and coworkers.[2,3] The reactivity of a number of representative functional groups toward BH_3·THF indicated the following relative order: carboxylic acids > olefins > ketones > amides > nitriles > epoxides > esters > acid chlorides. In addition, nitro compounds, sulfones, sulfonic acids, and organic halides are completely stable toward BH_3·THF.

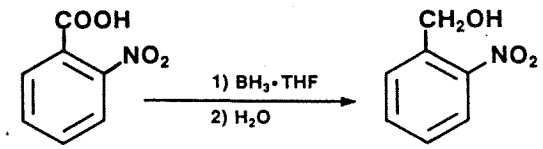
The possibilities for numerous selective reductions are obvious. However, the reactivity of any functional group can be greatly modified by structural considerations, *e.g.*, steric and inductive effects can decrease the reactivity of a carbonyl group. The different rates of reaction of the three hydrides on boron and the proximity of two reducible functional groups can also affect the relative reactivity. Thus, if two functional groups are sterically close in a molecular structure, the first hydride on boron in BH_3 may cleanly add to the more reactive group. The intramolecular reaction of the second hydride with the other, less reactive functional group may then be favored by a lower free energy of activation.

In ortho-substituted benzoic acids, the steric, electronic, and proximity effects may be expected to be most pronounced. Consequently, we have examined the reduction of o-nitrobenzoic acid and o-chlorobenzamide with BH_3·THF and the detailed procedures are given below.

Aliphatic and aromatic carboxylic acids are reduced rapidly (generally in less than 1 hr at 25°) and quantitatively to the corresponding alcohols.[4] This reduction occurs so readily that carboxylic acids can be reduced in the presence of almost any other functional group. However, introduction of an electron-withdrawing substituent decreases the rate of reduction. Thus, the reduction of *o*-nitrobenzoic acid required 24 hrs at 20-25° for complete conversion to *o*-nitrobenzyl alcohol. Fortunately, the close proximity of the two functional groups caused no problems.

Primary, secondary, and tertiary amide derivatives of both aliphatic and aromatic carboxylic acids are reduced to the corresponding amines by excess BH_3·THF.[5] The tertiary amides prove to be highly reactive and are reduced at moderate rates even at room temperature.[5] The reactivity follows the order: tertiary ≥ secondary > > primary aliphatic > primary aromatic. Introduction of an electron-withdrawing substituent also decreases the rate of reduction. Consequently, the reduction of *o*-chlorobenzamide required 18 hrs in refluxing THF to obtain a high yield of *o*-chlorobenzylamine using the required 2 1/3 equivalents of BH_3 per equivalent of primary amide with one equivalent of BH_3 in excess. The excess BH_3·THF is added to compensate for loss of hydride during reflux.

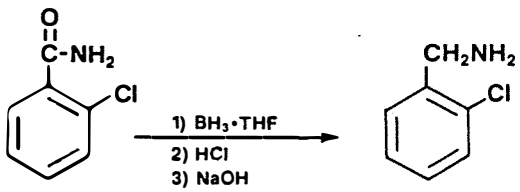
Preparation of *o*-Nitrobenzyl Alcohol [Note 1]



M.W. 167.12 M.W. 153.14
99.8% yield

A one-liter, three-necked, round-bottomed flask equipped with a reflux condenser, magnetic stirring bar, and pressure-equalizing addition funnel is charged with 50.1g (300mmol) of *o*-nitrobenzoic acid. After flushing the system with dry, high-purity nitrogen for one min, 100ml of tetrahydrofuran is added using a double-tipped needle. The clear, orange-colored solution is stirred in a 20-25° water bath as 315ml of 1*M* BH_3·THF solution in THF (315mmol) is transferred to the calibrated addition funnel using a Flex-needle.™ Hydrogen gas evolves during the dropwise addition of the first one-third of the BH_3·THF solution (addition time ~ 30 min) and essentially no gas evolution occurs during the addition of the final two-thirds of the BH_3·THF solution (addition time ~ 30 min). After stirring for 24 hrs at 20-25°, the excess hydride is destroyed at 20-25° by the dropwise addition of 300ml of water-saturated diethyl ether at such a rate that the gas evolution does not become too vigorous (addition time 45-60 min). Water (100ml) is then added and the aqueous layer is saturated with 35-40g of potassium carbonate. The clear, orange-colored organic layer is decanted and the aqueous layer extracted twice with 100ml portions of diethyl ether. The ether extracts and the organic layer are combined, dried over anhydrous potassium carbonate, filtered, and concentrated on a rotary evaporator to give 45.8g (99.8% yield) of *o*-nitrobenzyl alcohol as a yellow, crystalline solid, mp 69-71°, with an ir spectrum identical to that reported for the authentic material.[6] Recrystallization from water gives colorless needles, mp 70-72° (uncorrected) (Lit.[7] mp 74°).

Preparation of *o*-Chlorobenzylamine [Note 1]



M.W. 155.58 M.W. 141.60
85.9% yield

A one-liter, three-necked, round-bottomed flask equipped with a reflux condenser, magnetic stirring bar, and pressure-equalizing addition funnel is charged with 23.3g (150mmol) of *o*-chlorobenzamide. After flushing the system

with dry, high-purity nitrogen for one min, 100ml of tetrahydrofuran is added using a double-tipped needle. The resulting slurry is stirred in a 20-25° water bath as 500ml of 1*M* BH_3 THF solution in THF (500mmol) is transferred to the calibrated addition funnel using a Flex-needle™ and then added dropwise to the slurry over a 90 min period. The reaction mixture becomes clear and colorless after the addition of ~50ml of BH_3•THF solution and hydrogen gas evolves only during the addition of the first 100ml. Following the BH_3•THF addition, the reaction mixture is heated to reflux and maintained at reflux for 18 hrs. After cooling to 20-25° in a water bath, the clear, colorless solution is hydrolyzed by the **careful, dropwise** addition of 100ml of water followed by 40ml of 6*N* aqueous hydrochloric acid [Note 2]. When the addition of the hydrochloric acid is complete, the THF is removed by distillation at atmospheric pressure until a head temperature of 85-90° is reached. This forces complete hydrolysis of the borane•amine complex and ensures formation of the amine hydrochloride. The amine is then isolated by adding 100ml of 6*N* aqueous sodium hydroxide and extracting three times with 100ml portions of diethyl ether. The combined ether extracts are washed once with saturated aqueous sodium chloride, dried over anhydrous potassium carbonate, filtered, and concentrated on a rotary evaporator to give 22.2g of a light-yellow oil. Short-path distillation of this oil on the Aldrich Kugelrohr[8] gives 18.2g (85.9% yield) of *o*-chlorobenzylamine as a clear, colorless oil, bp 100±3° (air bath temp.) at 8mm (water aspirator), with an ir spectrum identical to that reported for the authentic material.[9]

Notes

1) For handling BH_3•THF, the bulletin "Handling Air-Sensitive Solutions" should first be consulted. This is available upon request from Aldrich Chemical Company, Inc.

2) Vigorous hydrogen gas evolution and foaming of the reaction mixture occur upon addition of the water and aqueous acid.

References

1) For part I of this series, see *Aldrichimica Acta*, **6**, 36 (1973).

2) H.C. Brown, P. Heim, and N.M. Yoon, *J. Amer. Chem. Soc.*, **92**, 1637 (1970) and references cited therein.

3) For a recent review on selective reductions in general, see H.C. Brown, "Boranes in Organic Chemistry," Cornell University Press, Ithaca, N.Y., 1972, Chapters 12 and 13. (Aldrich Catalog no. Z10,080-3, $28.50).

4) N.M. Yoon, C.S. Pak, H.C. Brown, S. Krishnamurthy, and T.P. Stocky, *J. Org. Chem.*, **38**, 2786 (1973).

5) H.C. Brown and P. Heim, *ibid.*, **38**, 912 (1973).

6) C.J. Pouchert, "The Aldrich Library of Infrared Spectra," Aldrich Chemical Company, Inc., 1970, p 596H.

7) Beilstein, **6**(1), 448.

8) Aldrich Kugelrohr Distillation Apparatus, catalog no. Z10,046-3, $145.00.

9) C.J. Pouchert, "The Aldrich Library of Infrared Spectra," Aldrich Chemical Company, Inc., 1970, p 572C.

A BRIEF SURVEY OF POLYMER CHEMISTRY

INTRODUCTION

In the day of the alchemist, the tarry residues of chemical reactions were considered very bothersome. Today, after many discoveries and much work, these "tars" have evolved into the many useful materials we call plastics or polymers. In the past fifty years, the handful of natural and coal tar residue polymers has grown into such a large array of diverse molecular and structural designs that any individual is hard put to have but a general acquaintance with most of them. The following commercial polymer classification list[1] shows the diversity encountered. No matter in what field we apply ourselves, polymers and the chemistry of polymers play a very significant role.

ABS (Acrylonitrile Butadiene Styrene)	Polybutadienes
Acetals	Polybutylenes
Acrylics	Polycarbonates
Alkyds	Polymethyl Pentenes
Cellulose Esters	Polyesters
Diallyl Phthalates	Polyethylenes
Epoxies	Polyimides
Fluorocarbons	Polyamide-imides
Nylons	Polypropylene
Phenolics	Polyphenylene Sulfide
Phenylene Oxides	Polyether Sulfones
Polysulfones	Polystyrenes
Polyaryl Sulfones	Polyvinyl Chloride
	Silicones

From the standpoint of the organic chemist, the chemical structures are familiar. The same carbon, hydrogen, oxygen and nitrogen combinations are present. The difference is merely that they are in relatively gigantic (molecularly speaking) molecules. The science of polymer synthesis is concerned with polymerization - the reaction mechanisms which bond together the small reactive compounds called monomers into the long repeating structures called polymers.

Organic and inorganic molecules which are classified as monomers have the ability to attach to a reactive site and, in turn, provide a reactive site for the next monomer. The different reaction mechanisms by which polymers are synthesized are termed condensation polymerization, free radical polymerization and ionic polymerization. These mechanisms and the several variations of each will be briefly described.

FREE RADICAL POLYMERIZATION

When a free valence is associated with an atom in a group such as $\cdot CH_3$, it is termed a "free radical". Free radicals are normally low in stability and exist only as short-lived transient species. In polymerizations of vinyl compounds, free radicals (R·) are commonly produced by a polymerization initiator such as benzoyl peroxide.

$$\text{Initiator} \longrightarrow R\cdot$$

Free radical addition to a vinyl double bond readily occurs in a step known as an initiation reaction and results in

$$R\cdot + CH_2{=}CHX \longrightarrow RCH_2\text{-}\dot{C}HX$$

the formation of a second free radical. In turn, this free radical species can add to another monomer

$$RCH_2\text{-}\dot{C}HX + CH_2{=}CHX \longrightarrow RCH_2\text{-}CHX\text{-}CH_2\text{-}\dot{C}HX$$

and subsequently to other monomer units to form a long chain polymer molecule which might eventually contain thousands of monomer units. The multiaddition step is termed propagation.

The chain continues to grow until a termination reaction, which is usually the mutual interaction of two radicals, occurs.

$$R(CH_2CHX)_n\cdot + R(CH_2CHX)_m\cdot \longrightarrow R(CH_2CHX)_{m+n}R$$

Other reactions can occur to terminate chains depending on conditions and materials used, although the effect is essentially the same. Adjustment of chain lengths (molecular weight) by control of termination reactions provides a means of varying the physical properties of the final polymer.

There are essentially four types of processes by which free radical polymerizations are carried out - polymerization in bulk, suspension, emulsion and solution. A brief description of each of these processes is given below.

Bulk Polymerization

Bulk polymerization, sometimes referred to as mass polymerization, involves the direct conversion of monomers to polymers without the addition of a second medium. Catalysts, heat, or the combination of both are utilized to make the polymerization proceed at a reasonable rate. Although some monomers are known to polymerize in the solid state,[2] polymerizations are normally done in the liquid phase. As the reaction proceeds, a viscous solution of polymer dissolved in monomer is obtained if the polymer is soluble in the monomer phase. A precipitate is formed in the few cases where a polymer is not soluble in its own monomer. The percent of monomer which has become polymer is called the conversion and the number of monomer units per chain is called the degree of polymerization (D.P.).

Free radical bulk polymerizations can be carried out in test tubes or small flasks in the laboratory without much problem. However, the exothermic polymerization reaction coupled with poor heat transfer through viscous monomer-polymer mixtures, requires careful design of both equipment and reaction conditions in larger scale reactors. Inadequate control of temperature can lead to autocatalytic conditions

yielding products of undesired low molecular weights, broad molecular weight distributions and inferior color due to polymer degradation.

To avoid runaway reactions, several factors have to be taken into consideration. First, the inherent heat of polymerization varies widely, ranging from 7.0 kcal/mole to 41 kcal/mole for vinyl monomers[3]. Secondly, there is the reactivity of the monomer with its radical. Some monomers are so reactive as to preclude the possibility of controlling polymerization in bulk and, in fact, this makes them hazardous to store without proper precautions using inhibitors and refrigeration. Other monomers, such as styrene, behave quite well and can be polymerized in bulk without violence under the proper conditions. A third factor is heat transfer requirements. Heat must be removed by evaporation or conduction to maintain even temperatures required for controlled polymerization.

Bulk polymerization is useful for producing molding powders, casting resins, adhesives and viscous liquid low polymers used as plasticizers, tackifiers and lubricant additives.

Suspension Polymerization

A modification of the bulk polymerization process, which is designed to take care of the heat transfer problem, is called suspension or bead polymerization. This modified process involves the use of a second immiscible liquid phase. Monomers containing initiators are dispersed in the suspending liquid, which is usually water, in the form of small droplets. Suspension is maintained by the use of stabilizers, such as methyl cellulose, and agitation. Heat is applied to convert the monomers into polymer resulting in beads of polymer. At completion of the polymerization, the beads are filtered and the stabilizer removed by washing, leaving the polymer in a form convenient for handling.

The use of the suspension polymerization method is normally restricted to polymers with a high softening point so that the final product does not fuse into a solid mass on recovery. An inherent problem in this method of polymerization is the tendency for the partially polymerized beads to stick together during the polymerization, because at partial conversions, monomer swollen polymer is present. Careful consideration must be given to stabilizers, stirring and rates of polymerization to avoid serious difficulties.

From the standpoint of polymerization kinetics, the suspension process is identical to polymerization in bulk. Thus, suspension polymerization is essentially well-cooled bulk polymerization. However, because of the temperature control and convenient final form of the polymer, suspension polymerization is of outstanding industrial importance.

Emulsion Polymerization

Emulsion polymerization also employs a second medium, commonly water. However, in contrast with the suspension process, the kinetics of polymerization and the resulting polymer are significantly different from those of bulk polymerization. Aside from the obvious advantage of easy heat removal, emulsion polymerization provides very rapid reactions at low temperatures to give polymers of very high molecular weight.

Emulsion polymerization is different from suspension polymerization basically because the locus of polymerization is not in the monomer droplets but occurs in much smaller particles which originate in the aqueous phase. Aqueous emulsifiers are used to create much larger numbers of monomer clusters than monomer droplets derived from dispersing the monomer phase. These clusters usually originate in emulsifier clusters called micelles and the number is controlled by the emulsifier concentration. Polymerization occurs when a radical derived from a water soluble initiator such as potassium persulfate, enters the micelle. Radicals are preferentially captured by the micelles because of their greater number, and therefore larger surface area than monomer droplets.

As polymerization progresses within the micelle, the polymer concentration increases, the monomer concentration decreases and additional monomer diffuses from the aqueous phase. As the monomer concentration in the aqueous phase is depleted, monomer is supplied by the large monomer droplets. Thus the large droplets act as reservoirs for the growing micelles.

Since only one radical exists within our hypothetical micelle, termination by recombination cannot occur and a high molecular weight polymer results. Molecular weight can be regulated by controlling the rate of capture of radicals by a micelle since a second radical will terminate the first, stopping polymerization. A third radical will reinitiate polymerization until a fourth enters, etc.

The emulsion system then provides a means by which the radical concentration in the reactor can be very high and yet the termination rate is low because each radical is contained within its own minute monomer-polymer particle. Particle sizes resulting from emulsion systems are normally in the submicron range whereas those from suspension polymerization are in the 100+ micron size range.

Because of the very small size of emulsion polymer particles and the use of emulsifiers in the process, the polymer is difficult to recover in solid form. Therefore, as a general rule, the emulsion system is used to produce polymers which will be used in the form of the final latex (emulsion) such as water-based paints or for uses which require very high molecular weight polymers.

Solution Polymerization

Solution polymerizations allow better control over reaction conditions since the monomer concentration is reduced, resulting in a slower polymerization rate, and the viscosity at any given conversion is reduced allowing better heat transfer. These are accomplished by adding a compatible, non-monomeric, liquid solvent to the monomer. This method is very useful for the preparation of products which are to be used in solution form such as glues or solvent-based paints. Solution polymerization is also useful for the preparation of low-melting polymers which are normally hard to handle as they are viscous syrups at room temperature.

In solution polymerization, the solvent used must be sufficiently pure and non-reactive as not to interfere with the polymerization. Solvents can modify polymerization reactions

by inducing initiator decomposition, reacting with the radicals formed by the initiator, reacting with the growing polymer chain or providing an unfavorable environment for the polymer molecule.

The reduction of monomer concentration realized by the use of solvents reduces the molecular weight at a given radical concentration. Reaction with the growing chain by termination or transferring the radical to a solvent molecule also reduces the molecular weight. Thus, contrasted with suspension polymerization which produces molecular weights similar to those of bulk polymerization, and emulsion polymerization which produces much higher molecular weights, solution polymerization usually results in lower molecular weight polymers. Of course, conditions of polymerization and other mechanisms can be employed to considerably vary the molecular weight obtained by any method and considerable overlap occurs in molecular weight ranges produced by any of these methods.

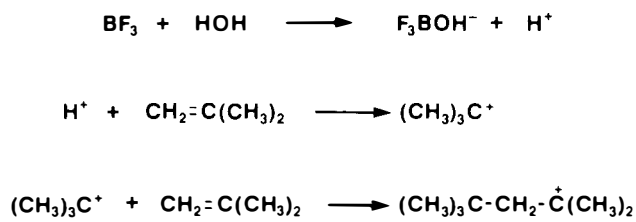
IONIC POLYMERIZATION

Ionic polymerization is a relatively new field of research compared to free radical methods. Study of the kinetics and mechanisms of ionic polymerization has often proven difficult as the reactions are sensitive and more difficult to control compared with free radical polymerization.

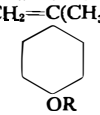
A decided advantage in some ionic systems is control over the stereochemistry of the polymer produced. Some systems allow the formulation of polymeric structures with regular placements to give syndiotactic or isotactic structures. Other systems allow precise control of molecular weights and block sequences in copolymers. The work of Natta in the heterogeneous catalyst anionic systems and that of Szwarc in homogeneous anionic systems have led to important commercial developments of ionic systems in the past fifteen years.

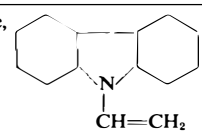
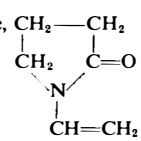
Cationic Polymerization

Monomers which lend themselves to cationic polymerizations are those bearing electron releasing groups attached to an ethylene group. Catalysts for cationic polymerizations are metallic salts which have strong electron affinities. Polymerizations are often carried out at very low temperatures and diluents of higher dielectric constants such as alkyl halides are used to speed up reactions. Initiation and propagation occur in much the same way as in a free radical mechanism except that an ion is transferred rather than a radical.



Due to steric factors and differences in polarity, all vinyl monomers do not polymerize cationically. Conversely, there are monomers which polymerize by ionic mechanisms but do not undergo free radical polymerization. The following Table[4] lists the polymerization methods suitable for some common monomers.

Cationic Only	Free Radical Only	Anionic Only
Isobutylene and derivatives, $CH_2{=}C(CH_3)_2$, $CH_2{=}C(CH_3)R$ Alkyl vinyl ethers, $CH_2{=}CHOR$, and related ether types, $CH_2{=}C(R)OR$, $CH_2{=}C(OR)_2$, $CH_3OCH{=}CHOCH_3$ Coumarone, indene Derivatives of α-methylstyrene, $CH_2{=}C(CH_3)$ 	Halogenated vinyls, $CH_2{=}CHX$, $CH_2{=}CX_2$, $CF_2{=}CFX$, $CF_2{=}CX_2$ where X = halogen, hydrogen (but $CH_2{=}CH_2$ not included) Vinyl esters, $CH_2{=}CHOCOR$	Vinylidene cyanide, $CH_2{=}C(CN)_2$, and related cyano derivatives, $CH_2{=}C(CN)Y$, where Y = SO_2R, CF_3, COOR Nitroethylenes, $CH_2{=}C(NO_2)R$

Cationic or Free Radical	Free Radical or Anionic
N-vinylcarbazole, 	Acrylic and methacrylic esters
N-vinylpyrrolidone, 	Vinylidene esters, $CH_2{=}C(COOR)_2$
	Derivatives of acrylonitrile, $CH_2{=}CRCN$
	$CH_2{=}CRCONH_2$

Cationic, Free Radical, or Anionic
Ethylene, $CH_2{=}CH_2$; butadiene, $CH_2{=}CH{-}CH{=}CH_2$; styrene, $CH_2{=}CH$  ; α-methylstyrene; methyl vinyl ketone

Coordination or Supported Metal Oxide Catalyst
α-Olefins including ethylene, dienes, alkyl vinyl ethers

A very significant commercial application of cationic polymerization has been the preparation of butyl rubbers. Copolymers of isobutylene with isoprene are produced in large quantities in continuous processes operating at -100°C utilizing catalysts such as $AlCl_3$ and BF_3. Other industrially important polymers made by cationic means are the polyvinyl alkyl ethers and coumarone-indene resins derived from hydrocarbon fractions.

Anionic Polymerizations

Although the commercial importance of anionic polymerization is much more recent than that of free radical methods, pioneering work was done as early or earlier. However, initially there was confusion over whether the mechanism was free radical or ionic.[5] The use of metallic initiators such as sodium led to the formation of radical-ions which rapidly dimerized. While free radical methods were being commercially applied, the understanding of ionic processes proceeded slowly for many years.

In essence, the mechanism of anionic polymerization involves the formation of a carbanion using a reactive metal such as sodium or a prepared initiator such as butyl lithium. When sufficiently stable, yet substantially reactive, the anion propagates by chain addition onto vinyl groups. Metallic initiators form radical ions which combine to form dianions.

$$Na + CH_2{=}CHX \longrightarrow Na^+ \; {}^-CH_2\text{-}CHX\cdot$$

$$2Na^+ + 2[{}^-CH_2\text{-}CHX\cdot] \longrightarrow$$

$$Na^+ \; {}^-CH_2CHXCHXCH_2{}^- \; Na^+$$

Butyl lithium is a commonly preferred initiator since it is easy to handle, is commercially available in solution and provides a homogeneous system.

A most significant feature of anionic polymerization, contrasted with free radical mechanisms, is the lack of a termination mechanism. Although this feature had been considered by others, Szwarc in 1956 realized the potential significance of the lack of a termination step and introduced his concept of a "living polymer". This recognition has provided the basis of a very scientifically useful and commercially important technique for controlling molecular weight distribution and copolymer structure. Thus, narrow molecular weight distribution polymers provide calibration standards for analytical procedures and controlled sequence block copolymers provide materials with unique combinations of thermoplasticity and elasticity.

A second feature of ionic polymerization is the ability to produce stereospecific polymers by the use of complex or coordination catalysts. This property was recognized and developed by Natta to polymerize α-olefins giving products with significantly improved properties depending on the stereoregularity of the polymer chain structure. Coordination catalysts are comprised of alkyls of metals of groups I-III combined with halides or other derivatives of transition metals of groups IV-VIII. The ability of these complex catalysts to produce stereospecific polymers is believed to be related to continual association of the catalyst structure with the growing end of the molecule and control over the position of the monomer which attaches to the active chain end. Exact mechanisms for coordination polymerization have not been conclusively developed although many schemes have been proposed.

The classification of anionic polymerizations into homogeneous and heterogeneous areas is not at all definitive. Homogeneous coordination catalysts are known although they are generally heterogeneous, and non-coordinated metallic catalysts such as sodium are certainly heterogeneous. Thus, the complexity of polymerization technology today is reflected in the physical as well as chemical forms of both monomers and catalyst systems.

CONDENSATION POLYMERIZATION

Polycondensation is a process for obtaining high molecular weight compounds by the simultaneous elimination of low molecular weight compounds such as water, alcohol, halides, etc.

A representation of the process is shown below, where a and b are functional groups.

$$n(a\text{-}X\text{-}a) + n(b\text{-}Y\text{-}b) \longrightarrow a(X\text{-}Y)_n b + (2n-1)ab$$

One can see from the above that a requirement for the compounds X and Y is that they are at least bifunctional for the polymerization to proceed.

Polycondensation reactions proceed in stages and a very important feature of these reactions is that they are reversible and have equilibrium properties. There are three stages in the formation of the high molecular weight condensation polymer: 1) initiation, 2) propagation (growth) and 3) termination. Although this terminology is the same as that of addition polymerization, the stages for condensation polymerization are quite different and are controlled by different rules.

Initiation

This step consists of the formation of a dimer from the reaction of two compounds as schematically shown below. This step is sometimes referred to as the "transesterification step".

$$R\text{-}C(=O)\text{-}OH + HO\text{-}R' \longrightarrow R\text{-}C(=O)\text{-}O\text{-}R' + H_2O$$

These reactions are normally catalyzed by strong acids such as p-toluenesulfonic acid, tetra-*n*-butyl titanate, etc.

This stage, like the subsequent stages, is reversible. Therefore, the by-product (H_2O shown above) must be removed to drive the equilibrium to the right. During this stage there are monomers, dimers and by-product, all competing for equilibrium. This stage of the reaction normally proceeds quite quickly and is carried out at a moderately low temperature, < 200°C.

Growth

This stage consists of the reaction of the dimeric species with

a monomer unit, another dimer unit or other units that have grown to tetramers, etc. This reaction may be expressed as follows:

$$a(X\text{-}Y)_n b + a\text{-}X\text{-}a + b\text{-}Y\text{-}b \longrightarrow a(\text{-}X\text{-}Y\text{-})_{n+1} b + 2ab$$

The expression above depicts the addition of monomeric species to the dimer unit. As the starting monomers are depleted, the reaction becomes dependent upon the reaction of dimer-dimer, dimer-tetramer, etc.

$$a(X\text{-}Y)_n b + a(X\text{-}Y)_m b \longrightarrow a(X\text{-}Y)_{n+m} b + ab$$

This growth step normally requires elevated temperatures and vacuum or inert gas sweep to facilitate removal of the by-product (ab) to drive the equilibrium to the right.

It has been shown for several condensation reactions that upon depletion of the monomers during the growth step, the molecular weight increase of the polymer drops off sharply and the process stops until the driving force (higher heat input) is increased. An increase in the flow of inert gas or application of vacuum does very little to drive the reaction further. This can be explained by the fact that chain growth takes place by the interaction of polymer chains with each other, therefore requiring higher energy input to impart free movement and interaction. Although the reactivity does not change with increased degree of polymerization, the freedom of movement to have end groups interact does.

Termination

As higher and higher molecular weight is achieved, the likelihood for depolymerization increases. Such a reaction is characteristic of condensation polymerization and not addition polymerization. This depolymerization can take place through the interaction of monomers, impurities or polymer chains reacting with themselves through the end groups. Depolymerization during the condensation reaction is proportional to the amount of depolymerization reagent. This depolymerization results in narrower molecular weight distributions than obtained from addition polymerization. Because of this depolymerization process, it is difficult to obtain high molecular weights unless quite pure catalysts and monomers are used.

This discussion has been limited to bifunctional condensation which is restricted to growth in only two directions, leading to finite chain lengths.

Nonlinear polycondensations are not restricted to two dimensional growth and it could be envisioned that a three dimensional network of polymer chains would lead to indefinitely large polymeric structures.

A characteristic of these nonlinear polymers is a phenomenon referred to as the "gel-point". This is a well-defined stage during the condensation reaction when the polymer changes from a liquid to a gel. These gel structures are infusible and insoluble in solvents. Upon heating, these polymers will decompose before melting. This characteristic is utilized widely in industry for producing infusible, solvent-resistant polymer products. Below is a list of some condensation polymers used widely in industry.

Polyesters (Fiberglass)
Polysulfides
Polyamides (Nylons)
Polyacetals
Polyanhydrides
Phenol-aldehyde
Urea-aldehyde
Polysiloxanes
Polyurethanes
Polyurea
Cellulose

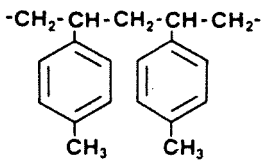
CHARACTERIZATION AND NOMENCLATURE OF POLYMERS

The characterization of non-macromolecular compounds usually involves physical and chemical data such as elemental analyses, boiling points, melting points, IR and UV traces, etc. Compounds with identical technical data are considered to be the same compounds.

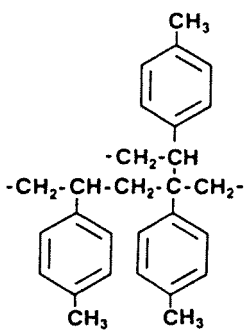
The characterization of polymers is a more difficult task due to the fact that classical analytical techniques such as VPC, boiling points, melting points (some crystalline polymers have melting points but even these are usually not sharp), etc., cannot be applied. Information such as number average molecular weight, weight average molecular weight, molecular weight distribution and degree of crystallinity (polymers having 20% or more crystallinity are considered crystalline in most cases, highly crystalline polymers may be only 50% crystalline) is important in polymer chemistry.

The difficulty in the characterization of polymers arises from the fact that the polymers are not as uniform as simple non-macromolecular compounds. The structure of polymers can be quite simple as in the case of linear homopolymers, or complicated as in the case of branched or cross-linked copolymers. As an example, three types of structure assignments to polyvinyltoluene are shown below.

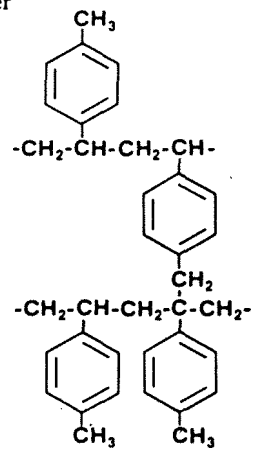
1) linear polymer



2) branched polymer



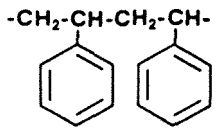
3) cross-linked polymer



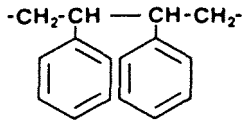
The repeating units are the same chemically, but they are quite different structurally which results in tremendous physical property differences.

Along with structural differences in polymers, we can also see isomers of similar structures, such as with polystyrene.

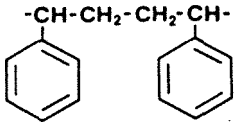
Head-to-tail isomer



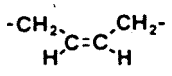
Head-to-head isomer



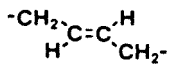
Tail-to-tail isomer



Not only can structural isomerism occur in polymers, but also stereoisomerism (*cis-trans*) as shown below:



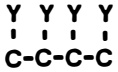
cis



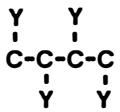
trans

Optical isomerism and tacticity are two other types of stereoisomerism. Tacticity has been classified into three categories.

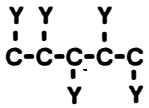
1) isotactic - substituents on same plane of backbone axis:



2) syndiotactic - substituents in ordered alternating sequence:



3) atactic - substituents in unordered sequence:



Optical activity is also apparent when asymmetric carbon atoms contain substituents Y.

When considering copolymers, other types of structure assignments can be made such as random, alternating, graft and block copolymers as shown below.

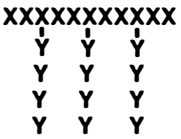
random copolymer

XXYYYXYXYYYXXXXY

alternating copolymer

XYXYXYXYXYXY

graft copolymer



block copolymer

XXX-YYY-XXX-YYY

Not only do structural assignments introduce problems in the characterization of polymers, but macromolecular chain lengths vary to give molecular weight distributions.

Molecular weight characterization of polymers is presently confined to essentially three absolute methods:

Light scattering
Ultracentrifuge
Osmotic pressure

Along with classical analytical chemistry, other characterization techniques for **polymers** are listed below. Each plays a vital role in the understanding of the macromolecular molecule.

Solubility
Thermodynamic properties (Tg, m.p., etc.)
Melt index
End group analysis
Density
Rheological properties
Optical properties
Electrical Properties
Crystallinity
Fractionation
Viscosity

Polymers affect all of us in our everyday lives. This brief survey of polymer chemistry is intended to acquaint those in the area of "plastics" with some of the chemistry involved and to lead those in the field of polymer science to Aldrich as a new source of high grade polymers. We hope Aldrich can contribute to the rapidly growing field of polymer science by providing products which will facilitate polymer research.

REFFRENCES

1) "1974 Materials Selector" issue of *Materials Engineering,* Reinhold Publishing Co., Inc., Stamford, Conn., 1973.
2) R.B. Mesrobian, *J. Chem. Phys.,* **22**, 565 (1954).
3) J. Brandrup and E.H. Immergut, Eds., "Polymer Handbook," Interscience Publishers, New York, N.Y., 1966.
4) Reprinted with the permission of John Wiley and Sons, Inc. from F.W. Billmeyer, "Textbook of Polymer Science," Interscience, New York, N.Y., 1962, p 292.
5) M. Szwarc, "Carbanions, Living Polymers and Electron Transfer Processes," Interscience, New York, N.Y., 1968.

Page intentially blank

ALDRICHIMICA ACTA

Volume 7
Number 2
1974

A publication of
Aldrich Chemical
Company, Inc.

ALDRICHIMICA ACTA

Volume 7, Number 2 1974

A publication of ALDRICH CHEMICAL COMPANY, INC.

Main Office:
940 W. St. Paul Avenue
Milwaukee, Wisconsin 53233
Telephone: (414) 273-3850

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

West Coast Service and Distribution Center:
2098 Pike Street
San Leandro, California 94577
Telephone: (415) 352-1186

Southern Service and Distribution Center:
3355 Lenox Road N.E.
Suite 750
Atlanta, Georgia 30326
Telephone: (404) 233-1678

In Great Britain:
Ralph N. Emanuel Ltd.
264 Water Rd.
Wembley, Middlesex
HAO IPY, England
Telephone: 01-998 4414

In Germany:
EHA-Chemie KG
7924 Steinheim am Albuch
Kreis Heidenheim, Germany
Telephone: (07329) 302

In Continental Europe:
Aldrich-Europe
B-2340 Beerse
Belgium
Telephone: 014/61431

Table of Contents

About the Cover

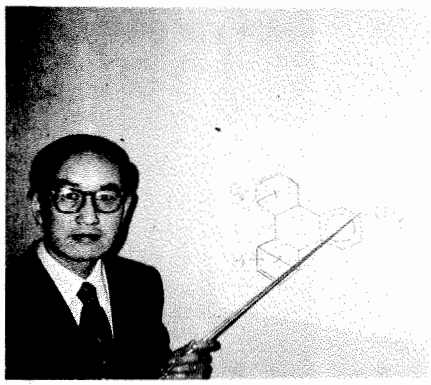
When we first saw the large *Tobias Healing his Father* (oil on panel, 92 x 122 cms), we were surprised that our chemist-collector had bought yet another depiction of this curious subject. Yet the more we looked at the painting and listened to the story of the son who healed his father's blindness, the easier it was to understand. The brilliant colors - lemon yellows and blues and reds - the flowing composition and particularly the harried face of the father that must have been modelled after the face of an Eastern Jew who wandered into Flanders in the early sixteen hundreds, must make this one of the finest works of the artist whose name has been forgotten. He painted many works, mainly of gypsies and musicians, and is known by the pseudonym Pseudo van der Venne. Many other baroque artists were also attracted to this story - not surprising when you consider the importance of eyesight to artists. Rembrandt for instance painted, drew and etched over 50 works depicting this apocryphal story, his interest probably heightened by his father's blindness.

The story of Tobias is one of the almost impossible: the story of the young man who saved his fiancee from the demon, and who cured his father's blindness. Hence it seems particularly appropriate on the cover of the issue that describes the work of Drs. Look, Hyman and coworkers - which is also of the almost impossible!

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, now is available to all chemist art-lovers.

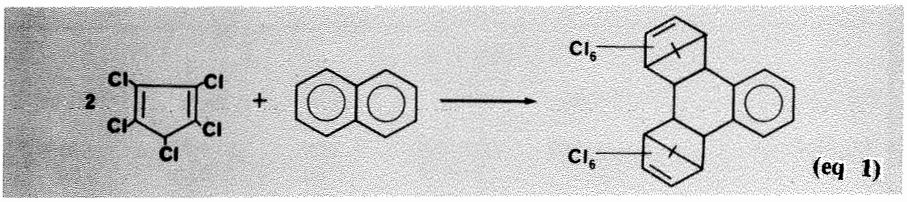
Hexachlorocyclopentadiene Adducts of Aromatic Compounds and their Reaction Products

Melvin Look,
Former Senior Research Chemist,
Hyman Laboratories, Inc.,
*Berkeley, California**

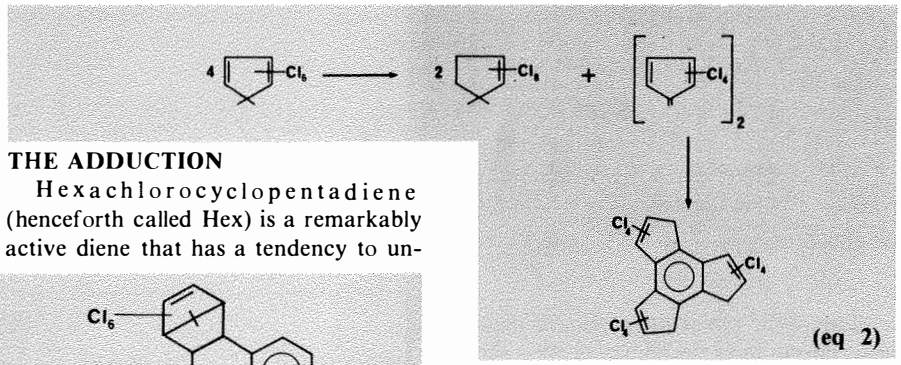


HISTORY AND BACKGROUND

In 1953, Hyman and Danish[1] disclosed that hexachlorocyclopentadiene forms an adduct with naphthalene (eq 1).



The adduct thus formed undergoes normal aromatic substitution reactions (preferably in the β-position), exclusively in the unadducted ring of naphthalene. Moreover, the substituted adduct can undergo a reverse Diels-Alder reaction when heated, yielding naphthalene compounds which are otherwise difficult to synthesize.[2] These reactions were developed further in the Florida Hyman Laboratories.[3] Efforts to develop these studies into commercial processes were conducted by the Berkeley Hyman Laboratories in 1958 to 1964. This report covers the work of this latter period. Much of the research is unpublished or has never been reported to the scientific community. It is hoped that the vast amount of new and specific reactions available to the organic chemist may broaden the horizon of these naphthalene and related polynuclear aromatic compounds.



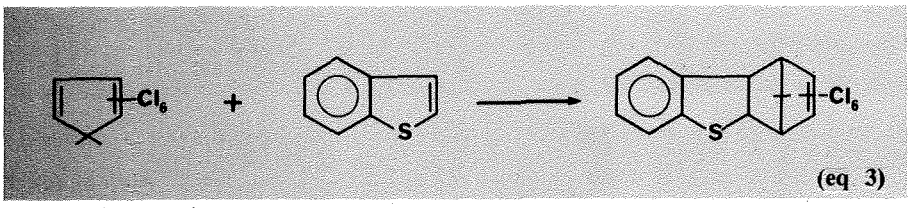
THE ADDUCTION

Hexachlorocyclopentadiene (henceforth called Hex) is a remarkably active diene that has a tendency to undergo Diels-Alder reactions.[4] Under normal conditions the reaction with polynuclear aromatic hydrocarbons is slow. Extensive studies in Berkeley showed a conversion of 25-35% to the adduct when a reaction mixture of naphthalene and Hex (1 to 3 mole ratio) was heated at 150-160° for one week (less than 1/4% per hour).[5] Petroleum-derived naphthalene consistently gave a purer product than coal tar naphthalene. Commercial grade Hex (purity 95%) was used. Glass vessels gave the cleanest material; however, Monel™ vessels were found to be feasible at plant scales. Usually, the adduct of naphthalene [1,2,3,4,5,6,7,8,13,13,14,14-dodecachloro-1,4,4a,4b,5,8,8a,12b-octahydro-1,4,5,8-dimethanotriphenylene — henceforth called Di-Hex-Adduct (DHA)] can be filtered off, the mother liquor reconstituted with fresh starting materials to the original 1:3 naphthalene-Hex mixture, and readducted. Generally 3 to 5 recycles can be made without a high accumulation of impurities. Runs up to 200 gallons have been conducted successfully in Berkeley.

Among the by-products formed during the adduction is an unusual tetracyclic compound formed by the disproportionation of Hex (eq 2).

The structure of the tetracyclic compound was determined simultaneously by Mark[6] and by our group in Berkeley. The reaction is minimal at 150-160° (less than 1% in one week). A serious impurity formed when coal tar naphthalene is used is a mono-Hex adduct of thianaphthene,

a common coal tar impurity (eq 3). This adduct is more active to substitution than DHA and causes the formation of tars when reactions are conducted on DHA.



(eq 3)

The adduction reaction was extended to other β-substituted naphthalenes (eq 4),[7] yielding, for instance, the very useful 2-methyl-DHA with 2-methylnaphthalene. Adduction attempts with α-substituted naphthalenes were nonproductive, and in some cases their very presence as impurities in β-substituted naphthalenes gave rise to impure and tarry DHA products. Other polynuclear aromatics form adducts (mono- and di-Hex), the notable exception being phenanthrene (eq 4).

Very little is known about the orientation and physical structure of the DHA molecule. The nature of the hindrance to substitution in the α-position is unknown.

REACTIONS OF DHA'S (eq 5)

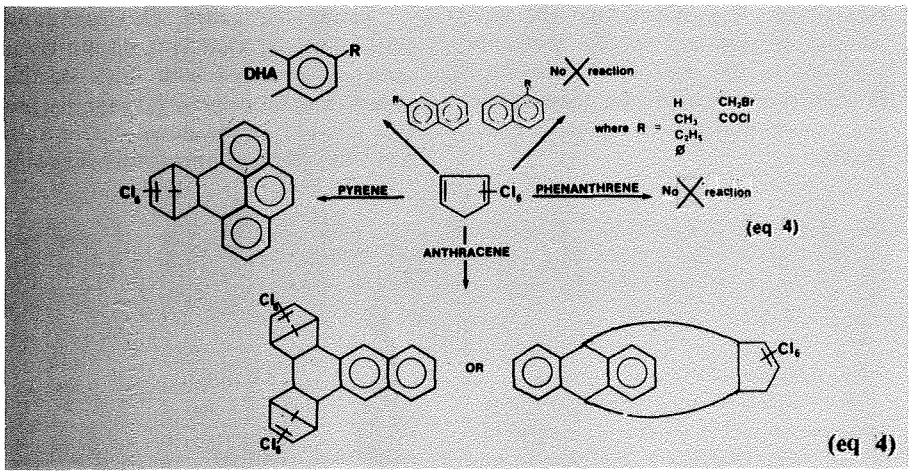
1) Nitration

Nitration of DHA does not form β-nitro-DHA exclusively as previously believed[3] but a mixture of 13% α-nitro-DHA and 87% β-nitro-DHA. Instead of the strenuous conditions formerly used,[2] we found that anhydrous nitric acid in either sulfuryl chloride or methylene chloride at reflux gave quantitative yields of nitro-DHA.[11] The isomers are separable by recrystallization from aqueous acetone. The ultraviolet spectrum of α-nitro-DHA is similar to that of 6-nitrotetralin, while the spectrum of β-nitro-DHA is similar to that of 7-nitrotetralin. The ratio of nitro isomers did not deviate greatly under varying nitrating methods and conditions, *e.g.*, nitrogen pentoxide in chloroform at 0°, 70% nitric acid at reflux, and anhydrous nitric acid in solvent. The possibility of two forms of DHA is disproved by the following experiments: Pure β-nitro-DHA was reduced to β-amino-DHA which was diazotized and reduced to DHA. Renitration of this DHA gave the normal α- and β-nitro-DHA mixture (eq 6).[12] α-Amino-DHA cannot be diazotized, probably because of stearic reasons.

Under slightly more stringent nitrating conditions, α-nitro-DHA is quantitatively converted to 1,3-dinitro-DHA.[13] Still more stringent nitration gives 2,3-dinitro-DHA from β-nitro-DHA.[14] The α-nitro-DHA is completely nitrated to 1,3-dinitro-DHA before β-nitro-DHA is formed. Nitration of 2-methyl-DHA gives a quantitative yield of 2-methyl-3-nitro-DHA (eq 7).

2) Halogenation

Chlorination of DHA gives 1,2,3,4-tetrachloro-DHA.[3] Depending on conditions, bromination or iodination with 3*N* nitric acid in methylene chloride solution gives 2-bromo-, 2,3-dibromo-, 2-iodo- or 2,3-diiodo-DHA. No noticeable amount of nitration is encountered if nitric acid remains at or below 3*N*.[15] No work was conducted on fluorination. Chlorination of 2-nitro-DHA gives 3,4-dichloro-2-nitro-DHA.[16] 3-Bromo-2-nitro-DHA is synthesized by nitrating 2-bromo-DHA.[16]

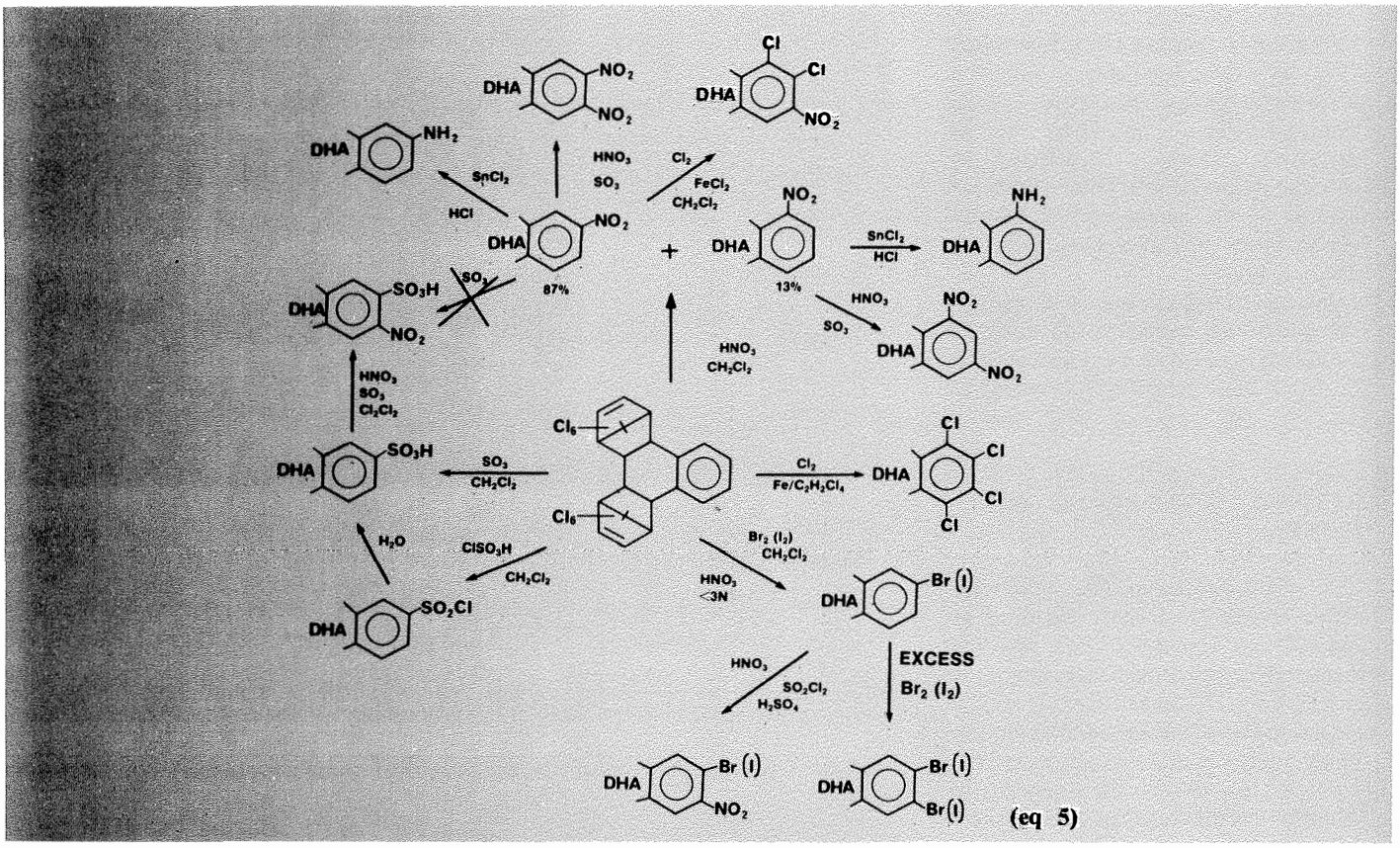


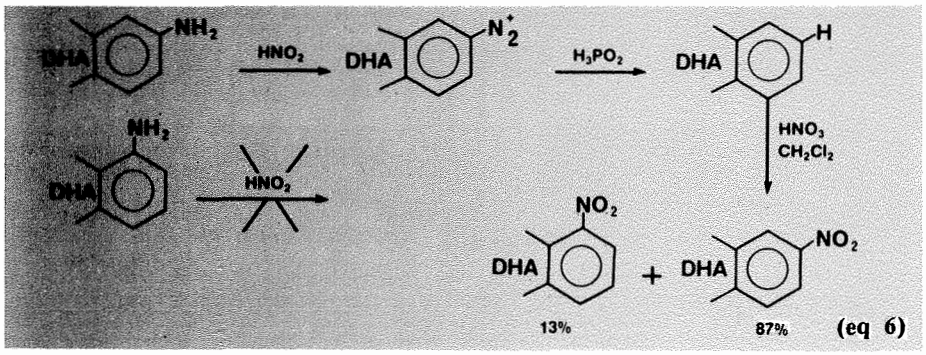
(eq 4)

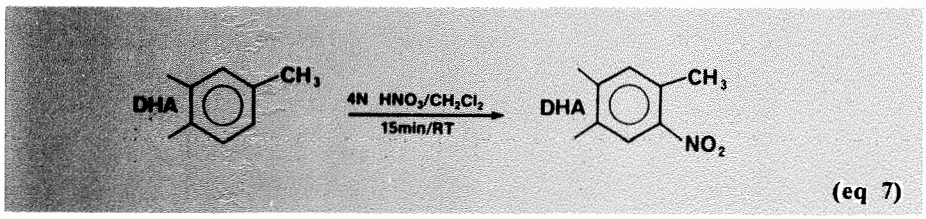
One of the major difficulties to commercialization of the adduct process was the extremely slow rate of the reaction. Since a considerable decrease in volume results from the formation of the diadduct, the age-old Le Chatelier principle in adduction was studied. Preliminary studies at 7000 psi and 150-160° showed a three-fold increase in rate. With specialized equipment,[8] our studies eventually culminated at a pressure of 100,000 psi and 300° where yields were quantitative in 3 minutes (Table 1).[9] One of the main advantages of high pressure adductions is that higher temperatures can be used, without formation of the undesirable by-products encountered in atmospheric reactions. The only comparable studies of the Diels-Alder reactions at high pressures are those of Plieninger.[10]

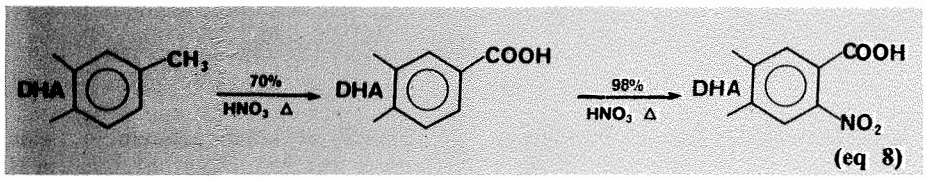
TABLE 1

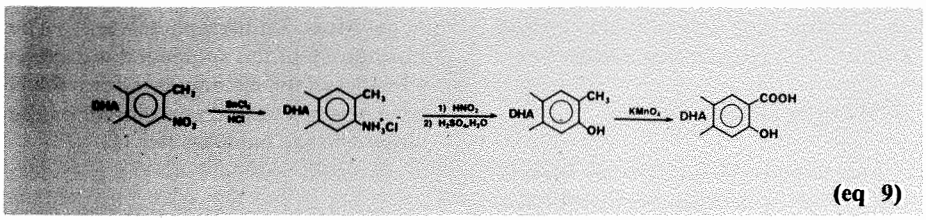
Dienophile	Temp.	PSI	Time/hr.	Yield	Yield/hr.
Naphthalene	150-160	(Atmos)	200	44%	0.25%
	160	6-7000	18	13.1	0.73
	160	15,000	18	22.9	1.23
	160	35,000	18	45.9	2.55
	200	35,000	4	75	18.75
	230	35,000	1	55.6	55.6
	235	100,000	1/120	1	(100)
	260	100,000	1/20	31	(100)
	160	100,000	2.75	12.1	4.4
2-Methylnaphthalene	160	(Atmos)	168	55	0.33
	160	35,000	18	27.9	1.55
	180	35,000	18	64.3	3.57
Pyrene	150	(Atmos)	168	0	0
	150	35,000	5	40	8











3) **Sulfonation**

Sulfonation of DHA's is accomplished with 30% oleum[3] or, preferably, with sulfur trioxide in methylene chloride.[17] We were never able to synthesize DHA-2,3-disulfonic acid. Chlorosulfonation of DHA is done in methylene chloride with chlorosulfonic acid.[18]

4) Multiple Reactions

Many of the common reactions on aromatic compounds have been carried out on the DHA compounds. A few examples include the oxidation of 2-methyl-DHA with concentrated nitric acid to DHA-2-carboxylic acid[18] which can be nitrated with white fuming (98%) nitric acid to 3-nitro-DHA-2-carboxylic acid (eq 8).

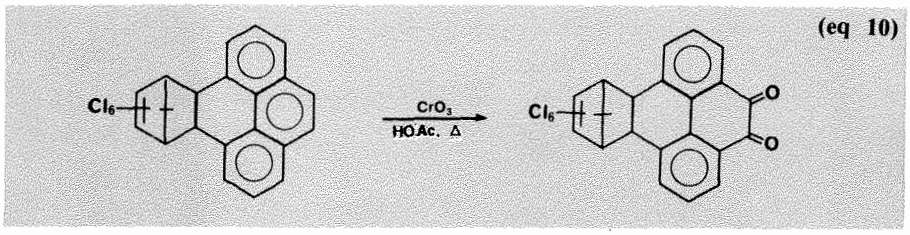
2-Methyl-3-nitro-DHA is reduced with stannous chloride to 2-amino-3-methyl-DHA. Hydrolysis of the diazonium salt of the amino-DHA gives 2-hydroxy-3-methyl-DHA. The latter can be oxidized to 2-carboxy-3-hydroxy-DHA (eq 9).[18]

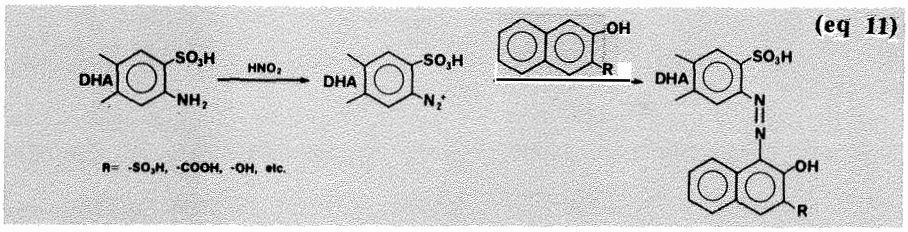
Preparation of 2-nitro-DHA-3-sulfonic acid may be effected by the nitration of DHA-sulfonic acid but not by the reverse sequence (eq 5).[15]

5) Other Reactions (and Non-Reactions)

We have never been able to perform a Friedel-Crafts reaction or a chloromethylation on DHA or its derivatives. DHA is unaffected by chromic oxide-acetic acid at reflux; oxidation of the pyrene adduct by this method gives the 1,2-pyrenequinone adduct (eq 10).[19]

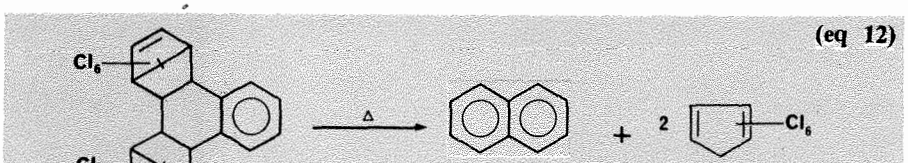
2-Amino-DHA-3-sulfonic acid can be diazotized and coupled to phenols and naphthols to give dyes and pigments with probable flame retarding properties (eq 11).

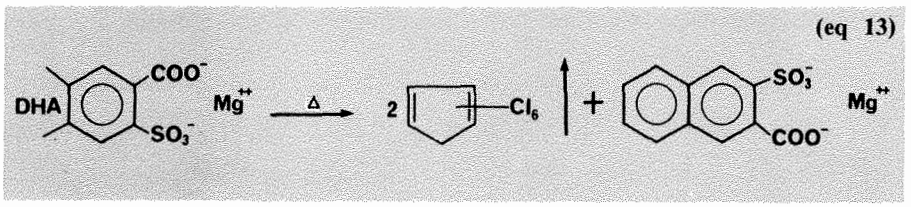




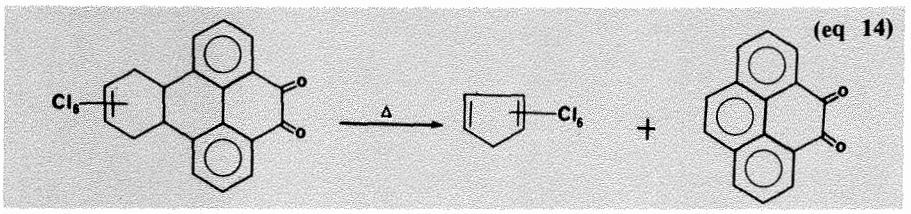
REVERSE DIELS-ALDER REACTIONS

All of the mentioned Hex adducts undergo reverse Diels-Alder reactions at 250-400° to regenerate Hex and the dienophile or substituted dienophile if the latter is stable to heat and does not readily react with Hex at these conditions (eq 12). Small quantities (0.5 to 2 gms) can be pyrolyzed in a test tube; the products tend to collect on the cooler part of the tube. Larger quantities are usually cracked in rotary flask equipment designed for solvent evaporation, using a nitrate-nitrite salt bath as a source of heat. Ideally, pyrolysis of larger quantities is carried out in a wipe-film still such as the ASCO molecular Rota-Film™ still. In the latter case, the DHA's are fed into the still as a slurry in Hex. In each case, a vacuum corresponding to the vapor pressures of the products at the temperature of pyrolysis is necessary. DHA derivatives were pyrolyzed continuously in hundreds-of-pounds scale in our plant using wipe-film pyrolyzers. DHA-acids are pyrolyzed as their salts, in which case the residue is the product (eq 13).

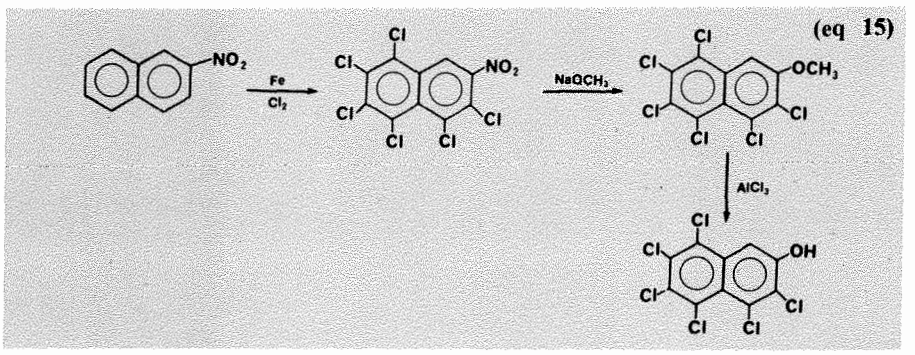




Mono-adducts are similarly pyrolyzed (eq 14).



The products are usually separated from Hex by hexane extractions. The products are usually insoluble in hexane, whereas Hex is completely miscible with aliphatic hydrocarbons.



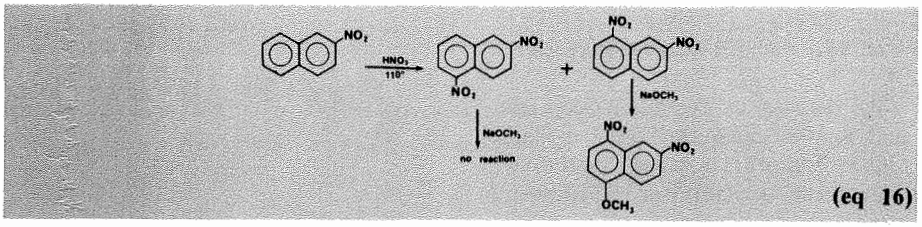
REACTIONS OF PYROLYZED PRODUCTS

Because the products made *via* the Hex adduction method were rare and otherwise difficult to synthesize by other processes, many of the reactions we studied were new. Only a few representative examples will be described for it will be impossible to discuss the hundreds of polynuclear aromatic compounds that were synthesized in Berkeley by direct or indirect use of our processes. Readers who are interested in the details of earlier naphthalene compounds should consult either of two references available.[20]

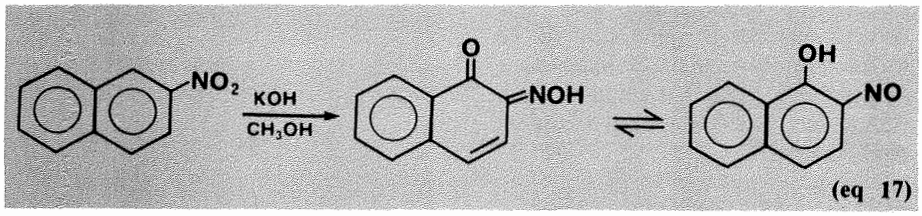
β-NITRONAPHTHALENE

This compound is prepared from 2-nitro-DHA by thermal decomposition at 250-375° at 12mm pressure in yields greater than 95%. β-Nitronaphthalene is chlorinated to form 1,2,3,4,5,6-hexachloro-7-nitronaphthalene.[21] The nitro-group of this compound is displaced with sodium methoxide to form the 7-methoxychloronaphthalene which can be cleaved to the naphthol (eq 15).

β-Nitronaphthalene is nitrated with concentrated nitric acid to form an equal mixture of 1,6- and 1,7-dinitronaphthalene.[22] The more valuable 1,6-dinitronaphthalene can be separated from the 1,7-isomer by reaction with sodium methoxide. The 1,6-dinitronaphthalene remains insoluble, while the 1,7-isomer is solubilized by the reaction (eq 16).[23]

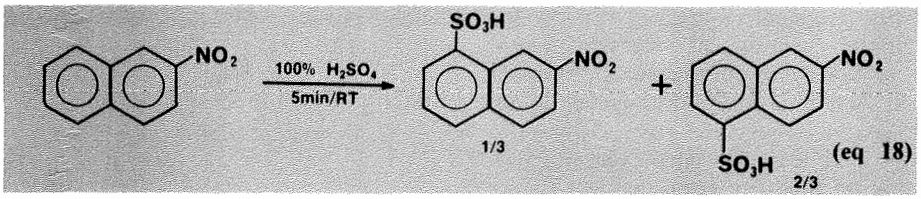


(eq 16)



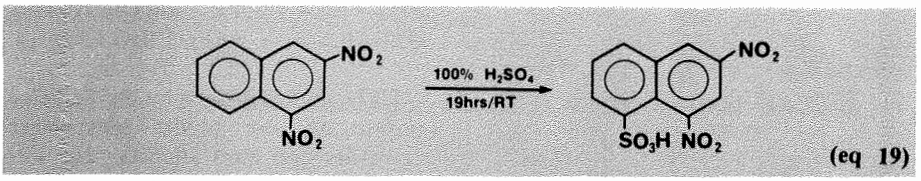
(eq 17)

β-Nitronaphthalene is reduced to β-naphthylamine by several methods. The amine is well known for its carcinogenic properties.[24] Though β-nitronaphthalene was once implicated in studies as being carcinogenic,[25] our cooperative studies show that the nitro compound is not carcinogenic.[26] It is of interest to note that 3-methyl-2-naphthylamine prepared from the corresponding nitro compound is a highly potent intestinal carcinogen.[27] No DHA's tested have been found to be carcinogenic.



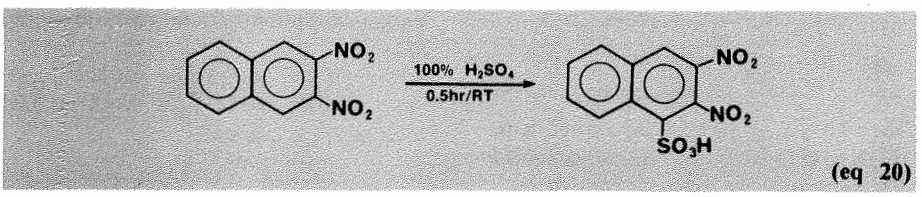
(eq 18)

β-Nitronaphthalene undergoes the Meisenheimer reaction to give a quinone oxime (eq 17). Mononitrated naphthalenes are usually sulfonated with anhydrous sulfuric acid (concd sulfuric acid boosted to 100% with oleum) at room temperatures (eq 18).



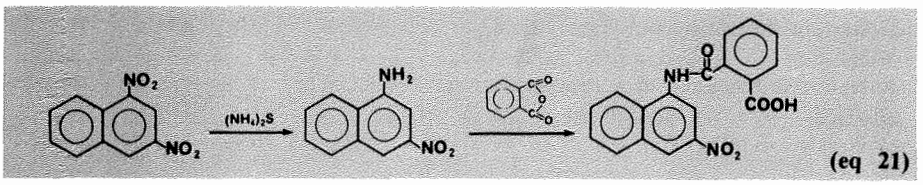
(eq 19)

Dinitronaphthalenes require more strenuous sulfonating conditions (eq 19, 20).



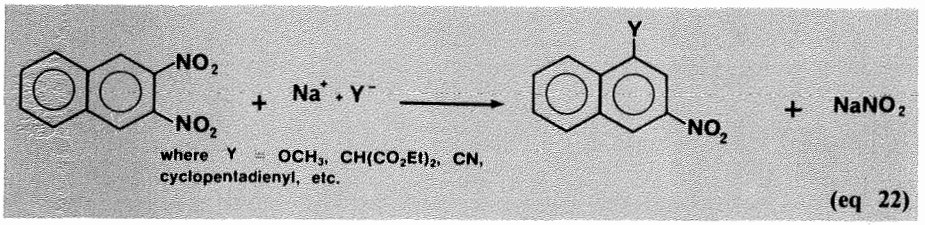
(eq 20)

1,3-Dinitronaphthalene can be partially reduced to 3-nitro-1-naphthylamine under a variety of conditions.[20] The phthalamic acid of the amine shows growth regulatory properties in bean plants (eq 21).[28]



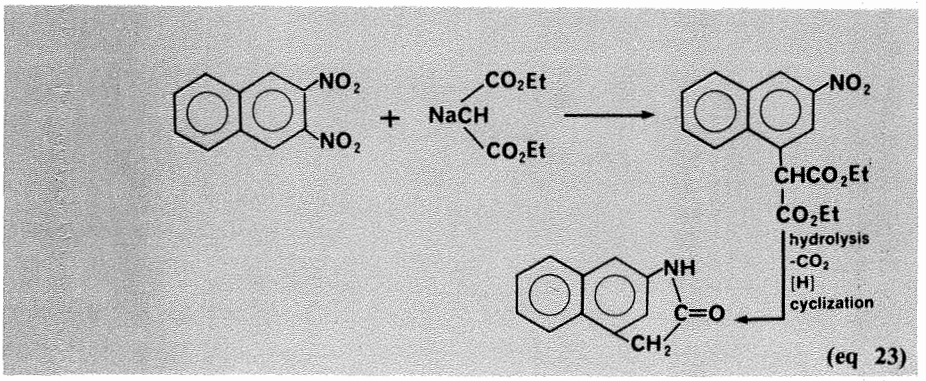
(eq 21)

2,3-Dinitronaphthalene undergoes many unusual reactions not attributed to other dinitro aromatic compounds. Reactions of the compound with numerous carbanions result in products where the 2-nitro group is removed as the carbanions enter the 1-position (eq 22).[29]



(eq 22)

Numerous biologically active compounds were synthesized by this method.[28] This type of reaction may offer an alternative route to the benzomorphan analgesic-type compounds described by May (eq 23).[30]



(eq 23)

HALOGENATED NAPHTHALENES

By the use of the DHA-nitric acid halogenation method and other methods, numerous rare halogenated naphthalenes were made available for experimental purposes (Figure 1). No mixed halogenated naphthalenes were synthesized, but there appears to be no reason why they cannot be made using our methods. Typical reactions of these compounds were described in one of our publications.[16]

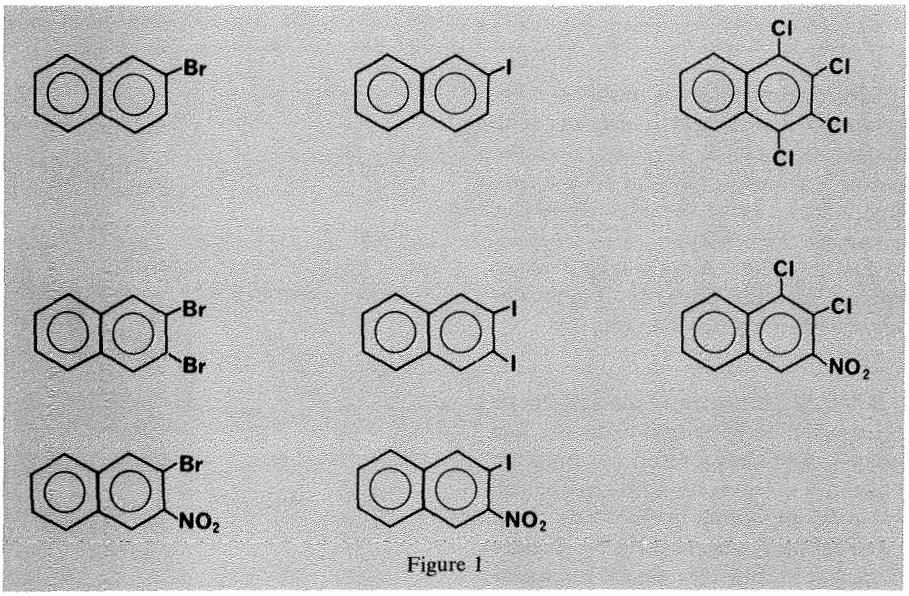
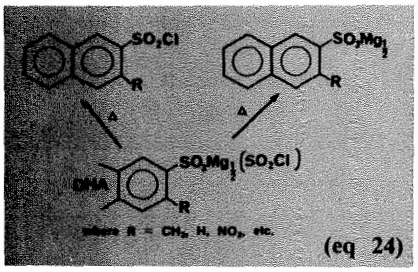


Figure 1

SULFONATED NAPHTHALENES

The chemistry of sulfonated naphthalenes is well documented, particularly in dye chemistry.[31] Sulfonated naphthalenes, if prepared from DHA's, are synthesized as their salts or acid chlorides (eq 24). Sulfonated 2-methyl-DHA is the



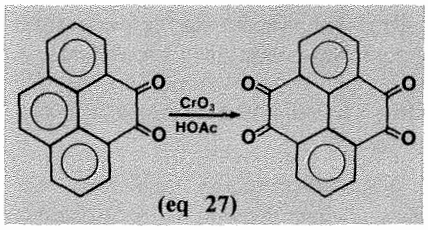
basis of a new process for synthesizing BON acid (3-hydroxy-2-naphthoic acid), an important dye intermediate (eq 25).[18]

2-Nitronaphthalene-3-sulfonic acid, magnesium salt, pyrolyzed from its DHA derivative is the basis of a process for another dye intermediate, 2,3-naphthalenediol (eq 26).[17]

POLYNUCLEAR AROMATICS OTHER THAN NAPHTHALENE

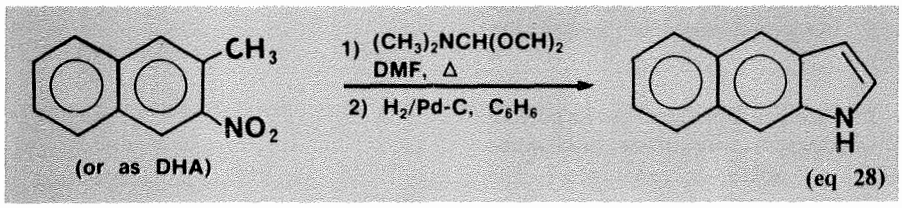
Little work was done by the Berkeley group on the higher polynuclear aromatics and their adducts. The 1,2-pyrenequinone can be oxidized to 1,2,6,7-pyrenediquinone with chromic anhydride (eq 27).[19]

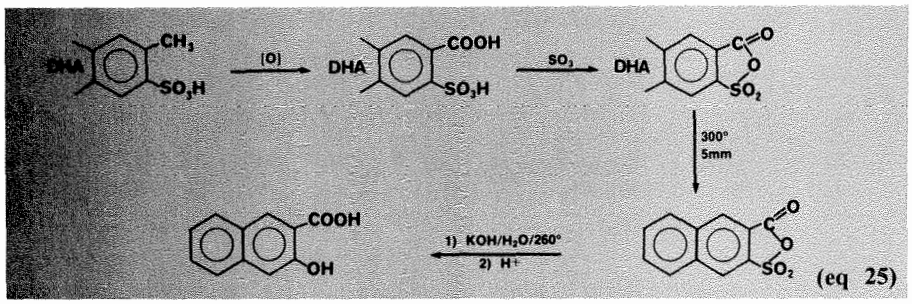
Although the anthracene adducts have been studied, most of the work in this area is still unfinished.

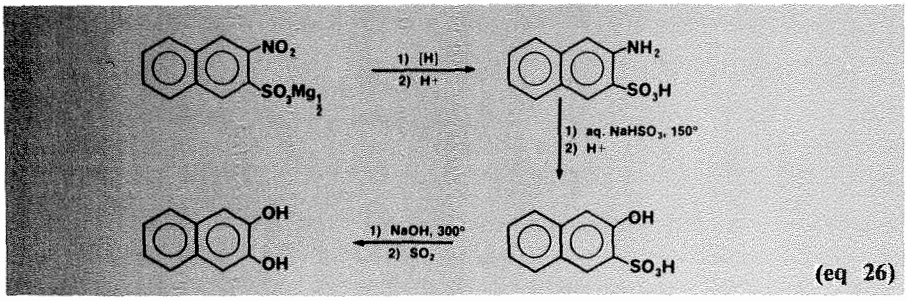


SIGNIFICANCE OF COMMERCIAL AND ACADEMIC POTENTIALS

A vast amount of work remains to be done on DHA's and their derivatives. Studies on the use of high pressures in Diels-Alder reactions are still in their infancy. The work in Berkeley shows that one can avoid the use of the dangerous β-naphthylamine intermediate for the preparation of dyestuffs. Naphthalene compounds made available by the Berkeley group have led to many potentially interesting commercial products and biologically active products, some of which were discussed in this article. Many newly discovered reactions were never pursued; *e.g.*, 2-methyl-3-nitronaphthalene can be utilized in the new indole synthetic reactions described by Leimgruber and Batcho[32] (eq 28) to produce benzoindole. There is an open challenge in DHA technology to all chemists.





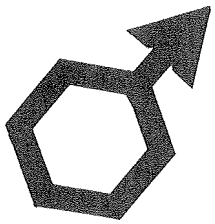


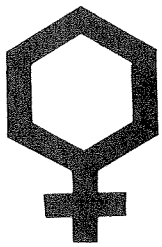
ACKNOWLEDGEMENT

The author wishes to acknowledge the work of chemists, J. Fenyes, D. Morrison and H. Lee; engineers, J. McLaughlin and W. Hoffman; research director, M. Padgett; and the President of Hyman Laboratories, Dr. J. Hyman and assistants. Their combined talents at the Berkeley laboratory resulted in the work which is only partially reported here.

1) J. Hyman and A.A. Danish, U.S. Patent 2,658,927 (1953).
2) J. Hyman and M. Silverman, U.S. Patent 2,658,913 (1953).
3) A.A. Danish, M. Silverman, and Y.A. Tajima, *J. Amer. Chem. Soc.,* **76**, 6144 (1954).
4) H.E. Ungnade and E.T. McBee, *Chem. Rev.,* **50**, 249 (1957).
5) M. Look, unpublished procedures.
6) V. Mark, *Tetrahedron Lett.,* 333 (1961).
7) M. Look, U.S. Patent 3,177,246 (1965).
8) High pressure equipment used was from the American Instrument Co. (35,000 psi), McCartney Manufacturing Co. (TR-20-375, 100,000 psi), and Harwood Engineering Co. (200,000 psi-type E-1634).
9) H.L. Cheifetz, W.B. Hoffman, J. Hyman, M. Look, and J.R. McLaughlin, U.S. Patent 3,177,245 (1965); and unpublished data.
10) W.H. Jones, D. Mangold, and H. Plieninger, *Tetrahedron,* **18**, 267 (1962); H. Plieninger, D. Wild, and J. Westphal, *ibid.,* **25**, 5561 (1969).
11) J. Hyman and H.P.C. Lee, U.S. Patent 3,248,433 (1966); Unpublished techniques of H.L. Cheifetz and M. Look.
12) M. Look, unpublished data.
13) H.L. Cheifetz, M. Look, and J.R. McLaughlin, U.S. Patent 3,065,278 (1962).
14) M. Look and H.L. Cheifetz, U.S. Patent 3,085,115 (1963).
15) J. Hyman and H.P.C. Lee, U.S. Patent 3,248,436 (1966).
16) J.G.E. Fenyes, *J. Org. Chem.,* **27**, 2614 (1962).
17) W.M. Padgett II, U.S. Patent 3,309,402 (1967)
18) M. Look, W.M. Padgett II, J. Hyman, J.G.E. Fenyes, and H.P.C. Lee, U.S. Patent 3,480,646 (1969).
19) M. Look, Abstracts, Joint Meeting of the American Chemical Society, and the Chemical Institute of Canada, Toronto, Ontario, May 1970, p Pest. 24.
20) F. Radt, Ed., "Elsevier's Encyclopedia of Organic Chemistry," Vol. 12B, Elsevier Publishing Co., Inc., New York, N.Y., 1949; N. Donaldson, "The Chemistry and Technology of Naphthalene Compounds," Edward Arnold, London (1958).
21) J.G.E. Fenyes, *J. Chem. Soc. C,* 5, (1968).
22) J. Hyman and H.P.C. Lee, U.S. Patent 3,065,277 (1962).
23) J. Hyman, D.C. Morrison, and H.P.C. Lee, U.S. Patent 3,132,184 (1964).
24) W.C. Hueper in "The Physiopathology of Cancer," 2nd ed., F. Homburger, Ed., Paul B. Hoeber, Inc., New York, N.Y., 1959, p 919-970.
25) W.B. Deichmann and J.L. Radomski, *Ind. Med. Surg.,* 32, 161 (1963).
26) Unpublished report of the School of Medicine, Univ. of California, San Francisco and Hine Laboratories, Inc., San Francisco.
27) Z. Hadidian, T.N. Fredrickson, E.K. Weisburger, J.H. Weisburger, R.M. Glass, and N. Mantel, *J. Nat. Cancer Inst.,* **41**, 985 (1968).
28) J.W. Mitchell, P.C. Marth, and G.D. Freeman, *J. Agr. Food Chem.,* **13**, 326 (1965).
29) D.C. Morrison, U.S. Patent 3,177,241 (1965); *J. Org. Chem.,* **27**, 296 (1962).
30) E.L. May, *Aldrichimica Acta,* **2**, 3 (1969).
31) See for instance: K. Venkataraman, "The Chemistry of Synthetic Dyes," Academic Press, New York, N.Y., 1952; H.E. Fierz-David and L. Blangey, "Fundamental Processes of Dye Chemistry," Interscience Publishers, Inc., New York, N.Y., 1949.
32) W. Leimgruber and A.D. Batcho, *3rd Int. Cong. of Hetero. Chem.,* Sendai, Japan, Aug. 23-27, (1971).

* Present Address: Forest Service, USDA Berkeley, California, 94701.



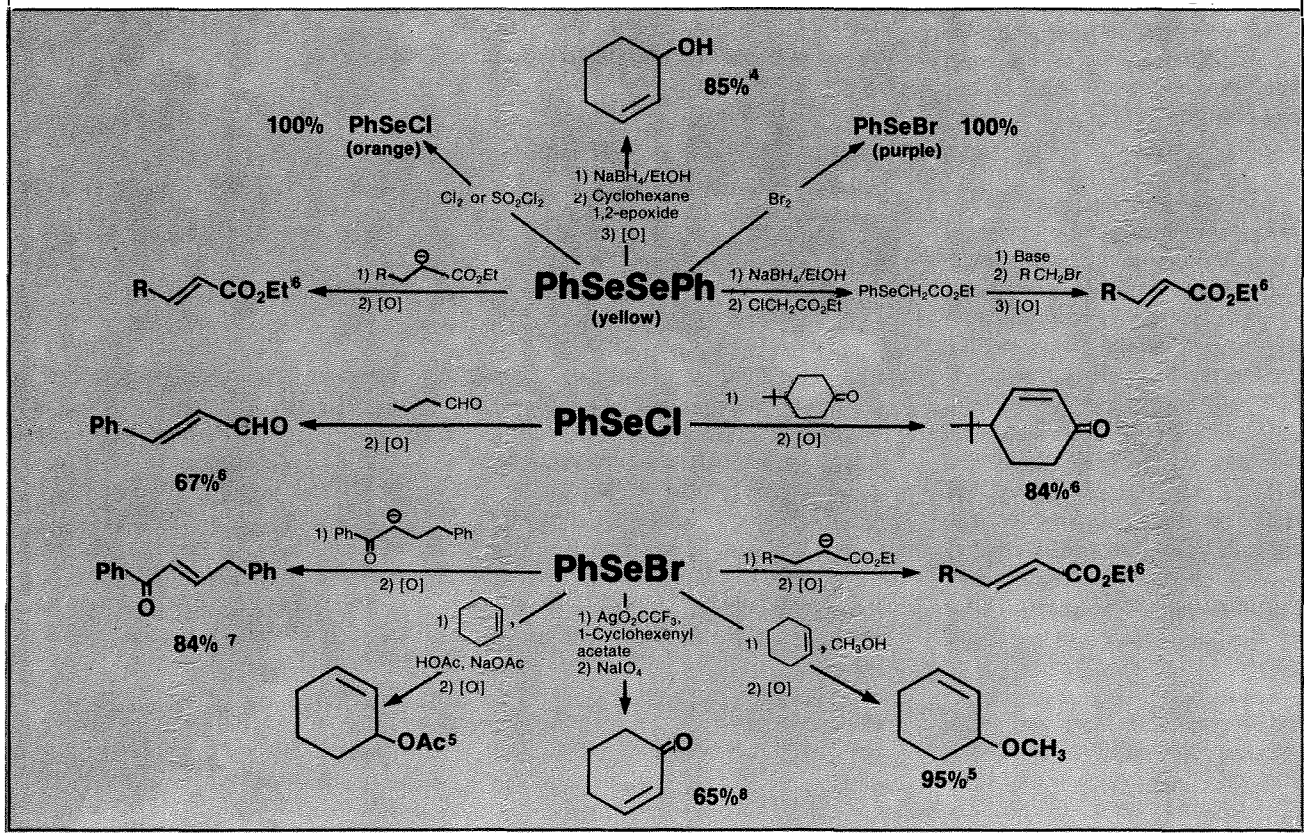


Could your reactions use a little Ph-SeX?

PhSeX (X=Br, Cl or PhSe)

The observation that alkyl phenylselenoxides undergo eliminations at room temperature to form olefins [1-3] is the basis for a new and convenient synthesis of allylic alcohols, [4] allylic ethers and acetates,[5] and α,β-unsaturated carbonyl compounds.[6-8] Diphenyl diselenide is a yellow, odorless, air-stable solid which is easily converted into the highly colored phenylselenenyl halides. The oxidations are conveniently carried out at or below room temperature, using a variety of oxidants (peracetic acid, sodium periodate, hydrogen peroxide, etc.).

1) K. B. Sharpless and R. F. Lauer, *J. Amer. Chem. Soc.*, **94**, 7154 (1972).
2) K. B. Sharpless and R. F. Lauer, *J. Org. Chem.*, **37**, 3973 (1972).
3) K. B. Sharpless, M. W. Young and R. F. Lauer, *Tetrahedron Lett.*, 1979 (1973).
4) K. B. Sharpless and R. F. Lauer, *J. Amer. Chem. Soc.*, **95**, 2697 (1973).
5) K. B. Sharpless and R. F. Lauer, unpublished results.
6) K. B. Sharpless, R. F. Lauer and A. Y. Teranishi, *J. Amer. Chem. Soc.*, **95**, 6137 (1973).
7) H. J. Reich, I. L. Reich and J. M. Renga, *J. Amer. Chem. Soc.*, **95**, 5813 (1973).
8) D. L. J. Clive *J. Chem. Soc., Chem. Commun.*, 695 (1973).



Ester Reductions with Super-Hydride™

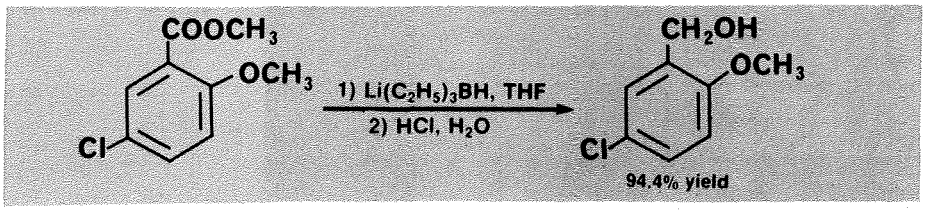
Clinton F. Lane
Aldrich-Boranes, Inc.

Lithium triethylborohydride (Super-Hydride™) is an exceptionally powerful borohydride reducing agent.[2] Recent applications of Super-Hydride™ include the dehalogenation of alkyl halides[3] and the regiospecific and stereospecific reduction of epoxides.[4] Also, various sterically hindered trialkylborohydrides, *e.g.,* our Selectride® reagents, have found an important application in the stereoselective reduction of ketones.[5]

This recent increased activity in the use of trialkylborohydrides for organic reductions is even more interesting when one realizes that this class of compounds was discovered over thirty years ago during war research at the University of Chicago. The results of this war research were finally made public in 1953,[6] but it took seventeen years before a reaction of synthetic importance was reported.[7] From 1953 to 1970, the only reported investigation on the reactions of trialkylborohydrides was in a Ph.D. thesis[8] where an extremely brief survey indicated that lithium triethylborohydride is a stronger reducing agent than lithium borohydride.

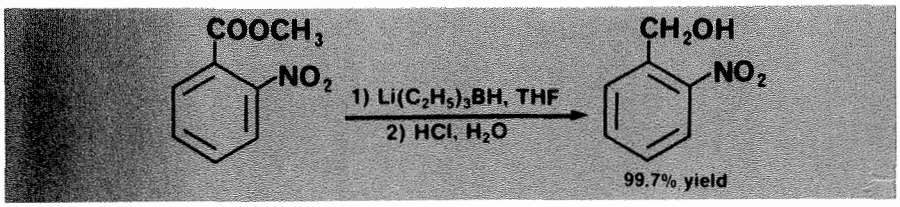
A number of reactions were reported in this thesis including a reduction of ethyl acetate, which appeared to occur quite readily.[9] However, only limited experimental details were given and the isolation of the reduction product from a preparative scale reaction was not reported. The following experimental procedures should now help to fill this definite void and should give some indication of the selectivity of this extremely facile reduction of esters with Super-Hydride.™

Preparation of 5-chloro-2-methoxybenzyl alcohol



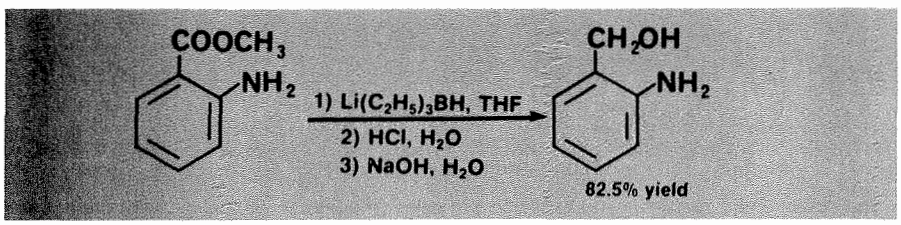
A one-liter, three-necked, round-bottomed flask equipped with a magnetic stirring bar, pressure-equalizing addition funnel, thermometer well, and reflux condenser connected to a mercury bubbler is flamed while flushing with dry, high-purity nitrogen. After cooling to room temperature under a positive pressure of nitrogen, methyl 5-chloro-2-methoxybenzoate (39ml, 250mmol) is added followed by 100ml of tetrahydrofuran (THF) using a dry syringe (note 1). The clear solution is stirred in an ice-water bath as 500ml of 1*M* Super-Hydride™ solution in THF (500mmol) is transferred to the calibrated addition funnel using a Flex-needle™ (note 1). The Super-Hydride™ solution is then added dropwise over a 2-3 hr period at such a rate that the reaction temperature does not exceed 15°. After an additional hour at 0-10°, 50ml of water is added (note 2) followed by 190ml of 3*N* aqueous HCl, at such a rate that the reaction temperature does not exceed 15°. The THF-triethylborane is then removed *via* bulb-to-bulb distillation (note 3) using a water aspirator. After 1.5-2 hr, the vacuum removal of the volatiles is complete as noted by the condensation of water in the upper, cooler parts of the air condenser. The residue in the reaction flask is treated with 400ml of ethyl ether and 350ml of 25% aqueous potassium carbonate. The organic layer is removed, dried over anhydrous potassium carbonate, filtered, and concentrated on a rotary evaporator to yield 43.2g of an oily, crystalline solid. This solid is purified by melting in 100ml of hot hexane and then allowing to cool slowly with rapid stirring. The resulting colorless crystals are collected by filtration and dried under vacuum to yield 40.7g (94.4%) of 5-chloro-2-methoxybenzyl alcohol, mp 55-56° (uncorrected), with ir and nmr spectra in accordance with assigned structure.

Preparation of 2-nitrobenzyl alcohol



The reaction apparatus is assembled as described in the foregoing experiment and charged with 35.4ml (250mmol) of methyl 2-nitrobenzoate and 100ml of THF. The addition funnel is charged with 500ml of 1 *M* Super-Hydride™ in THF (500mmol). The ester-THF solution is stirred in an isopropyl alcohol bath as dry ice is added to the bath until the reaction temperature is -10°. The Super-Hydride™ solution is then added over a 2-3 hr period with sufficient dry ice cooling and at such a rate that a reaction temperature of -10 to -5° is maintained (note 4). After an additional hour at -5 to 0°, 50ml of water is added (note 2) followed by 190ml of 3*N* aqueous HCl at -5 to 0°. The THF-triethylborane is removed *via* bulb-to-bulb distillation and the residue in the reaction flask is treated with 400ml of ethyl ether and 350ml of 25% aqueous potassium carbonate. The aqueous layer is removed and the organic layer is extracted with water (2 x 50ml) and saturated aqueous sodium chloride (1 x 50ml), dried over anhydrous potassium carbonate, filtered, concentrated to dryness on a rotary evaporator, then dried under vacuum to give 38.2g (99.7% yield) of 2-nitrobenzyl alcohol as a yellow, crystalline solid, mp 67-70°, with an ir spectrum identical to that reported for the authentic material.[10] Recrystallization from hexane gave light-yellow needles, mp 70-71° (uncorrected) (Lit.[11] mp 74°).

Preparation of 2-aminobenzyl alcohol



The reaction apparatus is assembled as previously described and charged with 520ml of 1 *M* Super-Hydride™ solution in THF (520mmol) and the addition funnel is charged with 32.4ml (250mmol) of methyl anthranilate dissolved in 60ml of THF. The Super-Hydride™ solution is stirred in an isopropyl alcohol bath as dry ice is added to the bath until the reaction temperature is -10°. The ester-THF solution is then added over a 1 hr period with sufficient dry ice cooling and at such a rate that a reaction temperature of -10 to -5° is maintained (note 5). After an additional hour at -5 to 0°, 175ml of 6*N* aqueous HCl is added at -5 to 0°. After 0.5 hr, the organic layer is removed and discarded and the aqueous layer is extracted with ethyl ether (4 x 300ml) (note 6). The aqueous layer is then made strongly alkaline (pH 10-11) with sodium hydroxide pellets and the resulting mixture is saturated with potassium carbonate and extracted with THF (1 x 300ml). The THF extract is dried over anhydrous potassium carbonate, filtered, concentrated to dryness on a rotary evaporator, and dried under vacuum to give 25.4g (82.5% yield) of 2-aminobenzyl alcohol as colorless crystals, mp 73-76°, with ir spectrum identical to that reported for the authentic material.[12] Recrystallization from heptane gave fine colorless needles, mp 82-83° (uncorrected) (Lit.[13] mp 83-85°).

Notes

1) For a description of syringe and double-tipped needle transfers, please consult the bulletin "Handling Air-Sensitive Solutions," which is available upon request from the Aldrich Chemical Company, Inc.

2) Vigorous hydrogen gas evolution may occur.

3) To facilitate the bulb-to-bulb distillation, the reaction flask is stirred in a 25-35° water bath and the receiver flask is cooled in a dry ice/isopropyl alcohol bath. The triethylborane-THF distillate is not pyrophoric and is most conveniently disposed of by combining with other waste solvents for eventual burning.

4) The lower reaction temperature was found to be necessary to prevent an apparent reduction of the nitro group.

5) The inverse addition procedure results in improved yield and purity of the crude 2-aminobenzyl alcohol.

6) Since the HCl salt of the reduction product is soluble in the aqueous layer, the triethylborane is conveniently removed by extraction.

References

1) For Part II of this series, see C.F. Lane, *Aldrichimica Acta*, **7**, 7 (1974).

2) For a review covering Super-Hydride™ and related reducing agents, please consult the bulletin "Trisubstituted Borohydride Reducing Agents," which is available upon request from the Aldrich Chemical Company, Inc.

3) H.C. Brown and S. Krishnamurthy, *J. Amer. Chem. Soc.*, **95**, 1669 (1973).

4) S. Krishnamurthy, R.M. Schubert, and H.C. Brown, *ibid.*, **95**, 8486 (1973).

5) H.C. Brown and S. Krishnamurthy, *ibid.*, **94**, 7159 (1972), and references cited therein.

6) H.C. Brown, H.I. Schlesinger, I. Sheft, and D.M. Ritter, *ibid.*, **75**, 192 (1953).

7) H.C. Brown and W.C. Dickason, *ibid.*, **92**, 709 (1970).

8) A. Khuri, Ph.D. Thesis, Purdue University, Lafayette, Indiana, 1960.

9) A detailed investigation of the reaction of Super-Hydride™ with selected organic compounds containing representative functional groups is in progress at Purdue University; H.C. Brown, S. Krishnamurthy, and S.C. Kim, personal communication, 1974.

10) C.J. Pouchert, "The Aldrich Library of Infrared Spectra," Aldrich Chemical Company, Inc., 1970, p 596H.

11) Beilstein, **6**(1), 448.

12) C.J. Pouchert "The Aldrich Library of Infrared Spectra," Aldrich Chemical Company, Inc., 1970, p 535F.

13) Beilstein, **13**, 615.

The Aldrich First System of Information Retrieval

David W. Griffiths
Aldrich Chemical Company, Inc.

Since the Aldrich **FIRST** (Fragment Information Retrieval of STructures) system was introduced more than six years ago,[1] we have processed thousands of inquiries for computer-generated lists of structurally similar compounds. Hopefully, this article will acquaint our readers with many of the advantages of using the Aldrich FIRST system. Lists of compounds for consideration as reagents in various research projects may be obtained at no cost to the inquirer.

One immediate advantage of using the Aldrich FIRST system is that the more than 20,000 compounds being surveyed represent the most current listing of products available from Aldrich and its Alfred Bader Chemicals Division. At present, there are approximately 800 Aldrich items and 2,000 Alfred Bader items in the Aldrich FIRST computer file that do not appear in "The Aldrich Handbook of Organic Chemicals". This gap will be reduced with the release of our newest catalog. However, because of the rate at which new compounds are added to our product line, a gap between catalog items and all available compounds will always exist. The Aldrich FIRST system helps to keep this gap at a minimum.

The Aldrich FIRST system of information retrieval is based on the various structure fragments which an individual molecule contains rather than on its chemical characteristics. More than 250 structure fragments have arbitrarily been assigned a two-character code designation. By means of these code designations, one can request a listing of substances having a particular structure fragment or a combination of fragments, while at the same time excluding other coded fragments.

CODING OF RING SYSTEMS

A significant structure fragment in any ring compound is the ring system itself. Unlike the arbitrary code designations given to other structure fragments, ring systems are coded according to a definite set of rules:

1) A number is used to indicate the total number of atoms in a ring.

2) Hetero atoms in a ring system are represented by the element symbol which is placed directly ahead of the ring size number.

3) If more than one hetero atom is present in a ring, the element symbols are listed in alphabetical order.

4) If more than one non-fused ring is present in a molecule, the rings are listed in increasing order of size.

5) If a molecule contains at least two non-fused rings of the same size, the rings are listed in increasing order of hetero complexity. If the degree of hetero complexity is the same, alphabetical order becomes the determining factor.

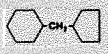
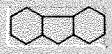
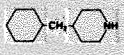
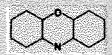
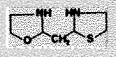
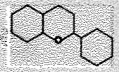
6) Fused ring systems are coded by applying the rules for non-fused rings just given.

7) If a molecule contains both a fused and a non-fused ring system, the non-fused ring is listed first.

8) An asterisk (*) is placed before the ring designation for a non-fused ring and the letter R before that of a fused ring system.

Examples of ring designations in the Aldrich FIRST system are given in Table I.

Table I. Ring Designations

Ring System	Ring Code	Rule	Ring System	Ring Code	Rule
	*6	1		R66	6
	*N5	2		RN56	6
	*NS5	3		RNN5NN6	6
	*56	4		R566	6
	*6N6	5		R66NO6	6
	*NO5NS5	5		*6R6O6	7
	R46	6			

The value of these systematic ring designations will become apparent as the utility of the Aldrich FIRST system is discussed.

RETRIEVAL OF BENZENE DERIVATIVES

It is possible to produce lists of a wide variety of benzene derivatives by means of the Aldrich FIRST system. The benzene ring itself can be retrieved from our computer file by means of its ring designation, the number 6. However, since cyclohexane, cyclohexene and cyclohexadiene all have the same ring designation as benzene, these rings are normally excluded from any request for benzene derivatives. This is done simply by excluding the arbitrary structure fragment codes which were assigned to the three cyclohexane ring systems.

The significant structure fragments in benzoic acid derivatives (in addition to the benzene ring) are the carboxyl and conjugated carbonyl groups. These fragments may be requested in order to obtain a listing of all of our benzoic acids. For other benzoyl derivatives, the carboxyl group code is replaced by the code for the carbonyl derivative being sought. In this manner, one can obtain lists of benzoyl halides, benzamides, benzaldehydes, phenyl ketones, benzoate esters and benzoic acid hydrazides (see Table II).

Cinnamic acid derivatives contain an additional structure feature which allows them to be distinguished from benzoic acid derivatives by the Aldrich FIRST system. That feature is the double bond which is in conjugation with both the carbonyl group and the benzene ring. By requesting this structure fragment along with the benzene ring and the carboxyl and conjugated carbonyl groups, a listing of all of our cinnamic acids may be obtained. If the carboxyl group code is replaced by other carbonyl derivative codes, lists of cinnamoyl halides, cinnamamides, cinnamaldehydes and cinnamate esters may be obtained (see Table III).

Although substituent orientation has not been encoded for all polysubstituted benzene derivatives, it is possible to specify orientation for certain nitrogen-containing compounds by means of coded structure fragments such as N-C-C-N, N-C-C-C-N, N-C-C-C-C-N, N-C-C-O and N-C-C-S. A listing of *o*-phenylenediamines can be produced by requesting benzene derivatives which contain an amino function together with the structure fragment N-C-C-N. Similarly, *m*-phenylenediamines and *p*-phenylenediamines can be located by replacing the N-C-C-N fragment code with those for the N-C-C-C-N and N-C-C-C-C-N fragments, respectively. The means by which lists of these and other nitrogen-containing benzene derivatives can be requested are summarized in Table IV.

Table II. Retrieval of Benzoyl Derivatives

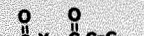
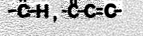
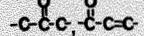
Class of Compound	Structure Fragments Required (other than benzene ring)
benzoic acids	
benzoyl halides	
benzamides	
benzaldehydes	
phenyl ketones	
benzoate esters	
benzoic acid hydrazides	

Table III. Retrieval of Cinnamoyl Derivatives

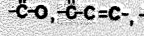
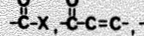
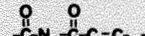
Class of Compound	Structure Fragments Required (other than benzene ring)
cinnamic acids	
cinnamoyl halides	
cinnamamides	
cinnamaldehydes	
cinnamate esters	

Table IV. Retrieval of Specifically Oriented Benzene Derivatives

Class of Compound	Structure Fragments Required (other than benzene ring)
o-phenylenediamines	$-NH_2$, N-C-C-N
m-phenylenediamines	$-NH_2$, N-C-C-C-N
p-phenylenediamines	$-NH_2$, N-C-C-C-C-N
o-aminophenols	$-NH_2$, -OH , N-C-C-O
o-aminobenzenethiols	$-NH_2$, -SH , N-C-C-S
o-nitroanilines	$-NH_2$, $-NO_2$, N-C-C-N
m-nitroanilines	$-NH_2$, $-NO_2$, N-C-C-C-N
p-nitroanilines	$-NH_2$, $-NO_2$, N-C-C-C-C-N
picrylamines (2,4,6-trinitroanilines)	$-NH_2$, $-NO_2$, N-C-C-N , N-C-C-C-N , N-C-C-C-C-N

Additional structure fragments of particular utility in the retrieval of benzene derivatives are the phenethylamine (C_6H_5-C-C-N) and benzhydryl (C_6H_5-C-C_6H_5) groupings. With these fragments, it is possible to produce lists of phenylacetamides (which contain both amide and phenethylamine fragments), phenylacetonitriles (nitrile and phenethylamine fragments) and benzophenones (ketone, conjugated carbonyl and benzhydryl fragments). The phenethylamine grouping is also present in many physiologically active benzene derivatives such as ephedrine and norepinephrine. A listing of these and related compounds can be obtained by requesting the phenethylamine, hydroxy and N-C-C-O fragments.

RETRIEVAL OF HETEROCYCLIC COMPOUNDS

The Aldrich FIRST system is also useful in the retrieval of heterocyclic compounds. As discussed previously, heterocyclic ring systems have been assigned specific ring designations which can be used to retrieve systems of interest. Most of the common monocyclics, as well as certain bicyclics such as indole, purine, quinoline and isoquinoline, also have been given arbitrary two-character code designations. This is necessary in order to distinguish between heterocyclic ring systems like pyridazine, pyrimidine and pyrazine, all of which have the ring designation *NN6. It is possible to produce lists of specifically substituted heterocycles by requesting a specific heterocyclic ring system and certain other structure fragments as summarized in Table V.

Certain heterocyclic alkaloids have characteristic structures which allow for their ready retrieval by the Aldrich FIRST system structure fragment approach. Compounds such as papaverine and laudanosine contain isoquinoline and phenethylamine fragments, which can be requested and subsequently retrieved. Harman alkaloids have a polycyclic fused ring system which includes an indole ring system, a pyridine (or piperidine) nucleus and the N-C-C-N fragment. These three fragments can be requested to produce a listing of harman alkaloids.

Some fused ring heterocycles which have not been assigned arbitrary two-character code designations can be retrieved by requesting a coded heterocyclic fragment and the specific ring code designation for the fused ring system as shown in Table VI.

Table V. Retrieval of Specifically Substituted Heterocycles

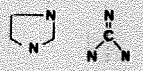
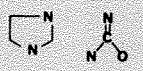
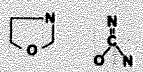
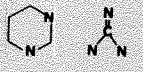
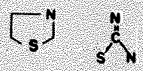
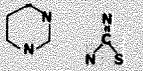
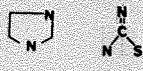
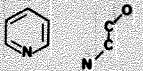
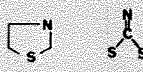
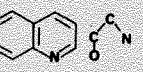
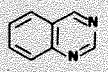
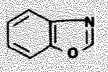
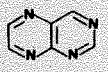
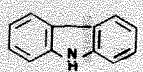
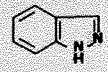
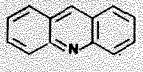
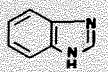
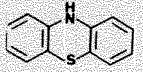
Class of Compound	Structure Fragments Required	Class of Compound	Structure Fragments Required
2-aminoimidazoles		2-hydroxyimidazoles	
2-aminooxazoles		2-aminopyrimidines	
2-aminothiazoles		2-pyrimidinethiols	
2-imidazoletbiols		3-hydroxypyridines	
2-thiazolethiols		8-hydroxyquinolines	

Table VI. Retrieval of Fused Ring Heterocycles

Class of Compound	Structure Fragments Required	Class of Compound	Structure Fragments Required
quinazolines	 R6NN6	benzoxazoles	 RNO56
pteridines	 RNN6NN6	carbazoles	 RN566
indazoles	 RNN56	acridines	 R66N6
benzimidazoles	 RNN56	phenothiazines	 R66NS6

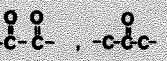
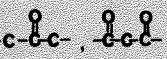
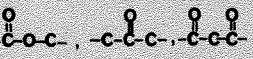
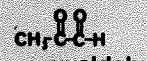
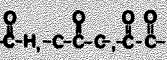
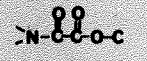
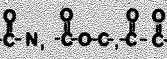
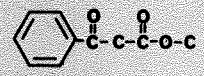
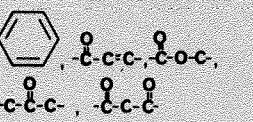
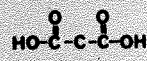
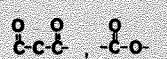
MISCELLANEOUS RETRIEVALS

Many types of amino acid derivatives can be retrieved by the Aldrich FIRST system because they contain other characteristic structure fragments in addition to the amino acid fragment. For example, phenylalanines contain the phenethylamine grouping; serines and threonines contain the N-C-C-O fragment; cysteines, including penicillamines, contain the N-C-C-S fragment; and N-carbobenzyloxy amino acids contain the carbamate ester grouping.

A wide variety of α- and β-dicarbonyl compounds can also be retrieved. Some examples are shown in Table VII.

Special mention should be made of a device used by the Aldrich FIRST system to insure that some listings of structurally similar compounds do not contain a large number of invalid items. When looking for malonic acids, one might request a listing of all compounds containing the carboxyl and β-dicarbonyl fragments (see Table VII). However, such a listing would also contain many β-keto carboxylic acids. In order to avoid this type of problem, the Aldrich FIRST system has been programmed so that either an exact or a minimum number of atoms of a particular element can be specified. Thus, in addition to structure fragment codes, a request for malonic acids will require that each valid compound contains a minimum of four oxygen atoms per molecule. This procedure can be used because the FIRST file contains both structure fragment codes and the molecular formula for each item listed. This also makes it possible to provide lists of compounds containing a particular element such as a listing of all of our organoboron compounds. Similarly, various elements may be excluded from a request.

Table VII. Retrieval of Dicarbonyl Compounds

Class of Compound	Structure Fragments Required
α-diketones	
β-diketones	
β-keto esters	
 pyruvaldehydes	
 oxamates	
 benzoylacetates	
 malonic acids	

GUIDELINES TO USERS OF THE FIRST SYSTEM

Some guidelines are given below for those who might wish to submit a computer search request:

1. Make your request as specific as possible. This is especially important when requesting such categories as benzene derivatives and chlorinated compounds. We list several thousand compounds in each of these categories, making a total listing useless to the inquirer as well as costly for us to provide. To avoid producing such listings, we often make assumptions based on the structure of interest which may have been included with the request. For example, if the structure does not contain any ring systems, we will exclude them unless given instructions to the contrary.

2. Try to keep the number of variables in your request at a minimum. A seemingly simple request for trisubstituted benzene derivatives can lead to an imposing number of individual requests if, for example, each of the three substituents could be three different functional groups. We try to overcome this problem by providing a more general listing than that requested if in our opinion such a listing would not be too large to diminish its usefulness. However, it would always contain compounds having the desired structure fragments.

3. When requesting nitrogen-containing compounds such as amines and amides, it is helpful to indicate the degree of substitution. Primary, secondary and tertiary amines as well as primary, secondary and tertiary amides are each considered to be a separate structure fragment in the Aldrich FIRST system.

4. If you are interested only in the specific compound included with your request, please indicate this. Such a request can be answered immediately upon inspection of our molecular formula file. This will also avoid the nuisance of receiving a listing of our products which contain all the structure fragments of the particular compound of interest but not the compound itself (if it should be unavailable).

5. If you receive a listing of our products which does not appear to be related to your request, please write to us concerning the problem. We will explain the particular structure fragment approach used on your request. Often, we are able to use a modified approach based on your additional comments which will allow us to provide you with a more useful list of products.

Although many examples have been given, these should not be considered to represent all the possibilities. They have been presented primarily to show the general utility of the Aldrich FIRST system of generating lists of structurally similar compounds. It is hoped that many of our readers will avail themselves of this free service.

REFERENCE

W.F. Buth, *Aldrichimica Acta*, **1**, No. 1, 3 (1968).

Page intentially blank

Page intentially blank

Aldrichimica Acta

Volume 7, Number 3
(Final Issue, 1974)

New Reagents for Hydroboration and for Synthesis via Boranes. See page 43.

Trialkylborohydrides as New Versatile Reducing Agents in Organic Synthesis. See page 55.

A publication of Aldrich Chemical Company, Inc.

Aldrichimica Acta

Volume 7, Number 3, 1974
A publication of ALDRICH CHEMICAL COMPANY, INC.

Main Office:
940 W. St. Paul Avenue
Milwaukee, Wisconsin 53233
Telephone: (414) 273-3850
Night number: (414) 273-3025

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

West Coast Service and Distribution Center:
2098 Pike Street
San Leandro, California 94577
Telephone: (415) 352-1186

Southern Service and Distribution Center:
3355 Lenox Road N.E.
Suite 750
Atlanta, Georgia 30326
Telephone: (404) 233-1678

In Canada:
Aldrich Chemical Co. (Canada), Ltd.
1500 Stanley Street
Suite 405
Montreal 110, Quebec
Telephone: (514) 845-9280

In Great Britain:
Ralph N. Emanuel Ltd.
264 Water Rd.
Wembley, Middlesex
HAO 1PY, England
Telephone: 01-998 4414

In Germany:
EGA-Chemie KG
7924 Steinheim am Albuch
Germany
Telephone: (07329) 6011

In Continental Europe:
Aldrich-Europe
B-2340 Beerse
Belgium
Telephone: 014/61431

Table of Contents

About the Cover

We have often asked our chemist-collector why he buys mainly Dutch 17th century paintings preferably, it seems, of biblical subjects. Why not acquire some really first class American paintings? He has just shrugged his shoulders and replied that, with a few exceptions (*e.g.*, Edward Hopper and Charles Munch), he does not like modern American paintings, and the best 19th century masters (*e.g.*, Thomas Eakins) are too expensive. Recently, however, on a trip to Washington to visit the N.I.H., he did buy an American mid-19th century landscape by William Sonntag. Looking at this, we understand why: the haunting beauty of this scene of a bend in the Ohio River east of Cincinnati reminds us of the long views and high skies of so many of the Dutch 17th century landscapes.

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 the late Professor Wolfgang Stechow; now available to all chemist art-lovers.

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.

New Reagents for Hydroboration and for Synthesis Via Boranes*

Herbert C. Brown
Research Professor
Richard B. Wetherill Laboratory
Purdue University
West Lafayette, Indiana

*An address presented before "The Robert A. Welch Foundation Conferences on Chemical Research. XVII. Organic-Inorganic Reagents in Synthetic Chemistry," which was held in Houston, Texas, November 5-7, 1973. The Aldrich Chemical Company expresses thanks to Dr. W. O. Milligan, Director of Research of the Robert A. Welch Foundation for permission to publish this paper.

1. INTRODUCTION

The original studies of the hydroboration reaction emphasized the application of the parent reagent, borane-tetrahydrofuran or other ether complexes.[1] Consequently, it was natural that the subsequent studies of the applicability of boron intermediates in organic synthesis emphasized the utilization of the trialkylboranes,[2] the usual products of such hydroborations.

Instances arose where it was desirable to achieve hydroboration with better regioselectivity than could be achieved with borane itself. This led to the development of a number of substituted boranes for hydroboration with improved regioselectivity.

Some reactions of organoboranes, such as oxidation with alkaline peroxide, carbonylation to tertiary alcohols, and brominolysis to alkyl bromides, utilize all three groups of the trialkylborane, R_3B. However, other reactions utilize only one or two groups. This made it desirable to utilize substituted boranes in these reactions to minimize loss of valuable R groups.

We have had considerable success in overcoming these difficulties with the new reagents. Consequently, it appeared that this symposium would provide an exceptional opportunity to review our work exploring these reagents.

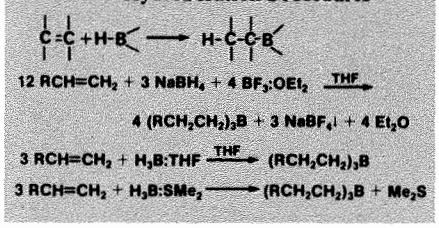
Developments in this area have been exceptionally rapid. Moreover, experience in working with organoboranes is not generally available. Consequently, we are faced with the major hurdle of teaching the chemistry to organic chemists interested in synthesis and of transmitting sufficient know-how to help create the confidence required to utilize this chemistry. To assist in this objective, I have prepared the manuscript for a new book, "Organic Syntheses *via* Boranes." I have also encouraged the Aldrich Chemical Company to set up a subsidiary, "Aldrich-Boranes, Inc." to make available the various intermediates we have found to be valuable in utilizing the fascinating chemistry of the organoboranes, and to participate in transmitting the techniques for work in this field. The time appeared particularly appropriate, therefore, to discuss these new reagents and their interesting possibilities.

2. HYDROBORATION WITH BORANE[1]

Let us first take a few minutes to review. Hydroboration is broadly defined as the addition of an H-B< bond to multiple bonds of carbon with oxygen, nitrogen, and carbon. In this discussion we shall be concerned primarily with hydroboration involving the addition of the H-B< bond to carbon-carbon double and triple bonds.

Hydroboration can be carried out very simply by starting with sodium borohydride (Fig. 1).

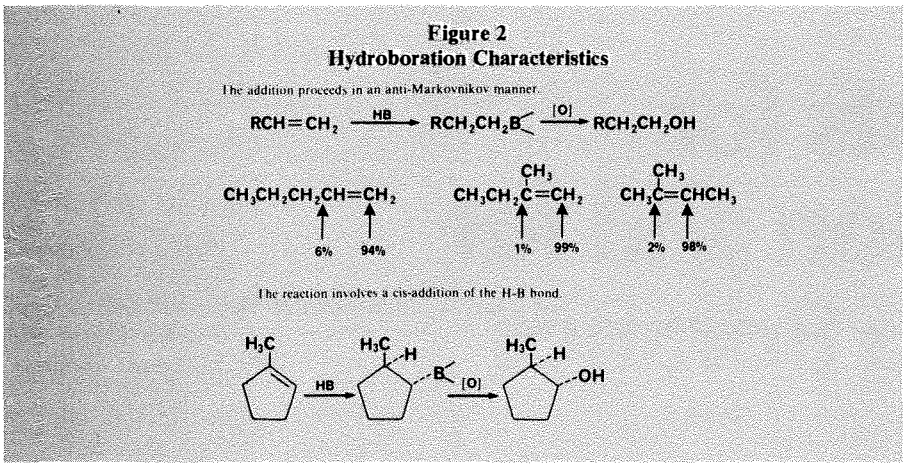
Figure 1
Hydroboration Procedures

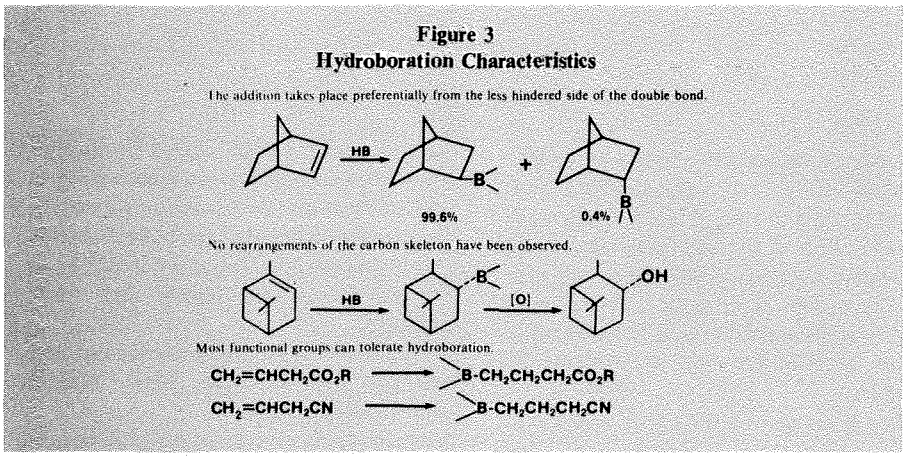


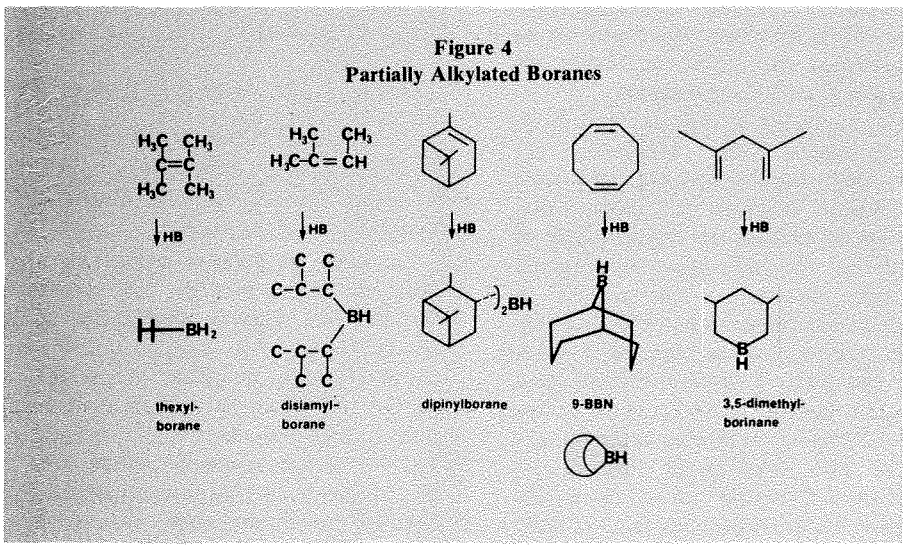
For many purposes it is desirable to avoid the presence of the salt, sodium fluoroborate. This is now easily accomplished by using borane-tetrahydrofuran complex or borane-methyl sulfide complex, both available from Aldrich Chemical Co., Inc. (Fig. 1). The use of borane-methyl sulfide complex makes it possible to synthesize the desired organoboranes readily in hydrocarbon media, ethyl ether and other solvents, so one is no longer restricted to tetrahydrofuran as the operating medium.

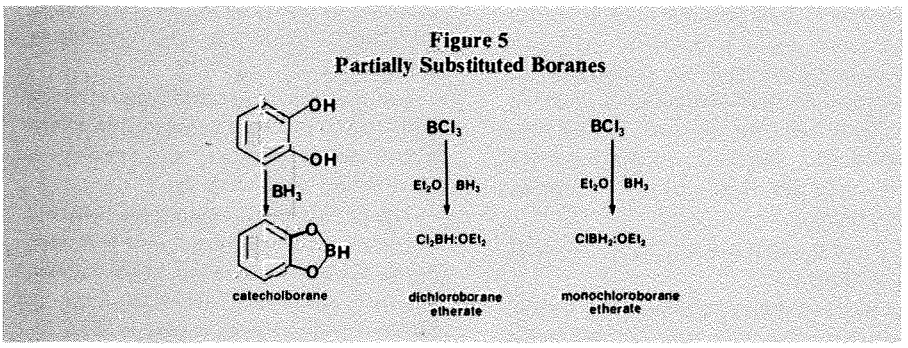
The reaction is essentially quantitative and instantaneous. It proceeds in an anti-Markovnikov manner, and involves a clean cis-addition (Fig. 2).

The addition takes place preferentially from the less hindered side of the double bond. No rearrangements of the carbon skeleton have been observed, even in molecules as labile as α-pinene (Fig. 3).









Finally, but perhaps most important is the fact that olefins containing functional groups can be hydroborated (Fig. 3). Thus, for the first time we are in position to synthesize reactive organometallic intermediates containing such functional groups. (Some people may object to considering the organoboranes as organometallics; however, they have many similar characteristics and fill many of the same applications.)

3. HYDROBORATION WITH BORANE DERIVATIVES[2-4]

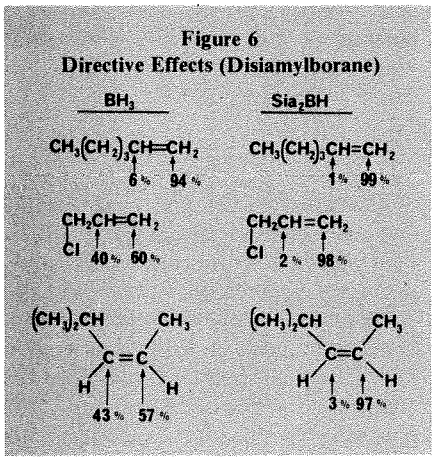
In an earlier work we converted the unsaturated organic compound to the R_3B derivative by treatment with borane and then utilized the organoborane in subsequent reactions. In many cases we observed that in such subsequent reactions only two of the three R groups were being utilized. Sometimes only one of these groups would be utilized. Clearly, this could be a serious handicap if R was derived from a valuable intermediate. Consequently, we began to explore the possibility of synthesizing hydroborating agents that had only one or two reactive centers by achieving the partial alkylation of borane (Fig. 4).

Thexylborane is the most readily available monoalkylborane.[10] Disiamylborane is perhaps the most readily available dialkylborane.[10] Dipinylborane (diisopinocampheylborane) is an asymmetric dialkylborane.[1,4] 9-BBN[2,4] is the first dialkylborane which is sufficiently stable to the atmosphere to permit handling in air with precautions comparable to those used with lithium aluminum hydride and sodium borohydride. It is now commercially available from Aldrich Chemical Co., Inc. Finally, 3,5-dimethylborinane[2,4] has found application in synthesizing the corresponding B-R derivatives for transfer of the R group in free radical reactions.

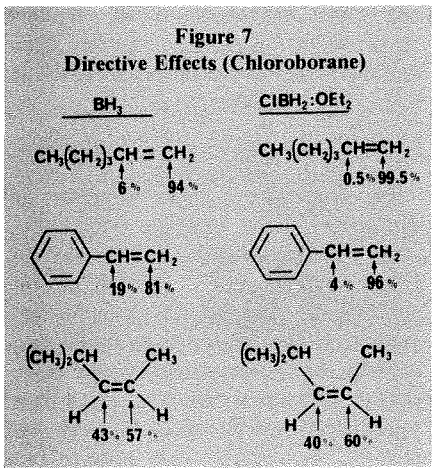
An alternative approach would be the introduction of alternative substituents into the borane molecule. Dimethoxyborane is readily synthesized. Unfortunately, it is not satisfactory for hydroboration. Presumably the resonance of the oxygen atoms with the boron atom so stabilizes the boron atom that it will not add to the carbon-carbon double bond. Such resonance should be less favorable in a phenol derivative. Indeed, catecholborane[2,4] proves to be a valuable hydroborating agent (Fig. 5).

The reaction of boron trichloride with borane in the presence of an ether can be controlled to yield either the dichloroborane etherates or the monochloroborane etherates,[2,4] which have valuable applications (Fig. 5).

It is helpful to be familiar with these various reagents and their similarities and differences in directive effects. Some of the advantages of disiamylborane over borane are indicated in Fig. 6.

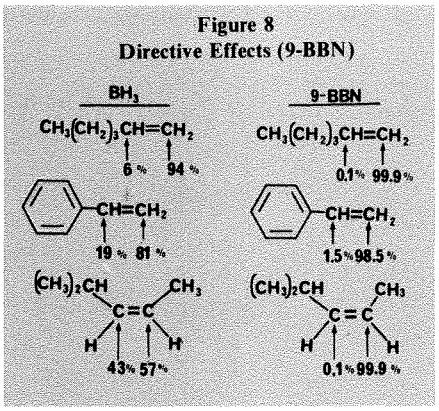


Chloroborane etherate exhibits a high directive influence for the hydroboration of terminal olefins (Fig. 7). However, it does not exhibit the large steric factor that makes disiamylborane so useful in the hydroboration of internal olefins, such as 4-methyl-2-pentene (Fig. 7).



9-BBN exhibits a remarkable directive influence, both for terminal and many internal olefins (Fig. 8).

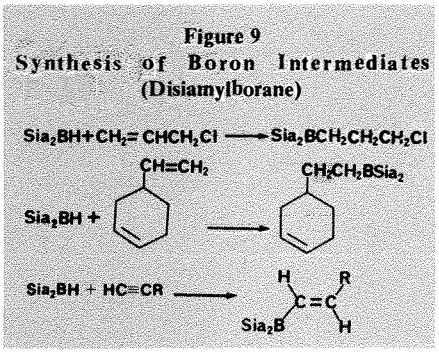
Obviously, the availability of these reagents facilitates the task of doing selective hydroborations at a particular double-bond or of doing regioselective hydroboration of many double-bonds.



4. SYNTHESIS OF BORON INTERMEDIATES[2,4]

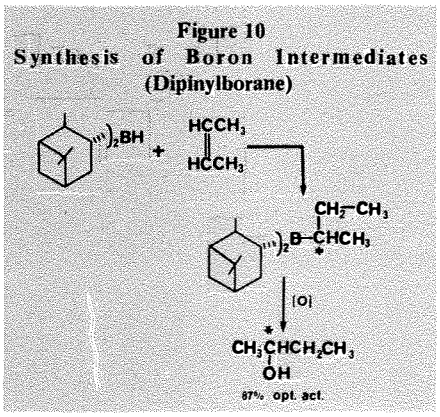
These reagents can be utilized to synthesize specific organoboranes (Fig. 9).

It is interesting that only a few years ago it was thought that mixed organoboranes (organoboranes with two or three different groups attached to boron) could not be synthesized and, if synthesized, would undergo spontaneous conversion into the corresponding symmetrical molecules. However, hydroboration makes these "mixed" organoboranes readily available and they can be converted into other products without loss of the original structure.



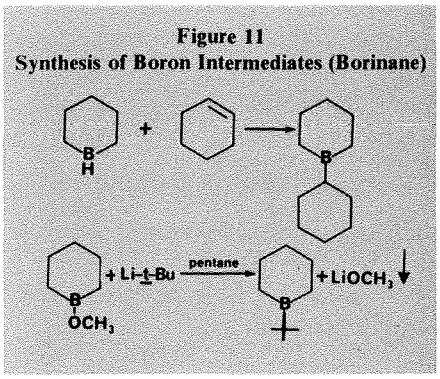
Optically active dipinylborane can be utilized to achieve asymmetric syntheses (Fig. 10).

Since the α-pinene utilized was only 90% optically active, hydroboration achieves an asymmetric synthesis almost as good as that induced by enzymes.

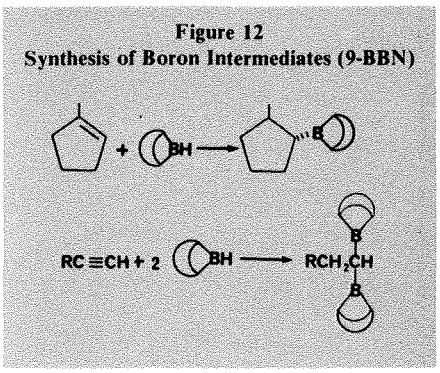


There are many promising reactions of dipinylborane. We used it to separate 3-methylcyclopentene into its antipodes. It has been used to obtain optically active allenes. Finally, it has been used recently to prepare optically active prostaglandin intermediates.

Boracyclanes, such as 3,5-dimethylborinane (Fig. 5) or borinane itself, can be used to hydroborate olefins to obtain the corresponding derivatives. (Fig. 11).



Various derivatives of 9-BBN are readily synthesized (Fig. 12). These derivatives find valuable applications, to be described later.



Catecholborane reacts more sluggishly than borane itself. In tetrahydrofuran at 0° the borane reaction is often over in less than one minute. However, the reaction of catecholborane with representative olefins requires a temperature of 100° and reaction time of approximately one hour. Acetylenes are somewhat more reactive, so that one hour at 67° is usually adequate (Fig. 13). An advantage of this reagent is that the products can be readily hydrolyzed to the corresponding borinic acids.

Figure 13
Synthesis of Boron Intermediates (Catecholborane)

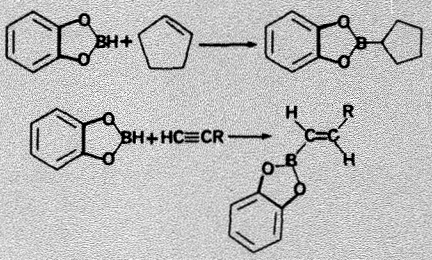


Figure 14
Synthesis of Boron Intermediates (Dichloroborane Etherate)

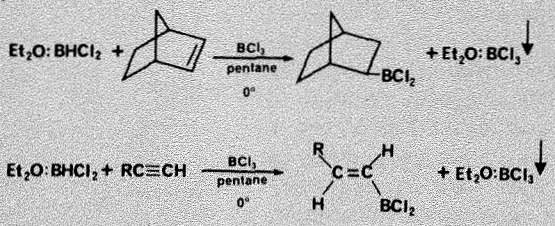


Figure 15
Synthesis of Boron Intermediates (Thexylborane)

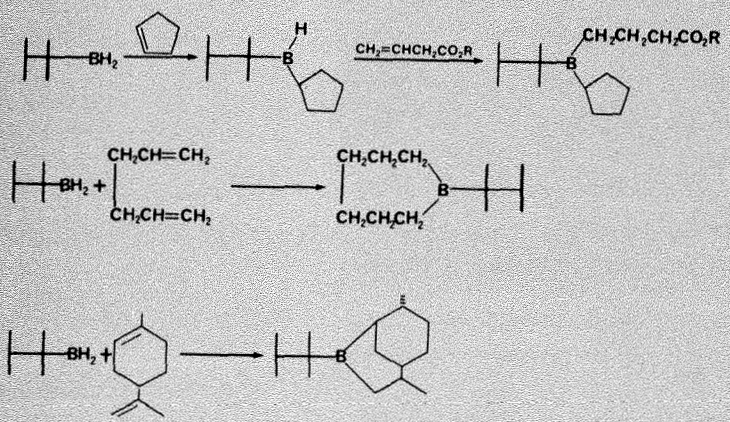
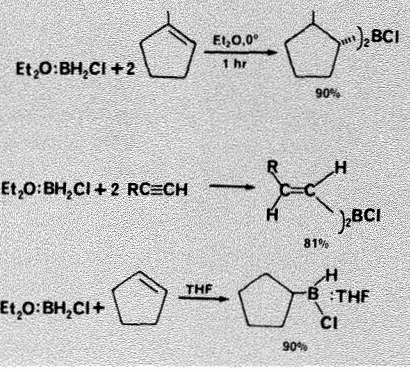


Figure 16
Synthesis of Boron Intermediates (Monochloroborane Etherate)



In the case of dichloroborane etherate, the complex is so stable that hydroboration does not occur at any convenient rate. Unfortunately, a higher reaction temperature or a long reaction time does not solve the difficulty, since the products obtained are no longer the pure monoalkyldichloroboranes desired. Fortunately, the addition of the reagent to a mixture of the olefin and boron trichloride in pentane at 0° solves the problem and provides the desired $RBCl_2$ derivatives (Fig. 14). The synthesis is readily extended to acetylenes.

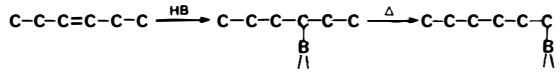
Thexylborane is the most readily available monoalkylborane. In the early days we used it empirically and often encountered phenomena we could not understand. More recently, we undertook a systematic study of thexylborane as a hydroborating agent and established the conditions which provide first, the monoalkylthexylborane and then the dialkylthexylborane[10] (Fig. 15).

One of the valuable applications of thexylborane as a bifunctional hydroborating agent, is the cyclic hydroboration of dienes. For example, the cyclic hydroboration of limonene controls the stereochemistry at three centers (Fig. 15) and provides a simple route to (-)-carvomenthol.

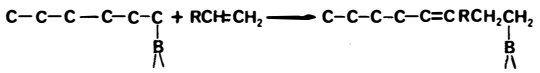
In contrast to the behavior of dichloroborane etherate (Fig. 14), monochloroborane etherate hydroborates olefins and acetylenes readily at 0°. This provides a simple new route to dialkylchloroboranes and their corresponding borinic acids and esters (Fig. 16). In the presence of one mole of tetrahydrofuran, the reaction can be controlled to yield the monoalkylchloroborane species (Fig. 16).

These developments make readily available a large number of borane derivatives. Consequently, we have been exploring the chemistry of these derivatives with emphasis on their utilization to facilitate organic synthesis.

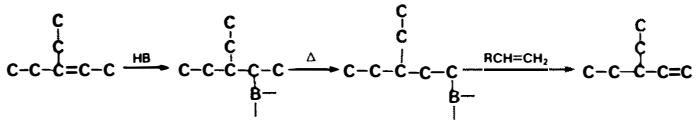
(5-A.) Isomerization[1]



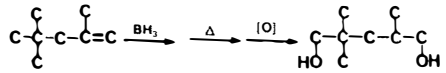
(5-B.) Displacement[1]



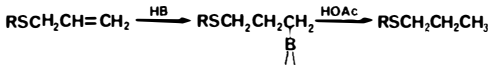
(5-C.) Contrathermodynamic isomerization of olefins[1]



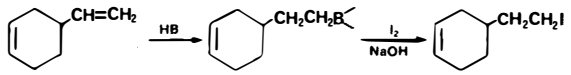
(5-D.) Cyclization[1]



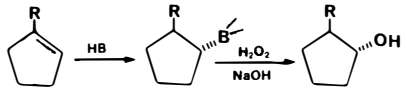
(5-E.) Protonolysis[1]



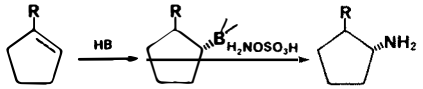
(5-F.) Halogenolysis[2-4]



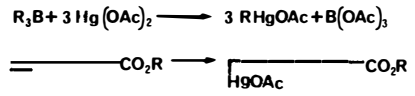
(5-G.) Oxidation[2-4]



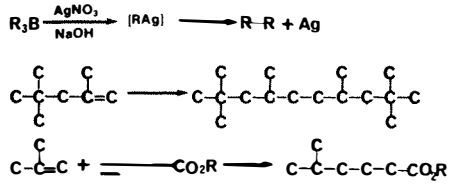
(5-H.) Amination[2-4]



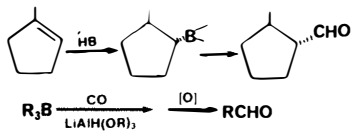
(5-I.) Metallation[2-4]



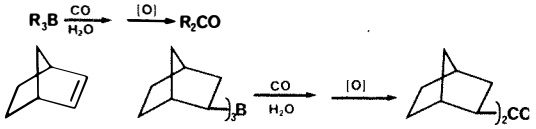
(5-J.) Coupling[1]



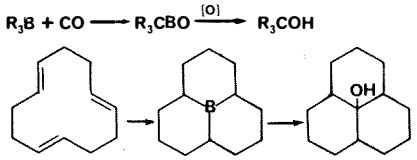
(5-K.) Carbonylation to aldehydes[5]



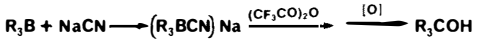
(5-L.) Carbonylation to ketones[5]



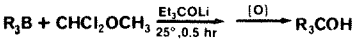
(5-M.) Carbonylation to tertiary alcohols[5]



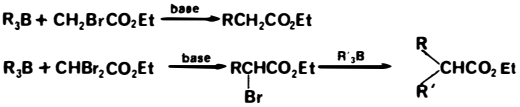
(5-N.) Cyanoboration to tertiary alcohols[2-4]



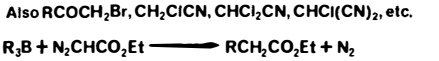
(5-O.) The DCME reaction[4]



(5-P.) Alkylations and arylations[2,4,7]

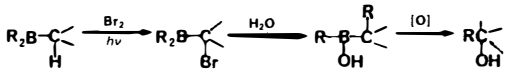


Also $RCOCH_2Br$, CH_2ClCN, $CHCl_2CN$, $CHCl(CN)_2$, etc.

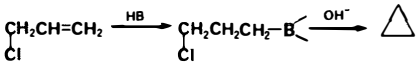


Also N_2CHCOR, N_2CHCHO, N_2CHCN, etc.

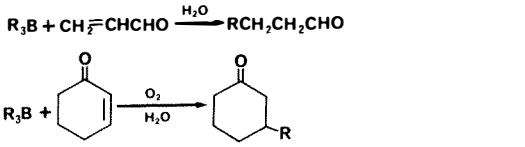
(5-Q.) α-Bromination[2-4]



(5-R.) Cyclopropane synthesis[2-4]



(5-S.) Conjugate addition[8]



(5-T.) Alkynylborate reactions[4]

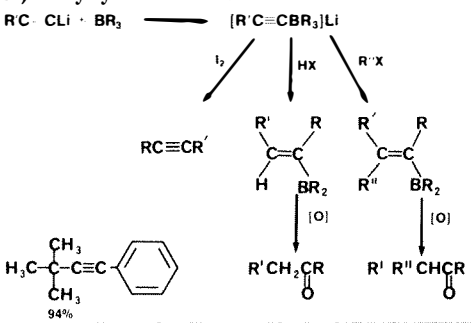


Figure 17
Synthesis of Boron Intermediates (Trialkylborohydrides)

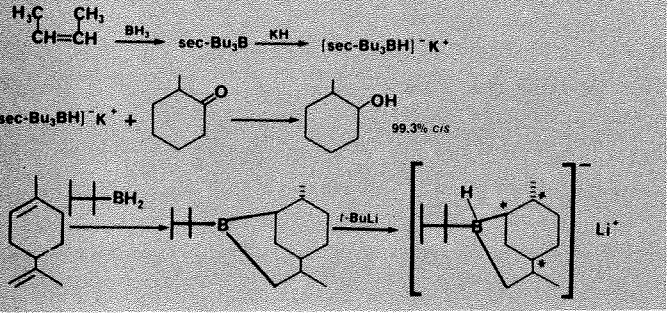
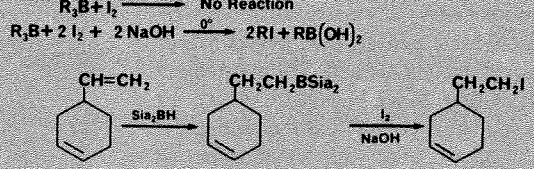


Figure 18
Application of Disiamylborane (Halogenolysis)



For example, triethylborane reacts with lithium hydride to produce lithium triethylborohydride, apparently the most active nucleophile known. The corresponding derivative from tri-*sec*-butylborane cannot be synthesized by direct reaction with lithium hydride, but can be made by reaction with lithium trimethoxyaluminohydride or potassium hydride. It exhibits remarkable selectivity for the reduction of ketones (Fig. 17). Both of these reagents are now commercially available from Aldrich Chemical Co., Inc., (Super Hydride® and Selectride®). The related derivative from thexylborane and limonene has been reported to be uniquely effective for the reduction of a prostaglandin intermediate.

It is important to realize the power of these new methods. At one time it was a major task to prepare pure isomeric alcohols, such as *cis*- and *trans*-2-methylcyclohexanol. However, hydroboration-oxidation of 1-methylcyclohexene yields *trans*-2-methylcyclohexanol. Oxidation to the ketone followed by reduction with Selectride® yields essentially pure *cis*-2-methylcyclohexanol (99.3%). Consequently, it is no longer a problem to provide these derivatives in quantity.

5. THE VERSATILE ORGANOBORANES[2-4,6,9]

The ready availability of the trialkylboranes via the hydroboration reaction prompted research to explore the chemistry of these derivatives. This exploration has been exceptionally fruitful. Time will not permit a detailed discussion of the developments in this area.[2-4] However, it may be helpful to outline the main features (A-T).

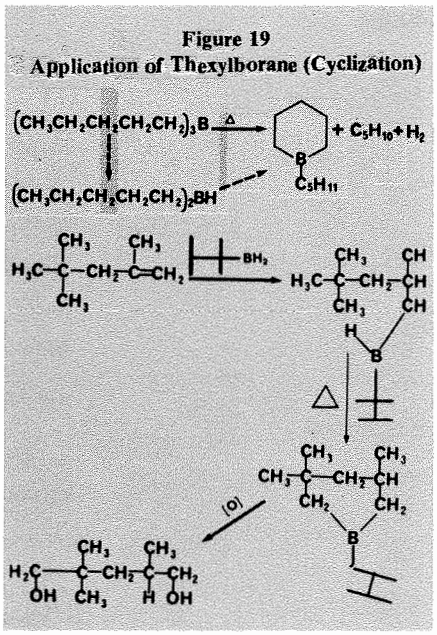
6. APPLICATIONS OF BORON INTERMEDIATES[2-4]

It was not feasible here to attempt a detailed discussion of the remarkable chemistry of the versatile organoboranes, summarized in the previous section. It seems more appropriate, for the special objectives of the present treatment, to consider some of the advantages of the new boron intermediates in some of these reactions.

The reaction of iodine with organoboranes is greatly facilitated by alkali. Unfortunately, only one or two of the alkyl groups of the R_3B intermediate react readily. Since primary alkyl groups react far more readily than secondary, it is possible to utilize disiamylborane[1] to achieve high yields of the desired iodide (Fig. 18).

The cyclization reaction (5-D) apparently proceeds through the formation of a dialkylborane intermediate formed in the thermal decomposition of the trialkylborane. Utilization of thexylborane[10] provides the thexylmonoalkylborane directly for cyclization (Fig. 19).

Figure 19
Application of Thexylborane (Cyclization)

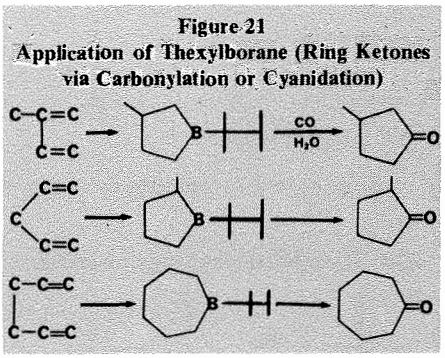


A disadvantage in applying the carbonylation reaction[5] to simple trialkylboranes (5-L) is the loss of one of the three alkyl groups. The use of thexylborane avoids this difficulty and makes possible the synthesis of ketones containing two different groups (Fig. 20).

The Pelter reaction (5-N), treatment with an alkali metal cyanide, followed by trifluoroacetic acid anhydride, provides an alternative route.

Cyclic hydroboration of appropriate dienes with thexylborane, followed by carbonylation or cyanidation, provides a simple route from such dienes to the corresponding ring ketones (Fig. 21).

Figure 21
Application of Thexylborane (Ring Ketones via Carbonylation or Cyanidation)



These reactions provide a new annelation reaction of wide applicability[10] (Fig. 22).

α-Bromination[2,4] in the presence of water provides an alternative means of converting organoboranes into carbon structures (5-Q). Thus, the same cyclic hydroboration intermediate (Fig. 22) is converted through this reaction into a different carbon structure (Fig. 23).

It is possible to utilize α-bromination[2,4] to achieve the synthesis of tertiary alcohols, many of them not readily available by classical methods (Fig. 24).

The Zweifel trans olefin synthesis provides a simple valuable route to the trans olefins.[2-4] However, it suffers from the disadvantage of requiring dialkylboranes as intermediates, and many of these are not readily available. Moreover, only one of the two alkyl groups in the dialkylborane is utilized. Use of the thexylmonoalkylborane circumvents these difficulties[4,10] (Fig. 25).

The thexylmonoalkylboranes also provide a convenient new route to the monoalkylboranes, making these derivatives readily available for the first time.[4,10] Treatment of the borane with a tertiary amine of low steric requirements, such as pyridine, results in the formation of a simple addition compound. However, a base of larger steric requirements such as triethylamine, results in the displacement of 2,3-dimethyl-2-butene and the formation of the aminate of the monoalkylborane (Fig. 26).

Figure 20
Application of Thexylborane (General Ketone Synthesis *via* Carbonylation)

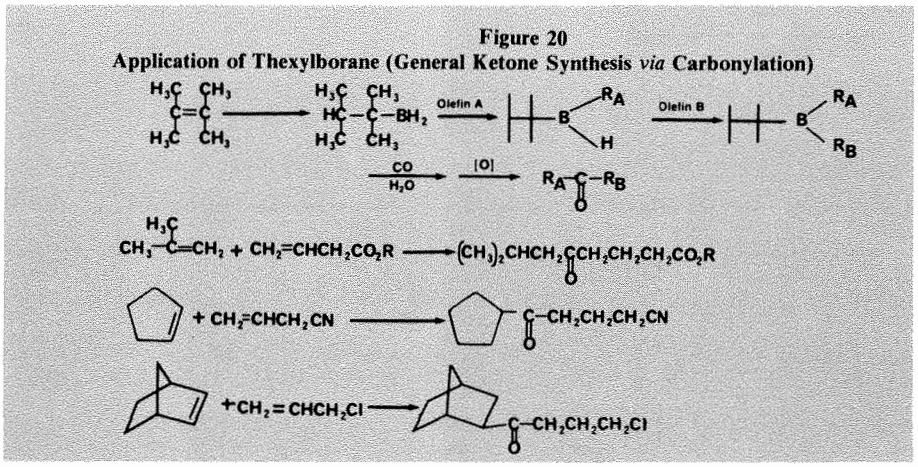


Figure 22
Application of Thexylborane (New Annelation Reaction *via* Carbonylation or Cyanidation)

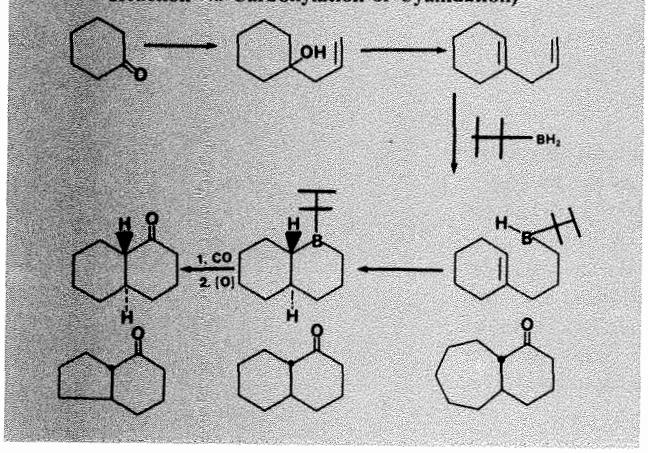


Figure 23
Application of Thexylborane (α-Bromination)

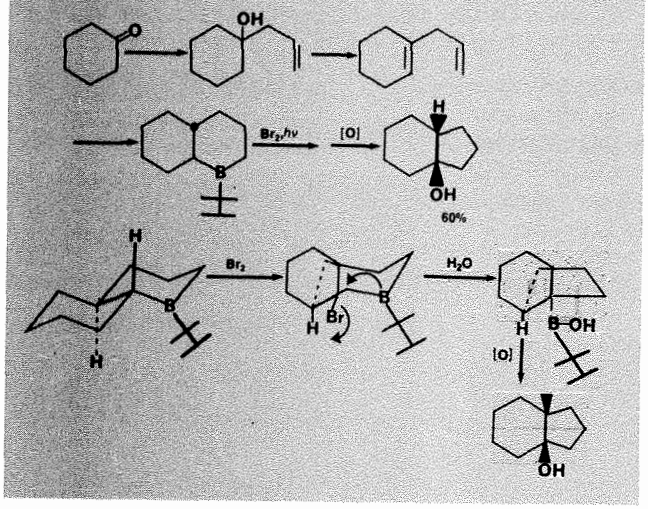


Figure 24
Application of Thexylborane (α-Bromination)

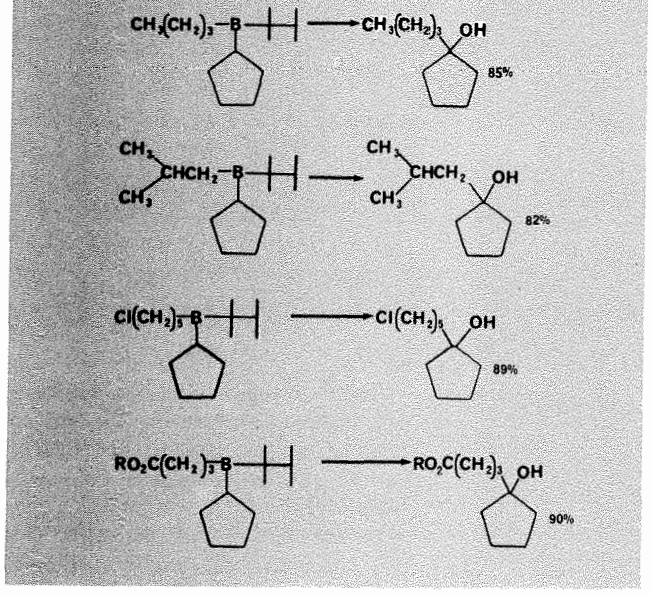
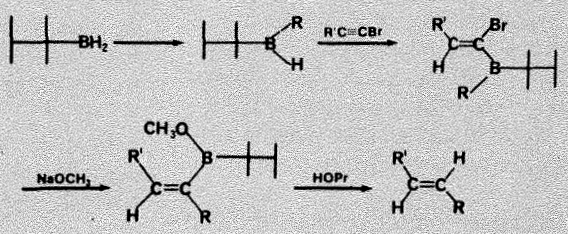


Figure 25
Application of Thexylborane (Zweifel *trans* Olefin Synthesis)



See also E.J. Corey, T. Ravindranathan, *J. Amer. Chem. Soc.*, 94, 4013 (1972)

R'	R	Yield %
n-Bu	2-methyl-1-pentyl	94
	3-hexyl	93
	2-methyl-2-butyl	86
	cyclohexyl	85
	trans-2-methylcyclopentyl	94

Figure 26
Application of Thexylborane (Synthesis of Monoalkylboranes)

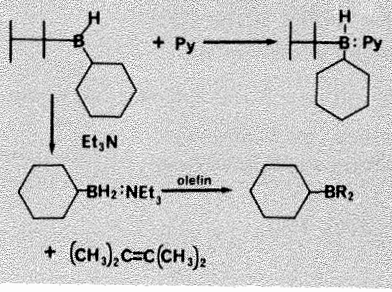


Figure 27
Application of 9-BBN (Cyclopropane Synthesis)

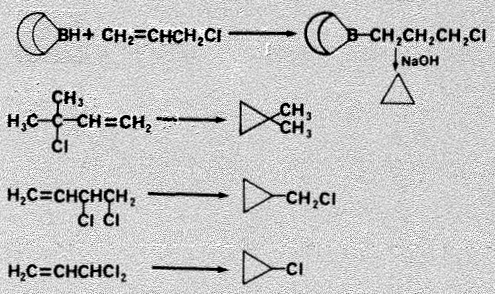
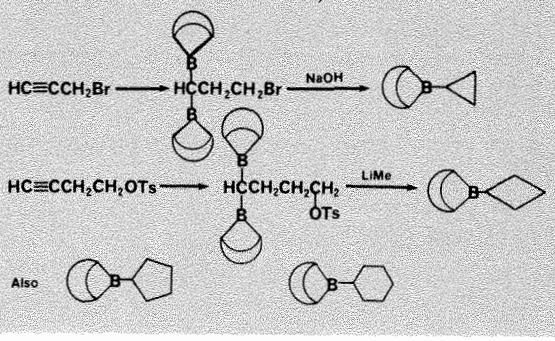


Figure 28
Application of 9-BBN (Synthesis of Cyclic Derivatives)



The boron derivatives realized from allylic halides provide a simple route to cyclopropanes (Fig. 27). 9-BBN possesses advantages in this application because its high regiospecificity for the terminal carbon atom overcomes the unfavorable directive influence of the allylic halogen.[2-4] The relative openness of the 9-BBN boron atom facilitates addition of the hydroxide ion leading to closure.

A similar cyclization reaction of di-9-BBN derivatives provides routes to the corresponding B-cycloalkyl-9-BBN compounds (Fig. 28). Oxidation of the B-cyclopropyl derivative yields cyclopropanol in excellent yield. The parent 9-BBN derivatives are also valuable to transfer the B-R group to the α-position of ketones, esters, nitriles, etc. (5-P).[7]

A highly useful reaction which should be in the repertoire of every chemist engaged in organic synthesis is the conversion of the B-R-9-BBN derivatives into the corresponding aldehydes[2,4,5] (Fig. 29).

It should be recalled that in this reaction, as in many others which have been mentioned, many functional groups can be accommodated (Fig. 30).

The B-alkyl- and B-aryl-9-BBN transfer selectively the B-R group to the α-position of α-halo ketones, esters, nitriles, etc. (5-P).[2,4,7] Moreover, this reaction, as do practically all which have been studied, proceeds with retention at the migrating center (Fig. 31).

In free radical reactions involving organoborations, such as the conjugate addition (5-S), secondary and tertiary alkyl groups participate in preference to primary.[2,4,8] Therefore, in such reactions, the B-R-9-BBN derivatives are unsatisfactory. Fortunately, the borinane derivatives are entirely satisfactory for many of these free radical reactions[4] (Fig. 32).

The B-alkylcatecholborane derivatives are readily reduced to the corresponding boranes.[2,3] This provides an alternative route for the synthesis of monoalkylboranes (Fig. 33).

The B-vinylcatecholborane derivatives react rapidly at 0° with mercuric acetate to produce the corresponding mercurials with complete stereospecificity[2,4] (Fig. 34). This approach has been utilized in the Pappo prostaglandin synthesis.[4]

Figure 29
Application of 9-BBN (Aldehyde Synthesis *via* Carbonylation)

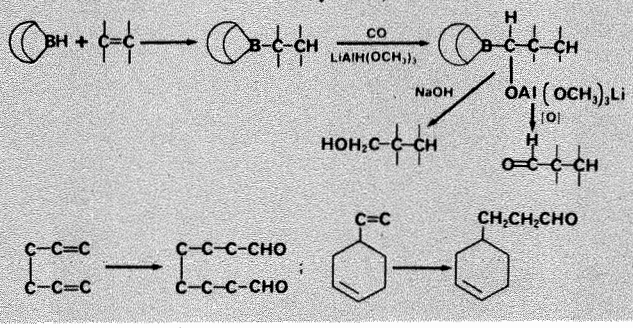


Figure 30
Application of 9-BBN (Aldehyde Synthesis *via* Carbonylation)

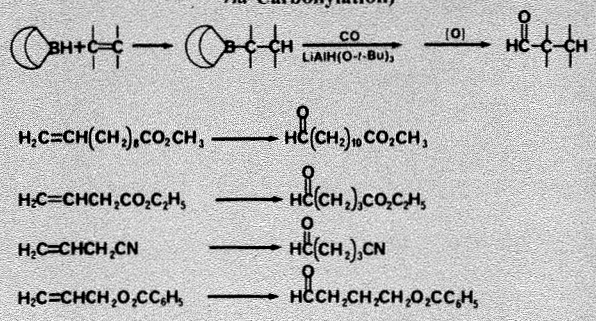


Figure 31
Application of 9-BBN (Alkylation and Arylation)

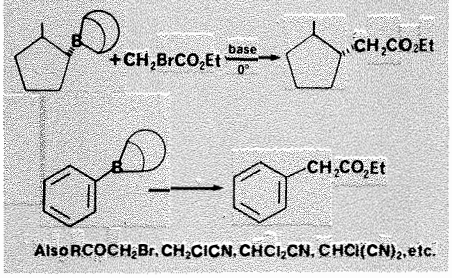


Figure 32
Application of Borinane (Free Radical Reactions)

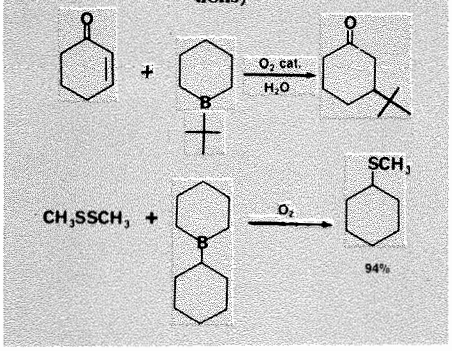


Figure 33
Application of Catecbolborane (Synthesis of Monoalkylboranes)

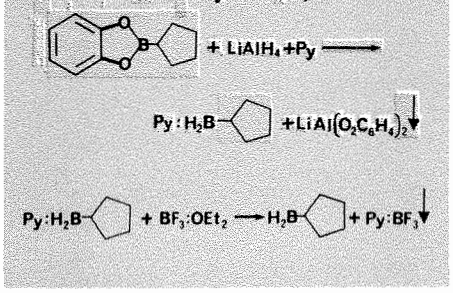
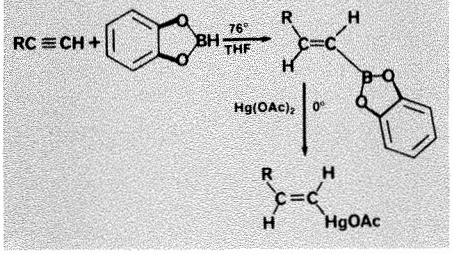
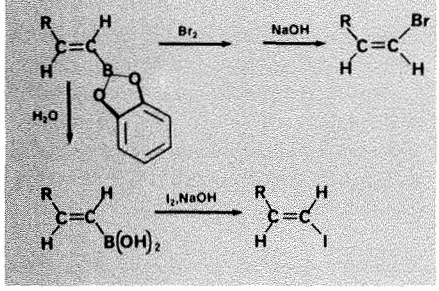


Figure 34
Application of Catecholborane (Vinyl Mercurials)



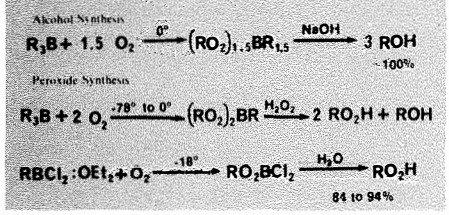
The B-vinylcatecholborane derivatives are readily transformed into the corresponding vinyl halides. The reactions can be directed to achieve the replacement of the boronic acid grouping either with inversion or with retention[4] (Fig. 35). This reaction has also been utilized in a prostaglandin synthesis.[4]

Figure 35
Application of Catecholborane (Vinyl Halides)



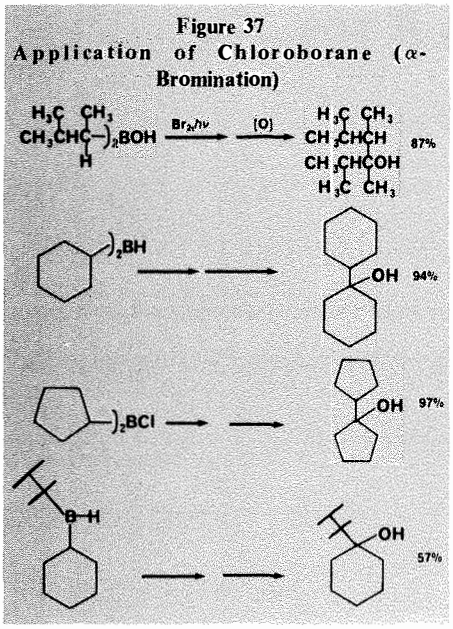
The synthesis of peroxides from organoboranes can be improved by utilizing the alkyldichloroborane etherate (Fig. 36). This avoids loss of one of the three alkyl groups and the need to separate the peroxide from the accompanying alcohol.[2,4]

Figure 36
Application of Dichloroborane (Synthesis of Peroxides)



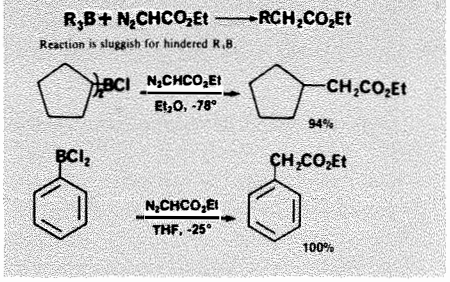
Dialkylborinic acids are especially valuable as intermediates in the α-bromination reaction (5-Q). While a few dialkylboranes (*e.g.,* disiamylborane, dicyclohexylborane) are readily available through hydroboration, many others are not. Fortunately, chloroborane provides a simple route to such borinic acids, as illustrated for the synthesis of dicyclopentylchloroborane and its conversion to 1-cyclopentylcyclopentanol in 97% yield[2,4] (Fig. 37).

Figure 37
Application of Chloroborane (α-Bromination)



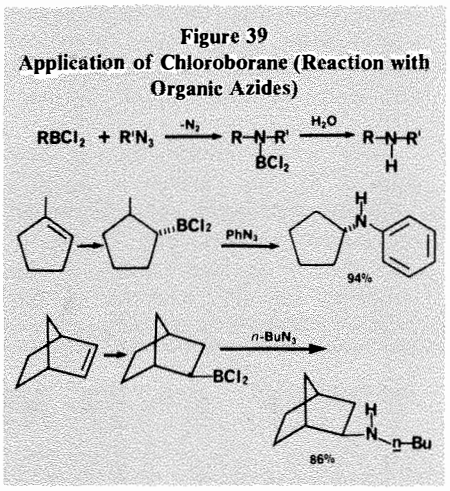
The greater acid strength of the R_2BCl and $RBCl_2$ derivatives over the parent R_3B compounds greatly facilitates the reactions with diazo derivatives and makes it possible both to extend the reaction to hindered groups and to achieve a higher utilization of the groups[2-4] (Fig. 38).

Figure 38
Application of Chloroborane (Hooz Reaction)



The related reaction with alkyl or aryl azides provides a stereospecific route to secondary amines (Fig. 39).

Figure 39
Application of Chloroborane (Reaction with Organic Azides)



The hydroboration of acetylenes with chloroborane provides a direct route to the dialkenylborinic acids and greatly facilitates the Zweifel synthesis of cis,trans-dienes[4] (Fig. 40).

The power of these new methods is illustrated by their utilization for the stereospecific synthesis of aziridines[4] (Fig. 41). In this synthesis the stereochemistry of the two centers of the ethylenimine ring can be controlled as well as that of the R′ group attached to the nitrogen atom.

The ready availability of the borinic acid derivatives through selective hydroboration to the dialkylborane or through reaction with chloroborane can be combined with the base-induced reaction with dichloromethyl methyl ether (DCME) (5-O) to provide a versatile, new synthetic route to ketones (Fig. 42).

7. CONCLUSION

The facile hydroboration of olefins was discovered in 1956. For the next decade we were engaged primarily in the study of this fascinating new reaction. This reaction made the organoboranes readily available. Consequently, we then began to shift our emphasis from the study of hydroboration to a study of the chemistry of organoboranes.

This proved to be an extraordinarily rich, albeit largely virgin, unexplored area.

Figure 40
Application of Chloroborane (Zweifel Diene Synthesis)

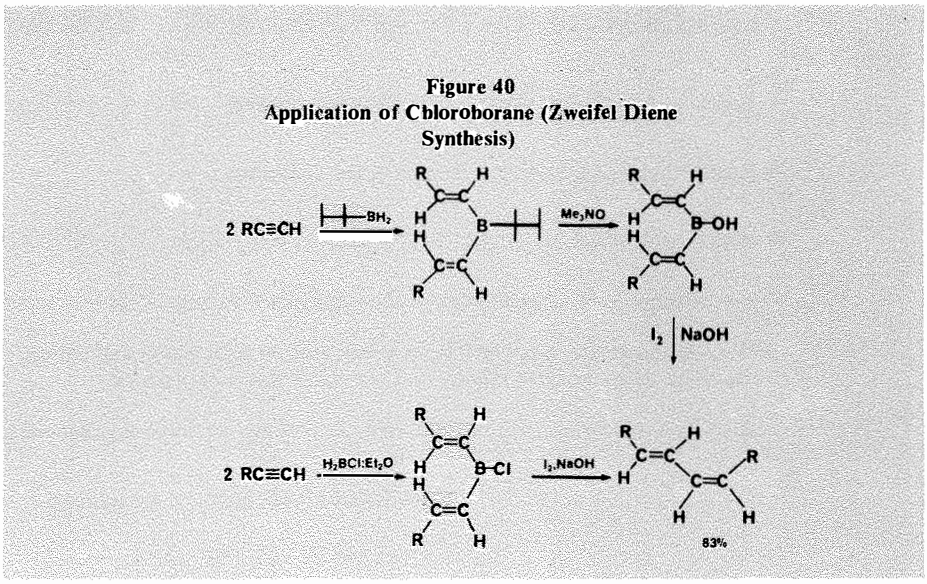


Figure 41
Application of Chloroborane (Stereospecific Synthesis of Aziridines)

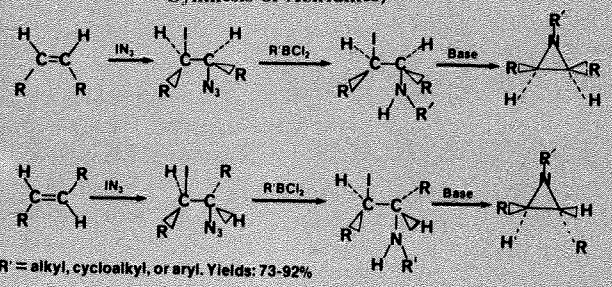
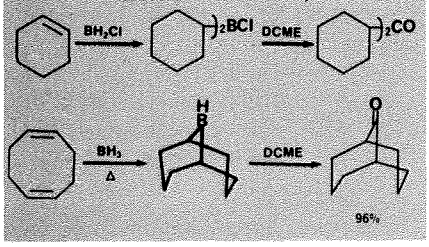


Figure 42
Application of Chloroborane (Synthesis of Ketones *via* DCME)



In this lecture I could present only a part of the remarkable chemistry of the organoboranes that we and others have uncovered. Clearly, these developments will have a major impact on synthetic organic chemistry. The problem is how to transmit this information to the workers in the field who hesitate to utilize organoboranes because of their inexperience with them.

One approach I have taken is to write a book, "Organic Syntheses *via* Boranes," which will give a) reviews of the chemistry, b) detailed procedures for the various syntheses, and c) a detailed description of the laboratory techniques. A second approach has been to persuade Dr. Alfred R. Bader of the Aldrich Chemical Company to set up a subsidiary, Aldrich-Boranes, Inc., to make readily available the basic chemicals and intermediates and certain specialized pieces of apparatus to facilitate application of these new methods by chemists.

Before us lies the utilization of these methods for the synthesis of complex molecules, such as natural products and pharmaceuticals. Before us lies the exploration of the applicability of this chemistry for the synthesis of fine chemicals. Before us lies the exploration of the utility of this chemistry in the petrochemical area.

But this is only the beginning. Before us also lies the exploration of the reaction mechanisms involved in the remarkably clean reactions of the organoboranes. The spectroscopy of organoboranes is in its infancy. Structural effects have yet to be explored systematically.

Clearly it will require another generation of chemists to conquer fully this new continent.

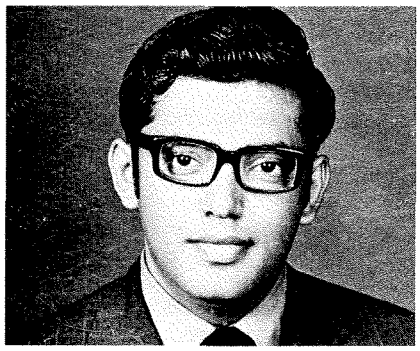
References*

*It appears impractical to give the individual references for the many items covered in this lecture. The books and reviews referred to provide a ready means for obtaining more detailed information and literature references.

1) H.C. Brown, "Hydroboration," W.A. Benjamin, Inc., New York, N.Y., 1962.
2) H.C. Brown, "Boranes in Organic Chemistry," Cornell University Press, Ithaca, N.Y., 1972.
3) G.M.L. Cragg, "Organoboranes in Organic Synthesis," Marcel Dekker, Inc., New York, N.Y., 1973.
4) H.C. Brown, M.M. Midland, G.W. Kramer, and A.B. Levy, "Organic Syntheses *via* Boranes," John Wiley and Sons, New York, N.Y., in print.
5) H.C. Brown, *Accounts Chem. Res.*, **2**, 65 (1969).
6) H.C. Brown, *Chem. Brit.*, 7, 458 (1971).
7) H.C. Brown and M.M. Rogić, *Organometal. Chem. Syn.*, **1**, 305 (1972).
8) H.C. Brown and M.M. Midland, *Angew. Chem. Intern. Ed. Engl.*, **11**, 692 (1972).
9) C.F. Lane, *Aldrichimica Acta*, **6**, 21 (1973).
10) E. Negishi and H.C. Brown, *Synthesis*, 77 (1974).

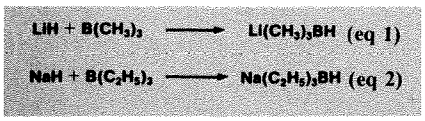
Trialkylborohydrides as New Versatile Reducing Agents in Organic Synthesis

S. Krishnamurthy
Postdoctoral Research Assistant
Richard B. Wetherill Laboratory
Purdue University
West Lafayette, Indiana



INTRODUCTION

Addition compounds of lithium hydride and sodium hydride with trialkylboranes were first discovered in the course of War Research in the period of 1942-45 at the University of Chicago by Professor H.C. Brown, the late Professor H.I. Schlesinger with their coworkers[1] (eq 1 and 2).

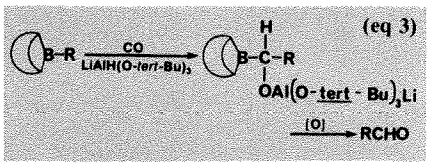


However, relatively little research was devoted to these derivatives. A brief study indicated that lithium triethylborohydride is a stronger reducing agent than the parent compound, lithium borohydride.[2] There was no reason to anticipate that these compounds would possess highly useful properties. However, developments within the past two years at Purdue University have altered this situation. This review summarizes the discovery of the exceptional properties of trialkylborohydrides, the various methods that have been developed for the synthesis of trialkylborohydrides and their utility in organic synthesis.

THE DISCOVERY OF EXCEPTIONAL PROPERTIES OF LITHIUM TRIETHYLBOROHYDRIDE (SUPER HYDRIDE®)[3]

The author may be permitted to describe how an unusual experimental observation, noticed in the exploratory program dealing with the carbonylation of organoboranes led to the discovery of exceptional characteristics of lithium triethylborohydride.

Lithium tri-*tert*-butoxyaluminohydride is a very mild reducing agent, stable indefinitely in tetrahydrofuran at 25°. However, we observed a puzzling feature in applying this reagent to the carbonylation of B-alkyl-9-BBN derivatives (to give the corresponding homologated aldehydes)[4] (eq 3).



To obtain a good yield, it was important that the reagent be added concurrently with the uptake of carbon monoxide. If the reagent was added to the organoborane prior to the introduction of carbon monoxide, the yield of the aldehyde decreased sharply.

Investigation soon revealed that the addition of an equimolar amount of triethylborane to a 0.5 *M* solution of lithium tri-*tert*-butoxyaluminohydride (LTBA) resulted in a very rapid loss of hydride, 72% of the active hydride disappearing in 5 min.[3] Upon hydrolyzing the reaction mixture, an equivalent quantity of 1-butanol was found. A catalytic quantity of triethylborane was also effective. The reactions were essentially complete in 3 hr (Figure 1). Thus, triethylborane induces a rapid, essentially quantitative reductive opening of the tetrahydrofuran ring at 25° (eq 4).

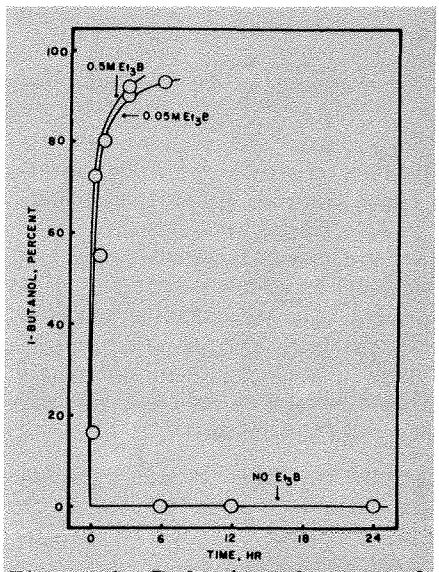
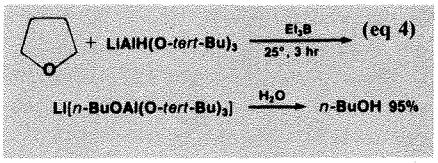
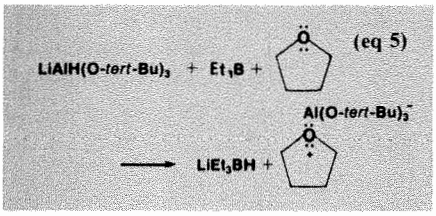


Figure 1. Reductive cleavage of tetrahydrofuran at 25° by lithium tri-*tert*-butoxyaluminohydride (0.5 *M*) in the absence and presence of triethylborane.



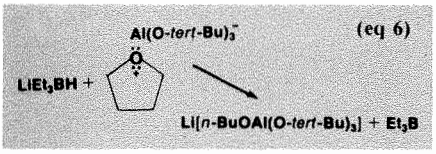
Surprisingly, triethylborane fails to induce a similar reductive cleavage of THF by the otherwise more powerful reducing agent, lithium trimethoxyaluminohydride. The significance of this will be discussed later.

How could even trace quantities of triethylborane cause the mild reducing agent LTBA to open THF, impervious to the most powerful reducing agents previously known? Further research in this area indicated that the reaction proceeds through the formation of a new type of hydride, lithium triethylborohydride ($LiEt_3BH$), and possibly the hitherto unknown monomeric aluminum-*tert*-butoxide, an exceptionally powerful Lewis acid capable of coordinating with the oxygen atom of THF[5] (eq 5).



(eq 5)

The highly active hydride reagent $LiEt_3BH$ then reacts (by displacement) with the polarized carbon-oxygen bond to open the ring and to regenerate triethylborane (eq 6).



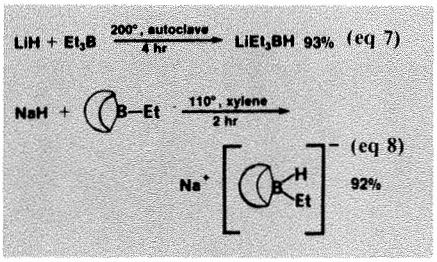
(eq 6)

These investigations led us to believe that lithium triethylborohydride should possess enormous hydride transfer ability. Accordingly, we undertook a major new program to synthesize a variety of lithium trialkylborohydrides with different alkyl substituents and to study their chemistry. Because of their superior hydridic property, these are named "super-hydrides", a term truly representative of their activity.

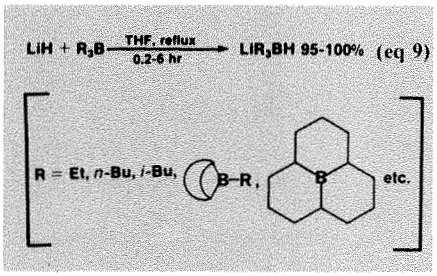
APPROACHES TO THE SYNTHESIS OF SIMPLE AND STERICALLY HINDERED TRIALKYLBOROHYDRIDES

As mentioned earlier, trialkylborohydrides were first prepared by Professor Brown and the late Professor Schlesinger at the University of Chicago.[1] In the period 1956-60, Dr. A. Khuri of our laboratory (a graduate student of Professor Brown) carried out a detailed study of the reactions of alkali metal hydrides (LiH and NaH) with trimethyl- and triethylboranes in a variety of ethereal solvents in vacuum lines.[2]

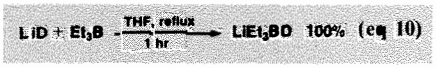
In 1968 Professor Köster and coworkers reported the synthesis of a variety of trialkylborohydrides and some of their properties.[6] Unfortunately, the majority of their reactions have been carried out neat or in aromatic hydrocarbon solvents requiring rather drastic reaction conditions (eq 7 and 8).



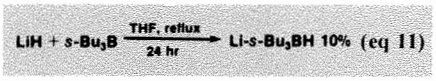
However, a systematic research directed towards the synthesis of various trialkylborohydrides in our laboratory, revealed that in tetrahydrofuran solvent lithium hydride reacts with a variety of simple organoboranes under mild conditions to give lithium trialkylborohydrides in quantitative yield[7] (eq 9).



Lithium hydride reacts quantitatively with triethylborane even at room temperature (24 hr). The corresponding deuterium derivatives are readily synthesized from lithium deuteride (eq 10).



Unfortunately, with the hindered trialkylboranes such as tri-*s*-butylborane, we encountered a major synthetic difficulty. The reaction is very sluggish and incomplete (eq 11).

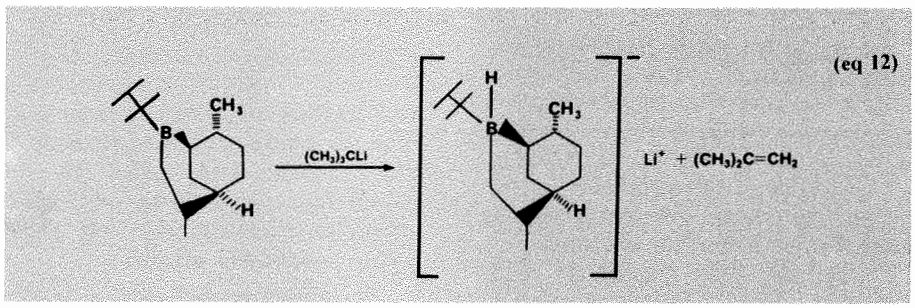


However, the preliminary experiments soon made it clear that the stereoselectivity achieved in the reduction of ketones with trialkylborohydrides increases remarkably with the steric bulk of the trialkylborane. Consequently, synthesis of highly hindered trialkylborohydrides was a necessity.

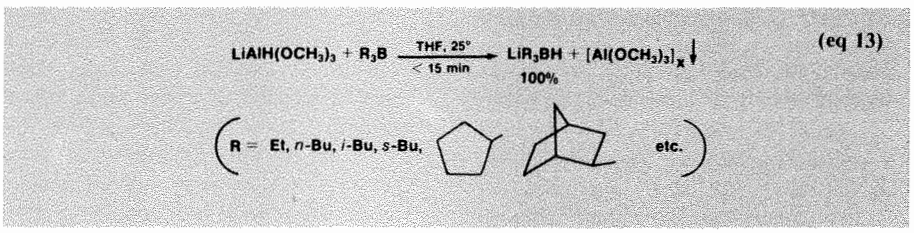
Professor Corey and coworkers also found that thexyllimonylborane[8a] (a hindered trialkylborane derived from limonene and thexylborane) fails to react with lithium hydride in THF.[8b] They circumvented the difficulty by using *tert*-butyllithium, which yields the corresponding trialkylborohydride (eq 12).

We were also actively exploring the methods for the synthesis of hindered trialkylborohydrides. Finally, after extensive research, we discovered that the addition of one mole equivalent of any trialkylborane (simple or hindered) to a THF solution of lithium trimethoxyaluminohydride (LTMA) at room temperature results in a facile and rapid displacement of aluminum methoxide to produce the corresponding lithium trialkylborohydride in quantitative yield[9] (eq 13). The reaction is highly general and aluminum methoxide does not interfere in the further reactions of LiR_3BH.

At that time Professor Charles A. Brown at Cornell University was uncovering many remarkable and unique characteristics of potassium hydride. For example, potassium hydride exhibits unprecedented reactivity toward weak organic acids, such as amines, sterically hindered alcohols, etc.[10] Further, he found that unlike lithium hydride and sodium hydride, potassium hydride

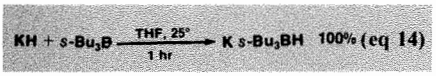


(eq 12)

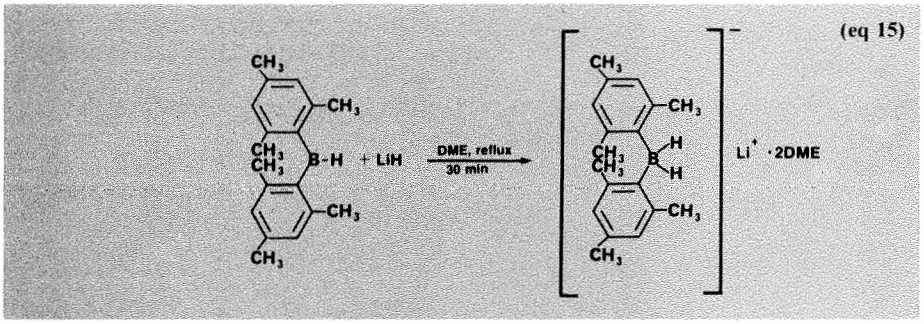


(eq 13)

reacts rapidly and quantitatively with the hindered trialkylboranes, such as tri-*s*-butylborane, yielding the corresponding potassium trialkylborohydride under mild conditions[11] (eq 14).



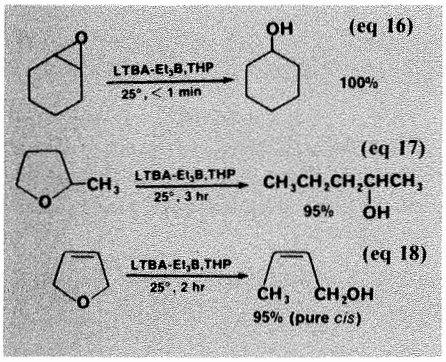
Recently Professor Hooz and coworkers have reported the synthesis of lithium dimesitylborohydride bis(dimethoxyethane)[12] (eq 15).

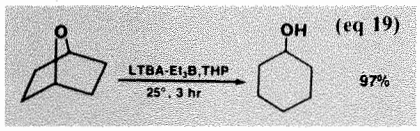


The discovery of the hydroboration reaction in 1956 has made possible the synthesis of organoboranes with a wide variety of structures.[13] These can now be readily converted to the corresponding trialkylborohydrides and dialkylborohydrides.

REDUCTIVE CLEAVAGE OF CYCLIC ETHERS[3]

The lithium tri-*tert*-butoxyaluminohydride-triethylborane system, discussed earlier, has been found to be one of the most active reagents currently available for the reductive cleavage of cyclic ethers. To our knowledge, no reducing system currently available is capable of achieving the reductive cleavage of THF so rapidly and cleanly. Both monoglyme (MG) and tetrahydropyran (THP) dissolve the LTBA-Et_3B system. At 25° monoglyme yields 47% 2-methoxyethanol. However, the reductive cleavage of THP is very slow as we observed only 17% of 1-pentanol after 24 hr. Consequently, we used this as the solvent for the following interesting synthetic transformations (eqs 16-19).





LITHIUM TRIETHYLBOROHYDRIDE AS A SUPERNUCLEOPHILE. FACILE DEHALOGENATION OF ALKYL HALIDES[14]

Lithium triethylborohydride has been found to be an extraordinarily powerful reducing agent, far more powerful than lithium aluminum hydride and lithium borohydride, as revealed by the rates of reduction of *n*-octyl chloride represented graphically in Figure 2. Further, kinetic studies reveal that the reagent is considerably more powerful than nucleophiles such as thiophenoxide and alkyl mercaptides, previously considered to be the most powerful simple nucleophiles available for S_N2 displacements (eq 20).

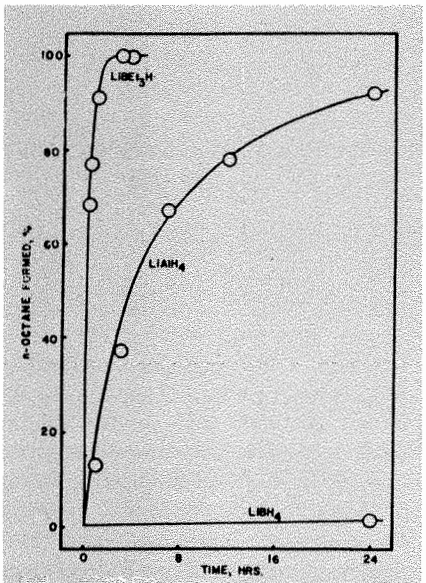
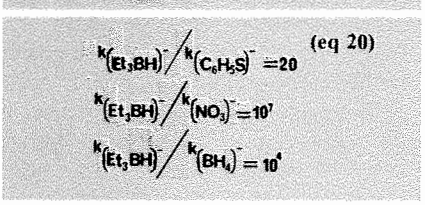
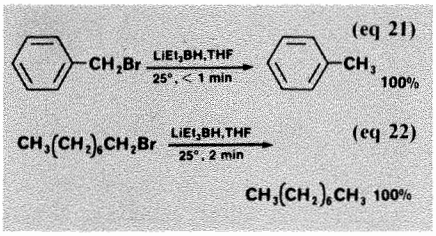


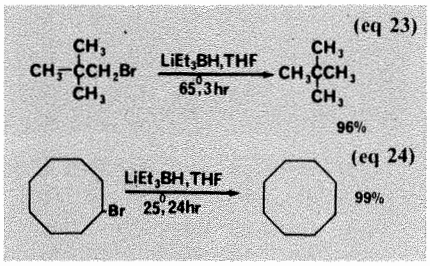
Figure 2. Rates of reduction of *n*-octyl chloride (0.25 *M*) with representative complex metal hydrides (0.5 *M*) in tetrahydrofuran at 25°.



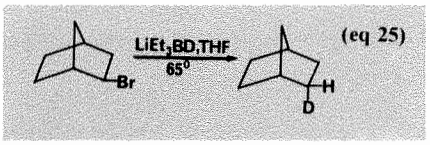
The reaction exhibits typical characteristics of a nucleophilic displacement of the S_N2 type. Simple primary alkyl bromides and allylic and benzylic bromides are reduced almost instantly (eq 21 and 22).



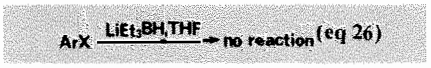
Super Hydride® reduces cleanly and with remarkable ease, even neopentyl bromide and cycloalkyl bromides which are highly resistant to S_N2 displacement reactions (eqs 23 and 24).



Lithium triethylborodeuteride provides a simple means of introducing deuterium with clean stereochemical inversion at the substitution center (eq 25).

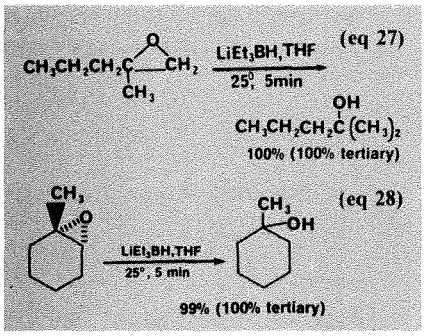


Unlike lithium aluminum hydride,[15] Super Hydride® is inert toward aryl halides and should therefore be valuable for the reduction of alkyl halides without simultaneous attack on aromatic halogen (eq 26).

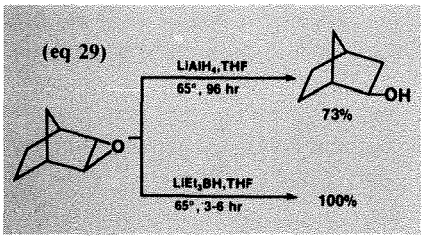


REGIOSPECIFIC AND STEREOSPECIFIC REDUCTION OF HINDERED AND BICYCLIC EPOXIDES[16]

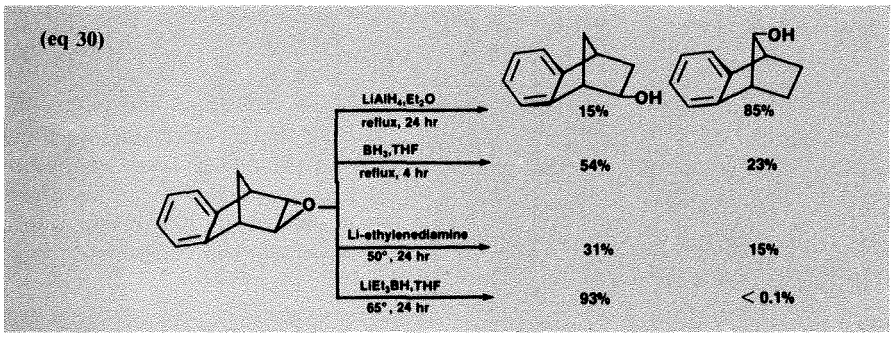
Lithium triethylborohydride in THF possesses remarkable ability for the facile, regiospecific and stereospecific reductive opening of epoxides to give the Markovnikov alcohol in excellent isomeric purity. The reaction is very general, applicable to epoxides with a wide range of structural features. Simple mono-, di- and trisubstituted epoxides are completely reduced in 2-5 min with this reagent, yielding the more substituted of the two possible isomeric alcohols in 100% isomeric purity (eq 27 and 28).



Such reactions are far faster and cleaner than those involving lithium aluminum hydride, Li-ethylenediamine, etc. (eq 29).



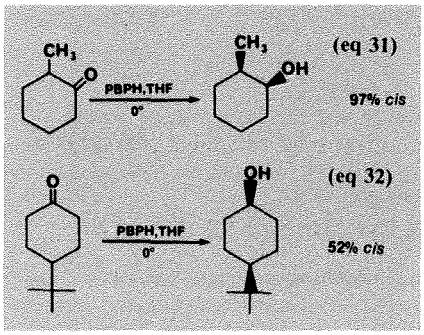
The advantage of Super Hydride® is especially evident in the reduction of labile bicyclic epoxides. Thus, benzonorbornadiene oxide which invariably gives rearranged products with conventional reducing agents undergoes facile reduction with Super Hydride® yielding 93% of *exo*-benzonorbornenol in > 99.9% isomeric purity (eq 30).



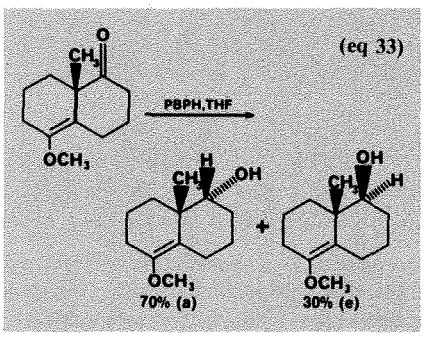
The high regio- and stereospecificity of the reaction, especially with the labile epoxides, enable us to use this reaction as a chemical tool to determine precisely the stereochemistry of epoxidation of such labile bicyclic olefins.[17]

ENZYME-LIKE STEREOSELECTIVE REDUCTION OF KETONES

One of the remarkable features of the trialkylborohydrides is their unusual ability to introduce steric control into the reduction of cyclic ketones. This ability was first recognized in our laboratory with lithium perhydro-9b-boraphenalyl hydride (PBPH).[18] Reduction of ketones with trisubstituted borohydride proceeds rapidly even at -78° and the yields of the corresponding alcohols are quantitative[19] (eq 31 and 32).



The discovery was quite timely as demonstrated by its immediate application in one of the stereoselective syntheses by Professor Ireland[20] (eq 33).

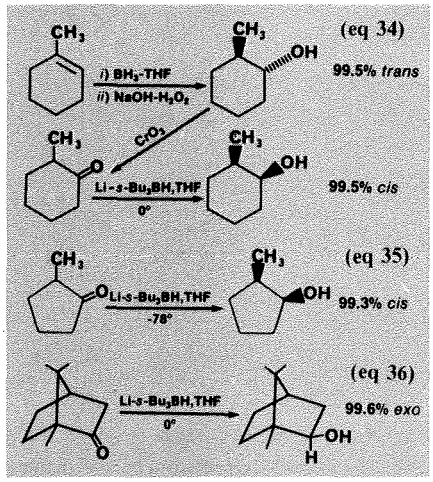


Conventional reducing agents gave only the more stable equatorial isomer.

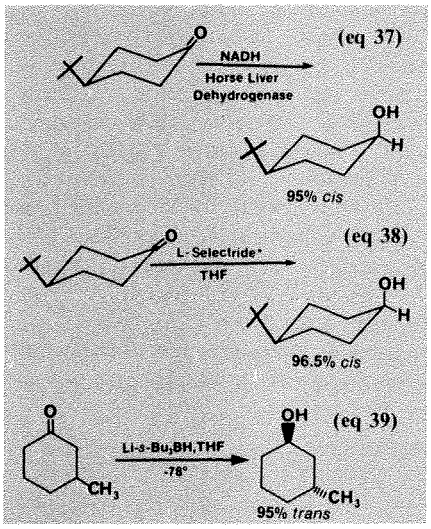
These results stimulated our further interest in this area. Consequently, we undertook examination of the influence of the steric bulk of the trialkylborohydride on the stereoselectivity of the ketone reduction.[21] For example, examination of $LiEt_3BH$, Li-*n*-Bu_3BH and Li-*i*-Bu_3BH clearly revealed that, unlike lithium trialkoxyaluminohydrides, increasing the size of the alkyl substitution on boron enhances the stereoselectivity (towards the less stable isomer). It appeared that a more hindered trialkylborohydride might improve the stereoselectivity.

Indeed our prediction became a reality when we first synthesized lithium tri-*s*-butylborohydride (L-Selectride®), the first simple and highly hindered trialkylborohydride.[9] It exhibits essentially an enzyme-like stereoselectivity in the reduction of cyclic and bicyclic ketones, unequalled by any other previously known reducing agents.

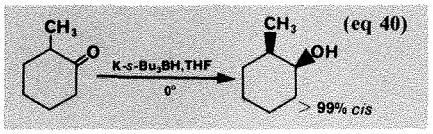
Hindered ketones, such as 2-methylcyclohexanone, 2-methylcyclopentanone, camphor, etc., are reduced rapidly and quantitatively with this new reagent, with over 99.5% stereoselectivity to the corresponding less stable epimers. The new reagent coupled with hydroboration-oxidation provides the synthesis of both the isomeric alcohols in high stereochemical purity (eqs 34-36).



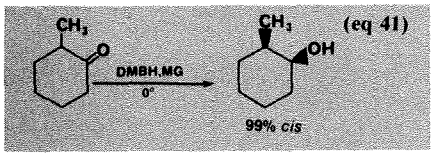
Even ketones with an alkyl group relatively remote from the reaction center, such as 3- and 4-alkylcyclohexanones, are predominantly (>90%) reduced from the equatorial side. The remarkable effectiveness of this reagent is demonstrated by the higher selectivity observed with L-Selectride® than with an enzyme in the reduction of 4-*tert*-butylcyclohexanone[22] (eqs 37-39).



The corresponding potassium derivative (K-Selectride®) prepared by Professor Charles A. Brown is equally effective for stereoselective reductions[11] (eq 40).



Recently, Professor Hooz and coworkers have reported that lithium dimesitylborohydride bis(dimethoxyethane) complex (DMBH) also reduces cyclic ketones with exceptionally high stereoselectivity comparable to that of the Selectrides®[12] (eq 41).



(eq 41)

Interestingly, unlike the trialkylborohydrides, this reagent reacts very sluggishly with hindered ketones such as camphor.

APPLICATIONS OF HINDERED TRIALKYLBOROHYDRIDES IN PROSTAGLANDIN SYNTHESIS

Many of these hindered trialkylborohydrides are finding attractive applications in the stereoselective synthesis of prostaglandins, where the use of other known reducing agents has failed. Professor Corey and coworkers first initiated work in this area by their elegant application of lithium thexyllimonylborohydride (TLBH) to the stereoselective reduction of the C_{15} carbonyl group;[8b] later this was remarkably improved by utilizing an exogenous directing group[23] (eq 42). It should be noted that the use of $NaBH_4$ or $Zn(BH_4)_2$ leads to a 1:1 mixture of 15S and 15R alcohols.

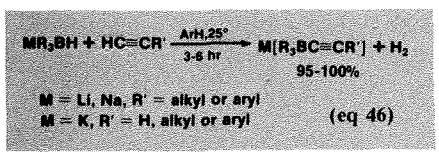
Further, the stereoselective conversion of prostaglandin E_2 to $F_{2\alpha}$ has been achieved using TLBH and PBPH. No $F_{2\beta}$ could be detected[24] (eq 43).

Drs. Miyano and Stealey have selectively reduced C_{15} carbonyl without affecting the C_9 carbonyl group in the total synthesis of prostaglandin E_1[25] (eq 44).

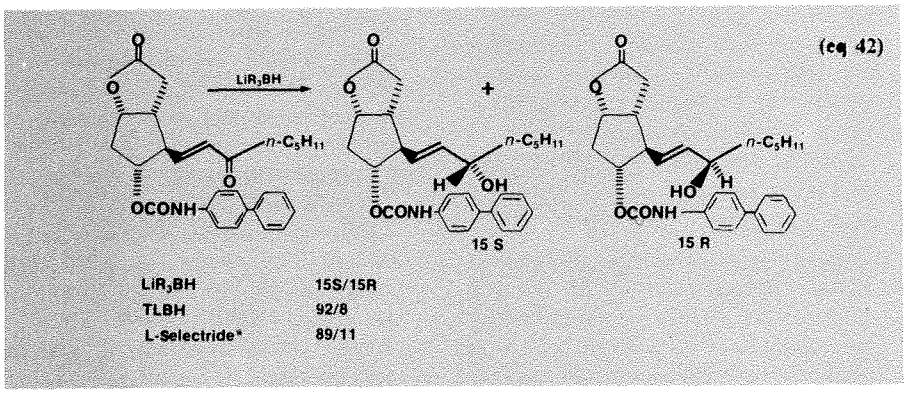
Dr. Weiss and coworkers have extensively utilized PBPH for stereoselective synthesis of various prostaglandin intermediates, especially 11-substituted derivatives of 11-deoxyprostaglandin $F_{2\alpha}$[26,27] (eq 45).

TRIALKYLALKYNYLBORANATES. VERSATILE INTERMEDIATES FOR THE SYNTHESIS OF CARBON STRUCTURES

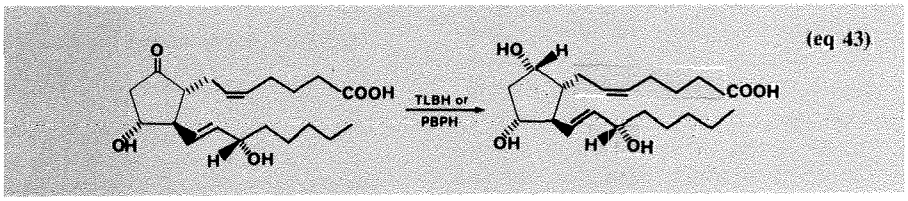
Alkali metal trialkylborohydrides react rapidly and quantitatively with terminal acetylenes to yield the alkali metal trialkylalkynylboranates[28] (eq 46).



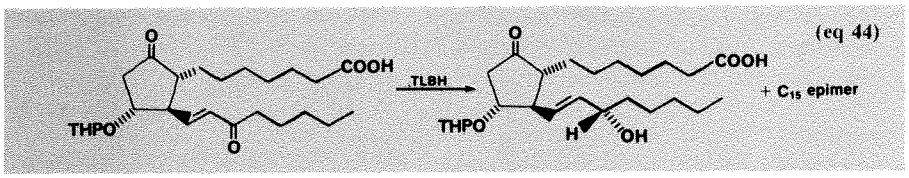
(eq 46)



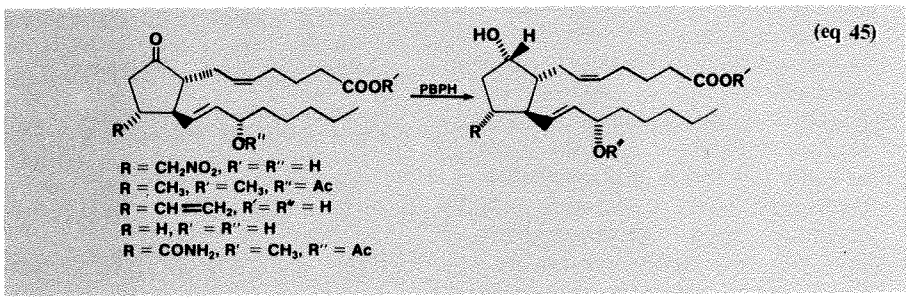
(eq 42)



(eq 43)

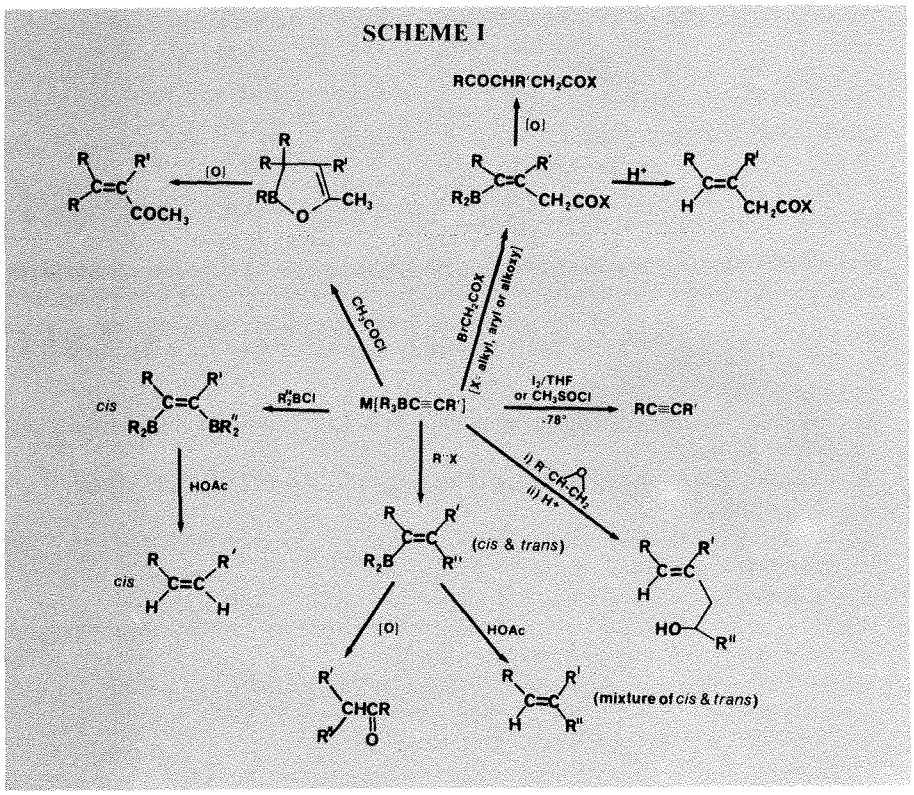


(eq 44)



(eq 45)

SCHEME I



These are highly versatile intermediates for the synthesis of carbon structures (Scheme I). Preliminary experiments indicate that it should be possible to synthesize functionalized alkynyl-"ate" complexes.[29]

CONCLUSION

In 1971 we first recognized the exceptional characteristics of trialkylborohydrides, especially lithium triethylborohydride.[30] Since then, further research in our laboratory and elsewhere has led to the synthesis of a number of trialkylborohydrides with different structural features and their application to organic synthesis. All prove to be highly active nucleophilic selective reducing agents. Many of these derivatives possess extremely attractive properties, such as the reduction of cyclic ketones with enzyme-like stereoselectivity. Research underway in our laboratory is leading to the discovery of many more attractive uses for these new reagents in organic synthesis.[31] In addition to their reducing properties, we are discovering certain new aspects of these reagents, useful for the regio- and stereoselective synthesis of carbon structures.[32] These new, exciting developments will be reviewed later. Finally, it should be pointed out that we are only in the beginning of the exploration of a vast new area of synthetic and theoretical interest. Continued research in this area together with the understanding of the structure-reactivity relationship should facilitate the development of highly specific reducing agents, similar to the enzymes developed by Nature, to achieve highly specific biological transformations.

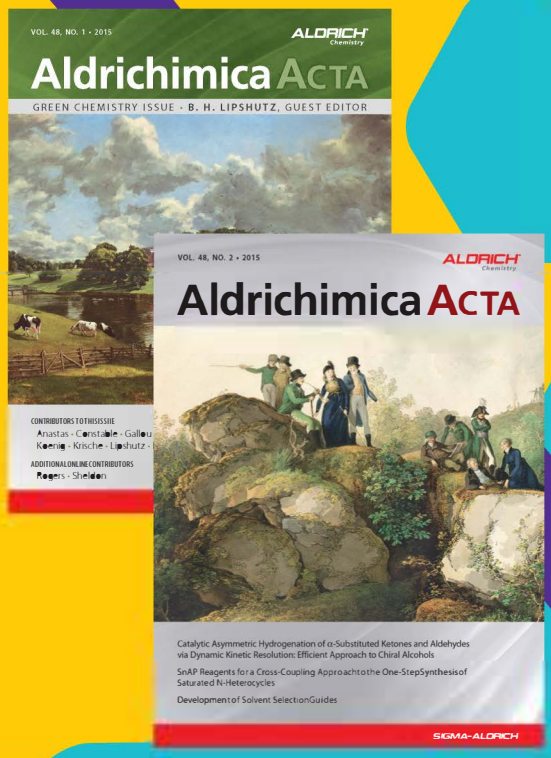
ACKNOWLEDGEMENTS

The author wishes to express his sincere appreciation and profound gratitude to Professor Herbert C. Brown of Purdue University for his advice, guidance and encouragement, under whose supervision most of this work was accomplished. The author also wishes to express his appreciation and thanks to Professor Charles A. Brown and Mr. S.C. Kim for stimulating and helpful discussions. The generous financial support of the U.S. Army Research Office (Durham) North Carolina (Grant Nos. DA-ARO-D-31-124-73-G1 and DA-ARO-D-31-121-73-G148) is gratefully acknowledged.

1) H.C. Brown, H.I. Schlesinger, I. Sheft, and R.M. Ritter, *J. Amer. Chem. Soc.*, **75**, 192 (1953).
2) A. Khuri, Ph.D. Thesis, Purdue University, West Lafayette, Indiana, 1960.
3) H.C. Brown, S. Krishnamurthy, and R.A. Coleman, *J. Amer. Chem. Soc.*, **94**, 1750 (1972).
4) H.C. Brown and R.A. Coleman, *ibid.*, **91**, 4606 (1969).
5) H.C. Brown and S. Krishnamurthy, *Chem. Commun.*, 868 (1972).
6) P. Binger, G. Benedikt, G.W. Rotermund, and R. Koster, *Ann. Chem.*, **717**, 21 (1968).
7) H.C. Brown and S. Krishnamurthy, to be published.
8) (a) H.C. Brown and C.D. Pfaffenberger, *J. Amer. Chem. Soc.*, **89**, 5475 (1967); (b) E.J. Corey, S.M. Albonico, U. Koelliker, T.K. Schaaf, and R.K. Varma, *ibid.*, **93**, 1491 (1971).
9) H.C. Brown and S. Krishnamurthy, *ibid.*, **94**, 7159 (1972).
10) C.A. Brown, *ibid.*, **95**, 982 (1973).
11) C.A. Brown, *ibid.*, **95**, 4100 (1973).
12) J. Hooz, S. Akiyama, F.J. Cedar, M.J. Bennett, and R.M. Tuggle, *ibid.*, **96**, 274 (1974).
13) H.C. Brown, "Boranes in Organic Chemistry," Cornell University Press, Ithaca, N.Y., 1972.
14) H.C. Brown and S. Krishnamurthy, *J. Amer. Chem. Soc.*, **95**, 1669 (1973).
15) H.C. Brown and S. Krishnamurthy, *J. Org. Chem.*, **34**, 3918 (1969).
16) S. Krishnamurthy, R.M. Schubert, and H.C. Brown, *J. Amer. Chem. Soc.*, **95**, 8486 (1973).
17) R.M. Schubert, Ph.D. Thesis, Purdue University, West Lafayette, Indiana, 1972.
18) H.C. Brown and W.C. Dickason, *J. Amer. Chem. Soc.*, **92**, 709 (1970).
19) Lithium triethylborohydride reduces cyclohexanone at -78° in 1 min to the extent of 95% (stoichiometric ratio).
20) R.E. Ireland, D.R. Marshall, and J.W. Tilley, *J. Amer. Chem. Soc.*, **92**, 4754 (1970).
21) H.C. Brown and S. Krishnamurthy, to be published.
22) J.M.H. Graves, A. Clark, and H.J. Ringold, *Biochemistry*, **4**, 2655 (1965).
23) E.J. Corey, K.B. Becker, and R.K. Varma, *J. Amer. Chem. Soc.*, **94**, 8616 (1972).
24) E.J. Corey and R.K. Varma, *ibid.*, **93**, 7319 (1971).
25) M. Miyano and M.A. Stealey, *Chem. Commun.*, 180 (1973).
26) R.E. Schaub and M.J. Weiss, *Tetrahedron Lett.*, 129 (1973).
27) C.V. Gnudzinskas and M.J. Weiss, *ibid.*, 141 (1973).
28) (a) P. Binger and R. Koster, *ibid.*, 190 (1965); (b) See Ref. 6; (c) A. Suzuki, N. Miyaura, S. Abiko, M. Itoh, H.C. Brown, J.A. Sinclair, and M.M. Midland, *J. Amer. Chem. Soc.*, **95**, 3080 (1973); (d) M. Naruse, K. Utimoto, and H Nozaki, *Tetrahedron Lett.*, 1847 (1973); (e) M.M. Midland, J.A. Sinclair, and H.C. Brown, *J. Org. Chem.*, **39**, 731 (1974); (f) E. Negishi, G. Lew, and T. Yoshida, *Chem. Commun.*, 874 (1973); (g) M. Naruse, T. Tomita, K. Utimoto, and H. Nozaki, *Tetrahedron Lett.*, 795 (1973); (h) M. Naruse, K. Utimoto, and H. Nozaki, *ibid.*, 2741 (1973); (i) A. Pelter, C.R. Harrison, and D. Kirkpatrick, *Chem. Commun.*, 544 (1973); (j) A. Pelter, C.R. Harrison, and D. Kirkpatrick, *ibid.*, in press.
29) S. Krishnamurthy, research in progress.
30) S. Krishnamurthy, S.C. Kim, and H.C. Brown, Abstracts, 168th National Meeting of the American Chemical Society, Atlantic City, N.J., September, 1974.
31) S. Krishnamurthy and S.C. Kim, research in progress.
32) S. Krishnamurthy, S.C. Kim, and J.L. Hubbard, research in progress.

Dr. S. Krishnamurthy was born in Coimbatore, Tamil Nadu, India. He received his B.Sc. and M.Sc. in Chemistry from the University of Madras in 1964 and 1966 respectively. He joined the Graduate School of Purdue University in February 1967 and earned his Ph.D. in 1971 with Professor H.C. Brown. Since then, he joined in his present position as Postdoctoral Research Associate to Professor Brown.

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