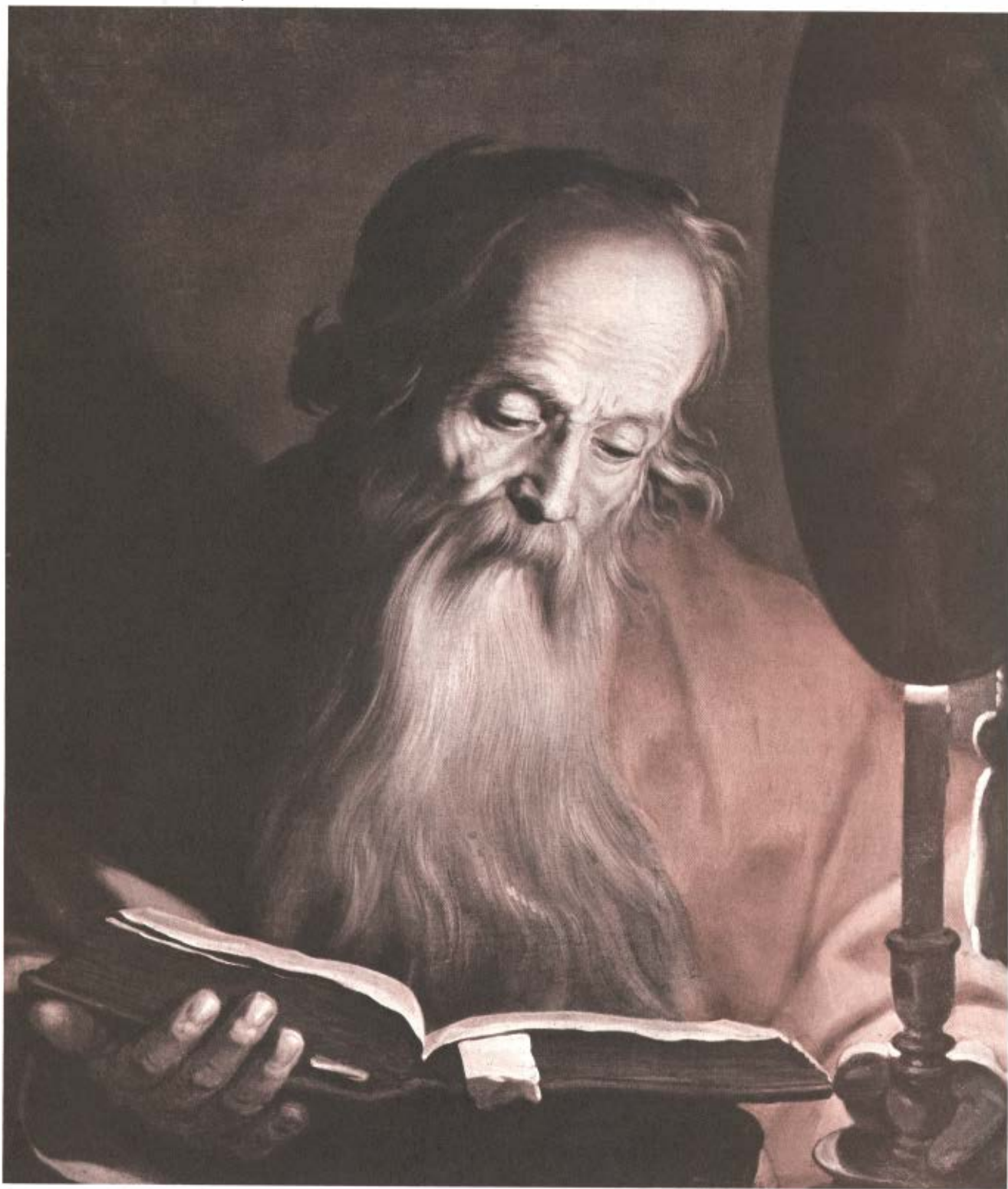


Aldrichimica Acta

Volume 9, Number 1, 1976



Crown Ether Chemistry. See page 3.
Polymeric Reagents. See page 15.

A publication of Aldrich Chemical Company, Inc.

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About Our Cover:

The painting (oil on canvas 25 $\frac{3}{8}$ x 20 $\frac{7}{8}$ inches) by Abraham Bloemaert reproduced on our cover has been known to art historians for many years, but only because the artist's son, Cornelis Bloemaert, engraved it shortly after it was painted in the sixteen twenties. The whereabouts of the original had been unknown for some 350 years, so you can imagine our chemist-collector's pleasure when he discovered it in an antique store in The Hague two years ago.



Magnus in Graeco Latine. A. B. Bloemaert. H. Hieronymus.

Kupferstich Cornelis Bloemaerts nach
Abraham Bloemaert. Hl. Hieronymus.

The inscription on the engraving answers all iconographic questions: this is *St. Jerome Studying the Old Testament* which he was the first to translate competently into Latin.

St. Jerome (ca. 340-420 C.E.) was one of those Church Fathers to whom the title of Saint was given not for his saintliness, but for his erudition and hard work. He was, in fact, anything but saintly: he was involved in arguments — often with more vituperation than reason — throughout his life, but is remembered far more for his scholarship than his fights with windmills.

Dr. Alfred Bader is the guest curator of an exhibition, *The Bible Through Dutch Eyes*, at the Milwaukee Art Center from April 9 to May 23. The exhibition of seventy Dutch and Flemish works includes twelve paintings which have been reproduced on *Aldrichimica Acta* covers.

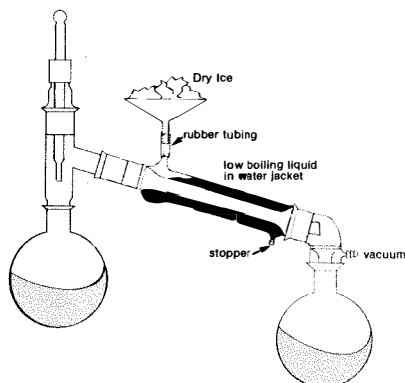
The fully illustrated catalog may be obtained post-paid from Mr. Hugh Morgan, Milwaukee Art Center, 750 North Lincoln Memorial Drive, Milwaukee, WI 53202 by sending a check or money order for \$8.00 (U.S. \$8.50 if outside the U.S. and Canada) payable to the Milwaukee Art Center.

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 is now available to all chemist art-lovers.

Lab Notes

Dear Sirs:

During distillation of a low-melting solid it is often difficult to prevent solidification of the distillate in the condenser. An air-cooled condenser is frequently employed to alleviate the problem, but a greater degree of temperature control can be obtained by closing the water inlet of the condenser jacket with a pipette bulb or a small cork and introducing into the water outlet a material of a boiling point close to the melting point of the distillate (e.g., a solvent such as methylene chloride or methanol). Boiling of the solvent thus



holds the condenser at a predetermined temperature. The solvent can be replaced as it evaporates, but it is generally more convenient to fashion a crude reflux condenser by connecting a funnel containing chunks of dry ice to the jacket outlet by means of a short length of rubber tubing.

*John L. Marshall
Department of Chemistry
University of New Hampshire
Durham, New Hampshire 03824*

Dear Sirs:

Most laboratory workers are able to carry out simple glass repair jobs, particularly if the glass is of a borosilicate type. Borosilicate glass (e.g., Pyrex, Corning Type 7740) can be readily distinguished from other formulations by its refractive index, which is 1.474.

A mixture of dry benzene and dry methanol, 84:16 (v/v) has the same refractive index at room temperature as borosilicate glass.
cont'd on page 17

Crown Ether Chemistry: Principles and Applications

George W. Gokel
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Background

The importance of macrocyclic polyethers and the field bearing the cognomen "crown ether chemistry" can be attributed largely to the work of Charles J. Pedersen of the DuPont Company, who reported many of these compounds and considerable complexation data in 1967.¹ Compounds of this type, *viz.*, glymes² and cyclic polyethers³ were known, but no alkali metal complexes had been reported. Many such complexes are now known and have been catalogued.⁴

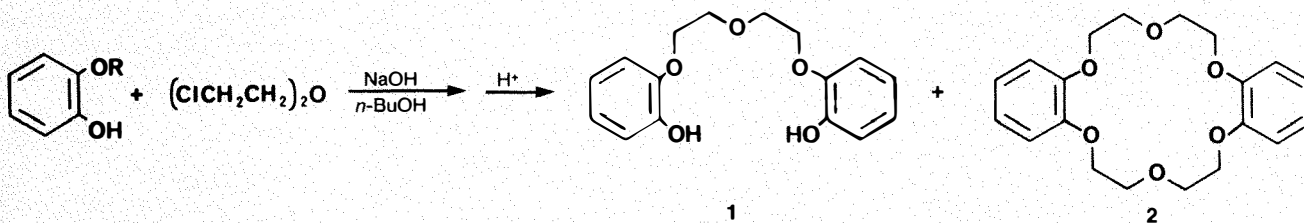
Pedersen's discovery of these compounds is interesting and the details are available in an earlier issue of this journal.^{1b} Pedersen was attempting a synthesis of bis-phenol **1** by the sequence illustrated below. Apparently, some of the incom-

plete carbon shorter (methyleneoxy) the repeating unit would be an acetal function and would exhibit hydrolytic instability. If longer carbon chains were involved, the CH-CH interactions would exert an effect on the overall conformation of the macrocyclic ring. The generic name "crown" was evidently suggested to Pedersen by the similarity of the (CPK) molecular models to a regal crown, and by the ability of these compounds to "crown" cations by complexation. The smallest value of *n* which fits the above definition is 2, *i.e.*, 1,4-dioxane. No smaller molecule satisfies the "repeating" requirement of the definition. The name for **2** is derived as follows: dibenzo— describes the non-ethyleneoxy substituents, 18— the total number of atoms in the ring, crown is the class name, and 6 is

the total number of heteroatoms in the ring portion of the macrocycle. Compound **7** would simply be called 18-crown-6.^{1a}

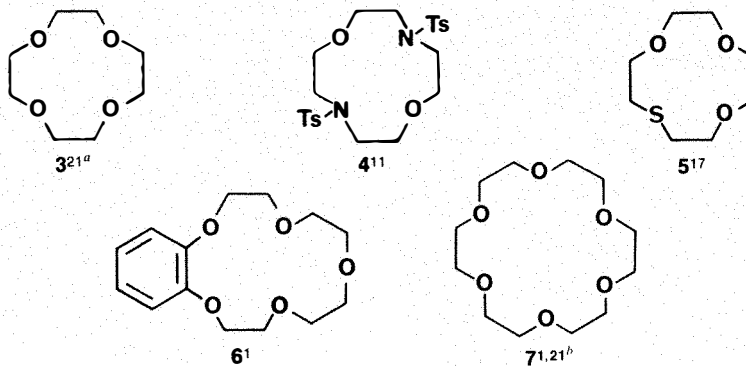
Structural Variation

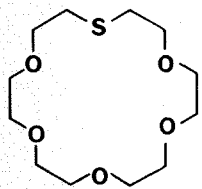
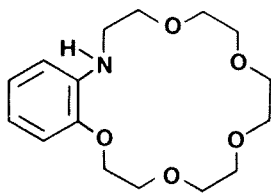
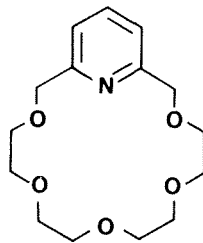
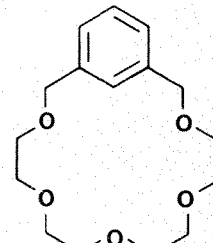
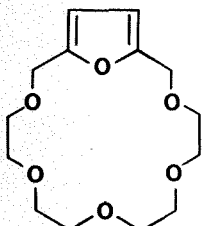
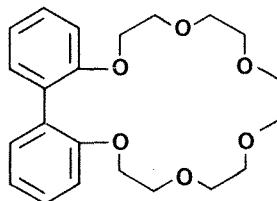
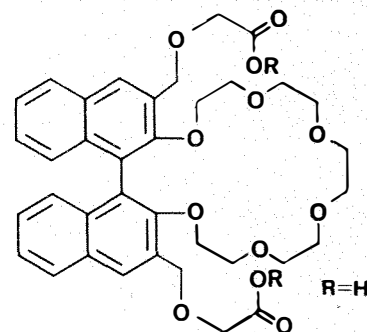
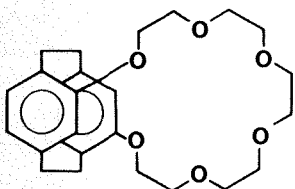
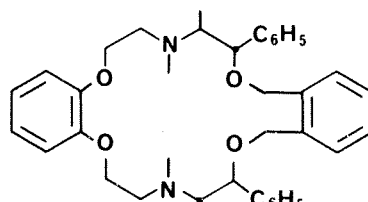
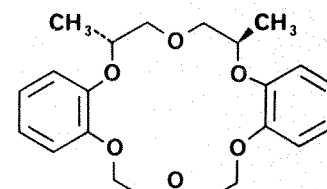
The principal variation in *X* has been to substitute NH or NR for O.⁶⁻¹⁶ Sulfur has also been substituted for oxygen and the efforts in this area have recently been reviewed.¹⁷ Other variations include replacement of O by P¹⁸ or CH₂.^{10,11,19,20} The structural variation is illustrated in formulas **3-17**. These are representative examples of the variety possible and are only a small fraction of the structures which have been reported. For more complete listings, the reader is directed to the extensive reviews which have appeared in the last five years.^{4,17,30-34}



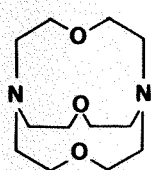
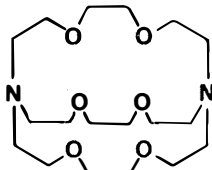
pletely protected mono-THP-catechol reacted with 2,2'-dichlorodiethyl ether to yield dibenzo-18-crown-6 (**2**). Although its analysis showed that compound **2** had no hydroxyl group, it exhibited a base-induced shift in the UV. This shift is now understood and is attributed to complex formation.⁵

The macrocyclic polyethers are generally defined as being cycles containing repeating $(-\text{X}-\text{CH}_2-\text{CH}_2-)_n$ units. For the cases where $\text{X}=\text{O}$, the repeating unit is ethyleneoxy. If the carbon portion were

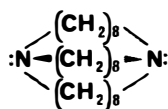


8¹⁷9¹²10²²11²³12^{24,25}13²⁶14²⁷15²³16²⁸17²⁹

A cursory examination of the structures formulated above will indicate that a feature common to all of them is an effective two-dimensionality. The polyheteroatom macrocycles may be made three-dimensional by adding a third (-X-CH₂-CH₂-) strand. Lehn and his collaborators have designed numerous three-dimensional polyheteroatom macrocycles which he has named "cryptates."^{7,33,35-39} The molecules which Lehn has designated the 1.1.1- and 2.2.2-cryptates are represented by structures 18 and 19. The conceptually

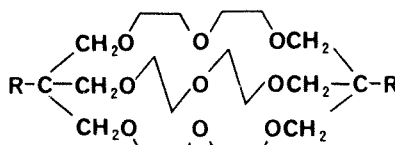
18
(1.1.1 Cryptate)19
(2.2.2 Cryptate)

related but independently developed "in-out" bicyclic amines which were developed by Simmons and Park,⁴⁰ are represented by structure 20. The molecule represented by



20

structure 21 is similar to a cryptate but the pentaerythritol unit replaces the bridgehead nitrogen.⁴¹ The elegant cryptate



21

chemistry developed by Lehn is closely related to that of the simpler crown ethers and it serves admirably for many of the applications discussed in later sections. Because of the greater cost of these bicyclic materials and their consequent relative unavailability, we will largely restrict further discussion of applications to the monocyclic crowns.

Complexes and the Template Effect

Despite the multiplicity of structural variation, the macroheterocycles would be little more than an interesting chemical curiosity were it not for the ability of these cycles to complex a wide variety of substrates. Pedersen, in his early papers,¹ demonstrated this property. He reported that crown ethers complex alkali and alkaline earth cations, transition metal

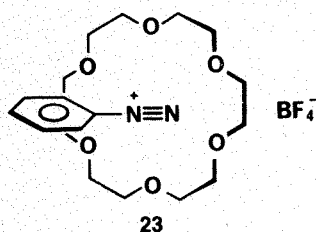
cations, and ammonium cations. The binding constants for metal ions generally are largest for the most similar relationships of cation diameter to hole size. Pedersen and Frensdorff³¹ have reported stability constants (*K*) for polyether-cation complexes with dicyclohexyl-18-crown-6 in water at 25°C (see Table 1). The hole size of 18-crown-6 has been estimated to be 2.6-3.2 Å.⁴² The available evidence suggests that the appropriately sized metal ion is lodged in the hole of the crown, coplanar with and equidistant from each oxygen atom.³³

Table 1³¹Stability Constants
K (in water) for Equation 1

Cation	Ionic diam. (Å)	<i>K</i> (l/mol)
Li ⁺	1.28	0.6
Na ⁺	1.93	1.7
K ⁺	2.66	2.2
Rb ⁺	2.96	1.5
Cs ⁺	3.66	1.2
NH ₄ ⁺	3.6*	1.4
Ag ⁺	2.39	2.3

*Authors' estimate based on CPK scale model examination. Note that the ammonium ion complex involves H-bonding to the face of the crown and not insertion. Its effective size is similar to K⁺ ion.

A number of other substrates have also been shown to form either solid or transient complexes. Examples include solid complexes of crown ethers with hydronium ion⁴³ and a complex of benzo-27-crown-9 with guanidinium ion.⁴⁴ In addition, evidence has been developed for a complex between benzene diazonium ion and crown ethers in a non-polar solution.⁴⁵ The presumed structure is formulated as 23. Other

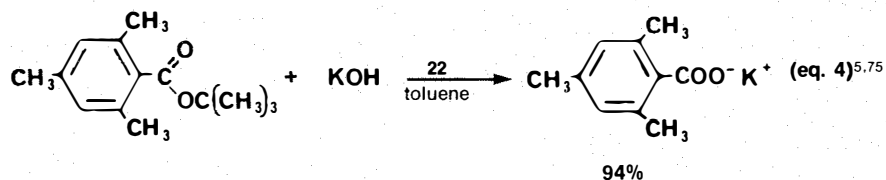
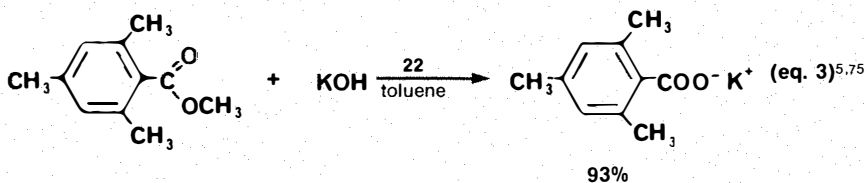
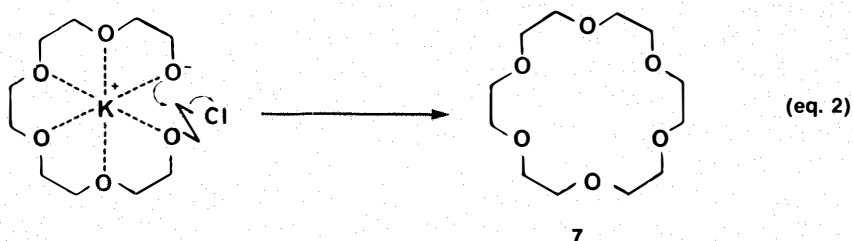
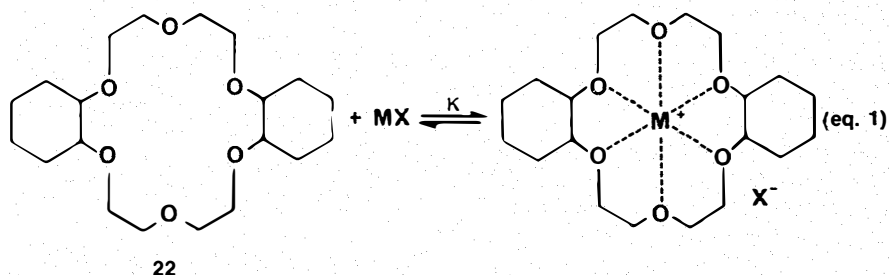


solid materials which may be complexes, solvates or clathrates between crown ethers and acetonitrile,²¹ thiourea,⁴⁰ THF²² and dimethyl acetylenedicarboxylate⁴⁷ have been reported.

The complexation of the Lewis acid is also crucial to the formation of these rings. Apparently, the final step in the Williamson ether synthesis of these compounds involves a wrapping of the polyheteroatom chain about the metal ion, bringing the alkoxide and the carbon bearing the leaving group into proximity (see eq. 2). Because of this, the crown ethers can be prepared in relatively concentrated solution, while most large ring syntheses require high dilution. Pedersen's dibenzo-18-crown-6 is routinely prepared in 39-48% yield working at a concentration of *ca.* 0.75 molar.⁴⁸ Compound 7, 18-crown-6, is prepared in about 1 molar solution.^{21^b}

Application in Synthesis

The synthetic utility of crown ethers is derived from their ability to solvate cations in a non-polar environment. A large body of work has developed over the last ten years on phase-transfer (PT) chemistry⁴⁹ using quaternary ammonium cations to transfer otherwise insoluble anions into non-polar media. The development of synthetic reactions using crown ethers clearly parallels the development of the quaternary ammonium (or phosphonium) catalysts. The synergistic power of crown ethers was first pointed out by Pedersen^{1,48} who showed that potassium hydroxide could be solubilized in toluene and that the crown-complexed potassium hydroxide was a powerful base. Pedersen found that esters of mesitoic acid (2,4,6-trimethylbenzoic acid) could be hydrolyzed using the crown-complexed potassium hydroxide salt (eq. 3). Not only was the methyl ester hydrolyz-



ed (no reaction was observed in the absence of a crown ether) but the *t*-butyl ester was also cleaved in high yield (eq. 4). Pedersen also reported that this reagent may be used for the anionic polymerization of anhydrous formaldehyde and the trimerization of aromatic isocyanates.

The major difference between crown-catalyzed reactions and the quaternary ammonium catalysts is that crown ethers may catalyze a direct solid/liquid phase-transfer of salts into non-polar solvents whereas most quaternary ammonium-catalyzed reactions are done from a liquid (aqueous) phase into non-polar solvents. The success of crown ethers as reagents for solid-liquid PT can likely be attributed to two properties of these systems. The first is that crown ethers are multidimensional flexible molecules with a number of polar sites. When the crown ether interacts with the crystal lattice of a salt, it may assume the approximate geometry of the complex on the crystal surface and the subsequent transfer of the cation from its lattice site to the crown cavity is energetically favorable. The anion simply accompanies the cation

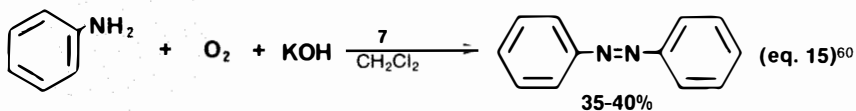
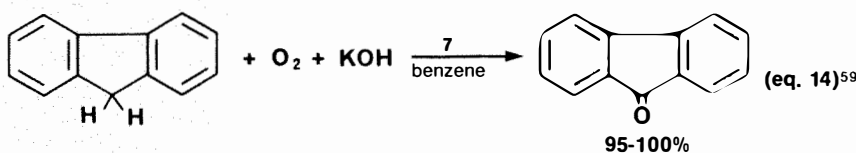
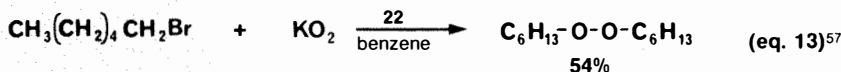
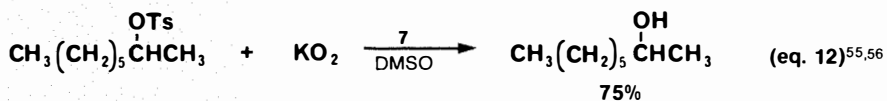
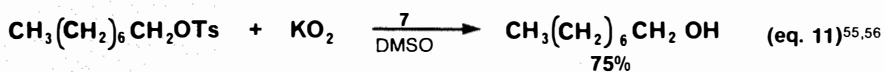
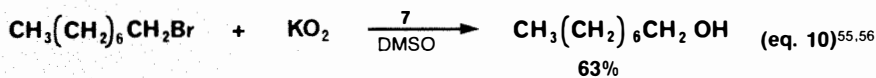
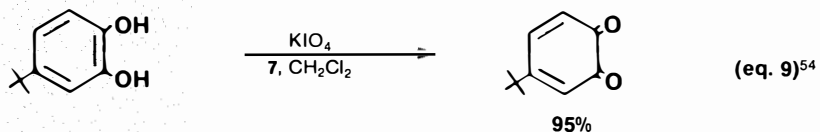
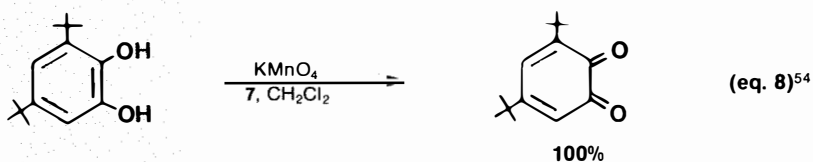
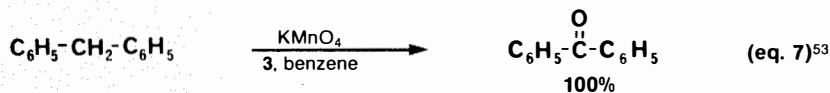
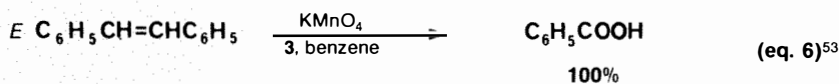
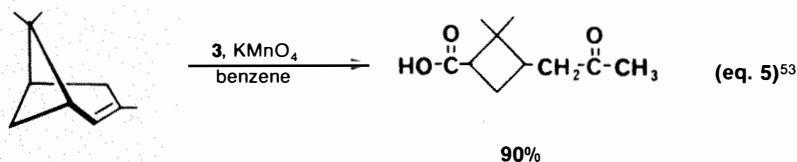
complex. In case of quaternary salts, the positive nitrogen is sterically shielded and therefore cannot achieve proximity to the lattice-bound cation. The second important property is the intrinsic difference between crown ethers and quaternary salts, namely that crown ethers are neutral ligands. Whereas the quaternary ion is always associated with an anionic species, the crown ether can be neutral both as a crown-cation-anion complex or as the free ligand. The efficiency of crown ethers as solid-liquid PT reagents may well be attributable to the fact that the complexed product salt can be deposited in a crystal lattice and the ligand freed to complex more reactant salt.

After Pedersen's initial observations, the first major interest in crown-complexed salts was in their ability to generate separated ion pairs.⁵⁰ Maskornick⁵¹ observed that potassium *t*-butoxide in DMSO initiated E-2 type reactions in the presence of 18-crown-6 (7) with great facility. Maskornick also observed that the reaction, in the presence of the crown ether, gave pseudo first order rates even in con-

centrated ($\approx 0.5 M$) solution. In the absence of the crown ether, the reaction showed pseudo first order kinetics only at low ($\approx 10^{-3} M$) concentrations. The crown-complexed base apparently inhibits aggregate formation, even at high concentration, dramatically increasing the reactivity of potassium *t*-butoxide. Bartsch,⁵² and others,⁵³ have studied the effect of the crown ether complexation in numerous nucleophilic substitution and β -elimination reactions. As a general observation, these reactions are substantially affected by the presence of the appropriately sized crown ether, especially in non-polar solvents. A comprehensive review of this reactivity has recently appeared.⁵²

In the initial work by Pedersen, the potassium hydroxide complex with dicyclohexyl-18-crown-6 (**22**) had to be preformed in methanol then used in toluene (or benzene) after the methanol was removed. Sam and Simmons,⁵³ also at DuPont, observed that direct solid-liquid phase transfer of potassium permanganate could be effected with **22**. This hydrocarbon-solubilized permanganate (commonly known as purple benzene) is a very mild, yet effective, oxidizing reagent. Under these conditions, α -pinene is oxidized to pinonic acid (eq. 5), stilbene to benzoic acid (eq. 6), and diphenylmethane to benzophenone (eq. 7). Solubilization of potassium permanganate with 18-crown-6 (**7**) in CH_2Cl_2 has been observed⁵⁴ to transform substituted catechols to *o*-quinones in high yields (eq. 8). The same solubilization of potassium periodate and potassium iodate was also observed to transform catechols to *o*-quinones in high yields⁵⁴ in a solid-liquid process (eq. 9). In all cases, only one equivalent of the oxidizing reagent is required. No evidence of over-oxidation to open ring products was observed under these conditions.

Recent work at Rutgers⁵⁵ and Upjohn⁵⁷ has shown that potassium superoxide may be solubilized by **7** and **22** in both DMSO and benzene. Once in solution, this reagent may be used as a very nucleophilic oxygen anion which reacts with alkyl halides and tosylates (eq. 10-13). The products seem to be solvent-dependent, *i.e.*, in DMSO,⁵⁶ the alcohol is produced as the major product (by a mechanism which remains obscure at present) whereas in benzene,⁵⁷ the major product is the dialkyl peroxide. A hydroperoxide⁵⁸ has been isolated in at least one case as an intermediate. Recent work⁵⁸ has also shown that dialkyl peroxides may be reduced to alcohols with potassium superoxide. Stereochemical studies^{56,57} indicate that the displacement occurs with virtually complete inversion of configura-



tion at the asymmetric carbon.

Crown ether **7** catalyzes the air oxidation of fluorene⁵⁹ to fluorenone in the presence of solid potassium hydroxide (eq. 14) in quantitative yields. Similarly, aniline⁶⁰ undergoes oxidative condensation to azo-

benzene (eq. 15), although in somewhat lower conversion. In the former case, the oxidation rate is enhanced by rapid stirring which presumably increases both interfacial contact and oxygen absorption. Boden⁶¹ has shown that the potassium salt

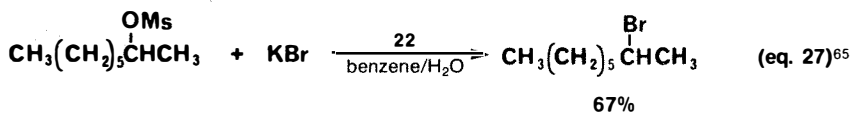
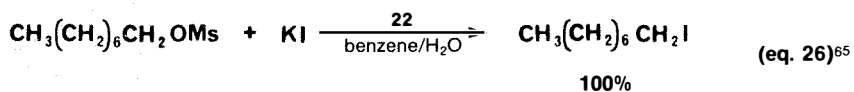
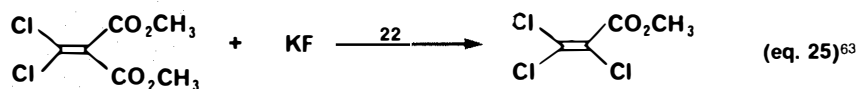
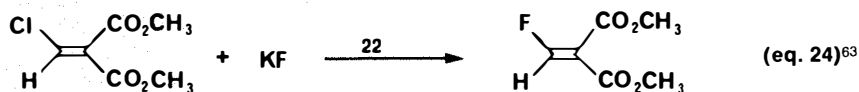
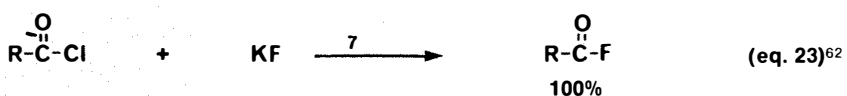
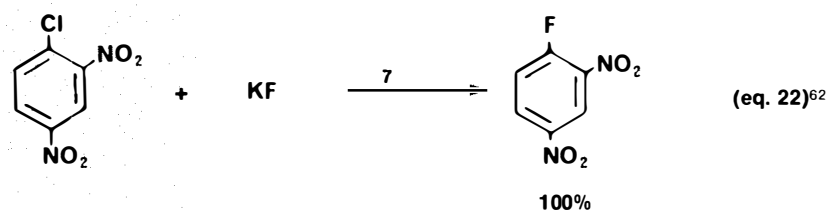
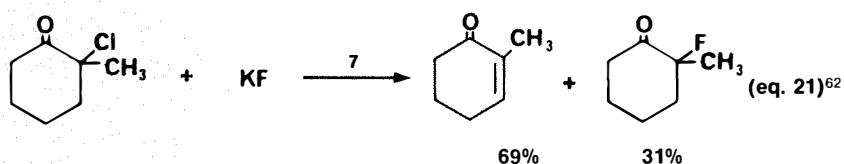
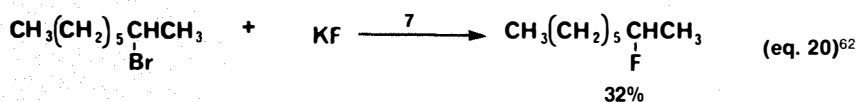
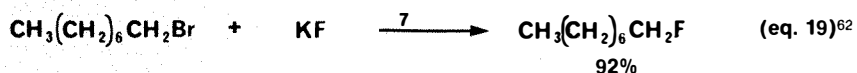
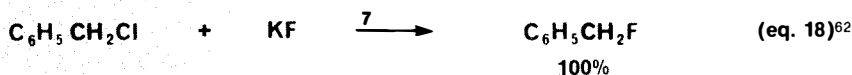
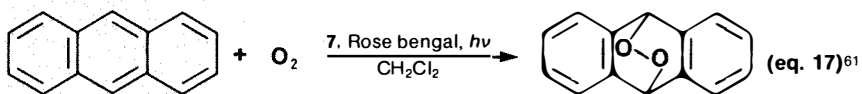
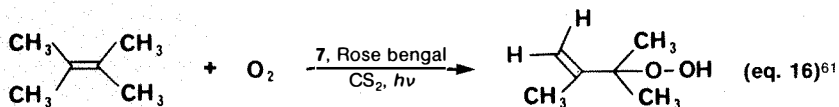
of rose bengal is solubilized by **7** in non-polar solvents. This crown-dye complex sensitizes the photoaddition of singlet oxygen to either tetramethylethylene (eq. 16) or anthracene (eq. 17). The reaction conditions are very mild and may be conducted conveniently in several aprotic solvents. An additional advantage is that singlet oxygen generated in aprotic solvents (such as CS₂) has a longer lifetime than singlet oxygen generated in protic solvents (such as methanol).

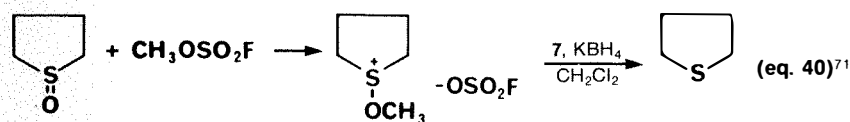
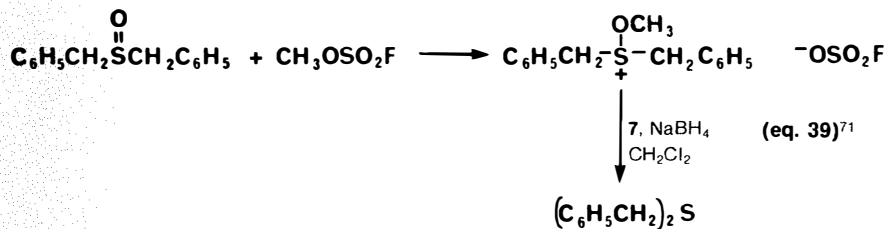
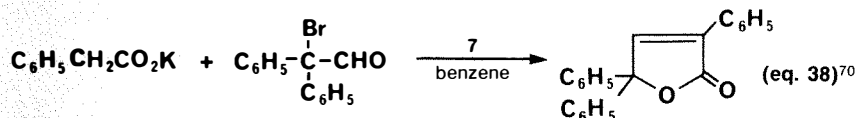
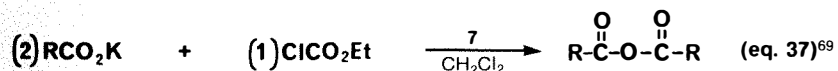
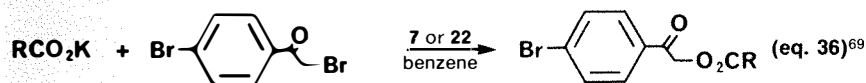
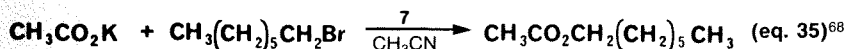
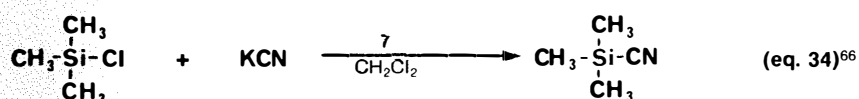
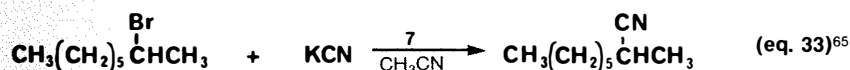
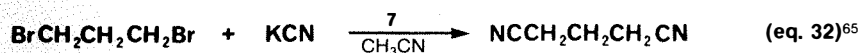
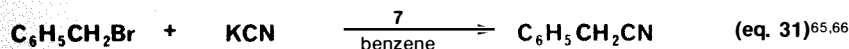
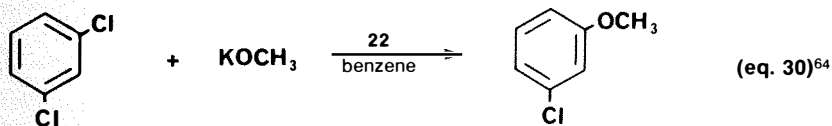
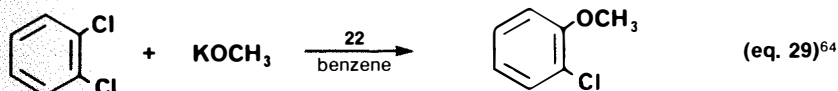
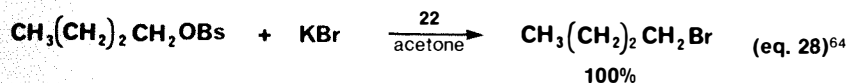
The remarkable ability of the macrocyclic polyethers to draw salts into non-polar solution has been utilized in reactions involving fluoride ion. 18-Crown-6 (**7**) assists the solubilization of KF in either acetonitrile or benzene and the poorly solvated fluoride anion exhibits potent nucleophilic properties.⁶² Two examples of fluoride substitution are illustrated in eqs. 18-21. In cases where elimination is more favorable than substitution, it becomes a major side reaction. Bromocyclohexane under these conditions yields only cyclohexene. In cases where elimination is unlikely, the substitution reaction works extremely well giving high yields of product (eqs. 22 and 23). The substitution reaction can also be applied to vinyl chloride, yielding vinyl fluorides (see eqs. 24 and 25).⁶³ This reaction proceeds *via* addition-elimination.

Other halides^{64,65} also exhibit reasonable nucleophilic behavior. In a liquid-liquid phase-transfer system,⁶⁵ the 1- and 2-octyl mesylates were converted to the iodide (eq. 26) and the bromide (eq. 27) respectively, by the appropriate nucleophiles. The lower yield reported in the latter case is presumably due to loss of product by elimination. The crown-mediated reaction of KBr in acetone yields the alkyl bromide in quantitative yield from the corresponding brosylate (eq. 28).⁶⁴ Methoxide ion also gives a net substitution reaction where halide is the leaving group.⁶⁴ This is illustrated for *o*- and *m*-dichlorobenzene in equations 29 and 30.

The pseudohalide cyanide ion exhibits similar behavior in S_N2 reactions, and a variety of nitriles have been prepared in good yield using PT techniques (eq. 31-33).^{65,66,67} A particularly interesting case⁶⁶ is illustrated in eq. 34. To our knowledge, the preparation of trimethylsilyl cyanide has not yet been effected under quaternary ion-catalyzed phase-transfer conditions.

The carboxylate ion is not generally considered a good nucleophile; its Swain-Scott constant is near 3. In non-polar media, however, it is quite nucleophilic. 18-Crown-6-complexed potassium acetate





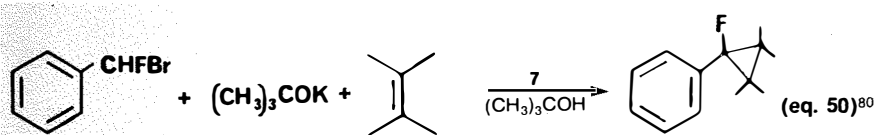
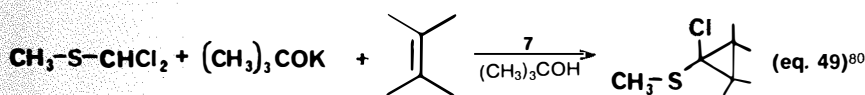
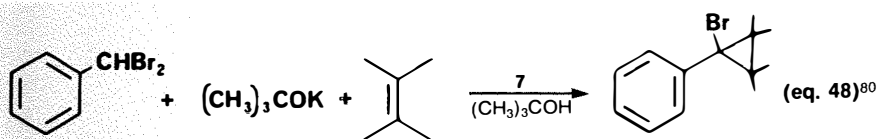
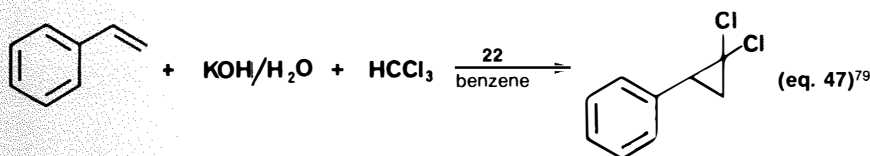
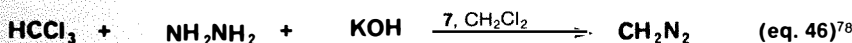
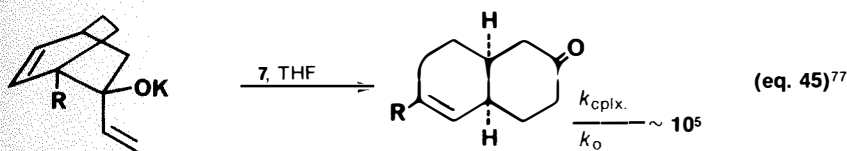
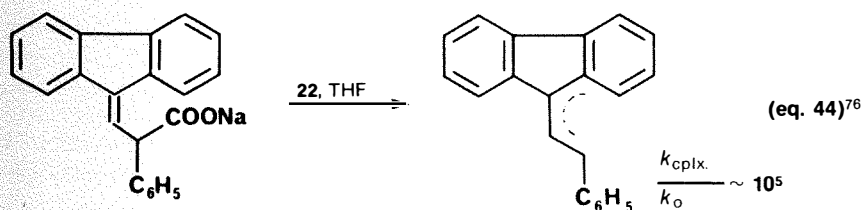
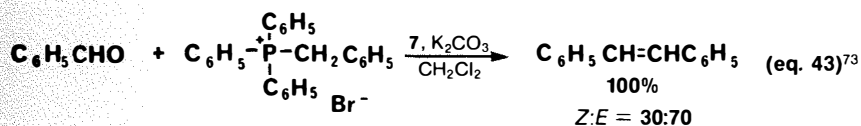
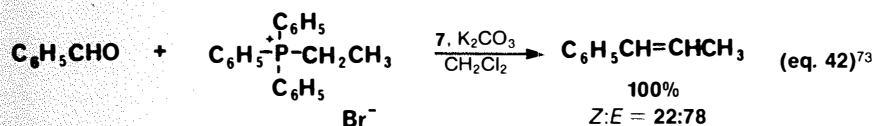
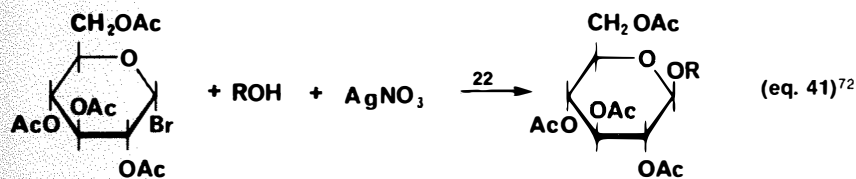
(sometimes called "bare acetate") reacts readily with *n*-heptyl bromide in acetonitrile to yield *n*-heptyl acetate (eq. 35).⁶⁸ Considerable utility has been demonstrated in the corresponding reaction of other carboxylate ions.⁶⁹ They have been used in the preparation of phenacyl ester derivatives (eq. 36), anhydrides (eq. 37), and some otherwise inaccessible lactone precursors (eq. 38).⁷⁰

Several other crown-assisted nucleophilic substitution reactions have been reported. The sequence of reactions formulated in eqs. 39 and 40 provides a mild and general method for the reduction of sulfoxides using crown solubilization in the reduction step.⁷¹ The Koenigs-Knorr alcoholysis of bromosugars (eq. 41) is also assisted by the presence of the crown ether.⁷²

The presence of crown ether has also been shown to influence product geometry in the Wittig reaction. The olefins formed from benzaldehyde and two phosphonium ylides are illustrated in eqs. 42 and 43. Note that the products exhibit predominant *trans* geometry.

Addition of polyethers to solutions containing configurationally mobile salts has yielded interesting results. Noe and Raban⁷⁴ have noted that the crown ether 7 causes a change in the preferred conformation of sodium acetoacetate. Gokel and coworkers^{75a} have developed evidence for crown ether-cation interaction in the Cannizzaro reaction. In other systems, crown ether-solvation of potassium-containing ion pairs evidently enhances reaction to a considerable extent. In the two reactions formulated, a rate acceleration of approximately 10⁵ was observed. The fact that both a decarboxylation (eq. 44)⁷⁶ and an oxy-Cope rearrangement (eq. 45)⁷⁷ exhibit similar rate enhancements is probably not coincidental: the Williamson reaction of potassium *t*-butoxide with benzyl chloride in THF is dramatically accelerated by addition of 7.^{75b}

The generation of carbenes or carbenoid intermediates has been reported by several groups. Weber and coworkers⁷⁸ have shown that diazomethane may be generated from aqueous potassium hydroxide, chloroform, hydrazine hydrate, and 18-crown-6 (7) in 48% yield (eq. 46). In Weber's procedure only 0.004 mole % of 7 is used. The advantages of this procedure over the classical methods of generating diazomethane are manifest. Markosza⁷⁹ also reports the generation of dichlorocarbene under the influence of 22 by a liquid-liquid (PT) process (eq. 47). The selectivity and reactivity of crown-catalyzed di-



chlorocarbenes mimic the quaternary ammonium PT dichlorocarbene formation.

Moss and Pilkiewicz⁸⁰ reported the reaction of activated dihalides (*i.e.*, benzal halides, thiomethyl dihalides) with the 18-crown-6 (7) complex of potassium *t*-butoxide. The rate of reaction, product yields, and selectivity are similar to those observed for carbenoid intermediates generated by the photolysis of diazirines (eqs. 48-50). Since the halides are generally more readily available than diazirines, this synthetic procedure makes this route to halophenyl carbenes quite attractive.

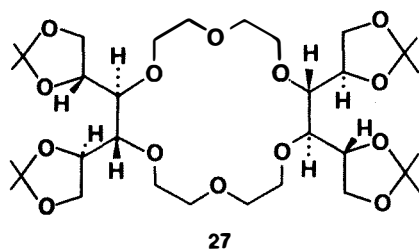
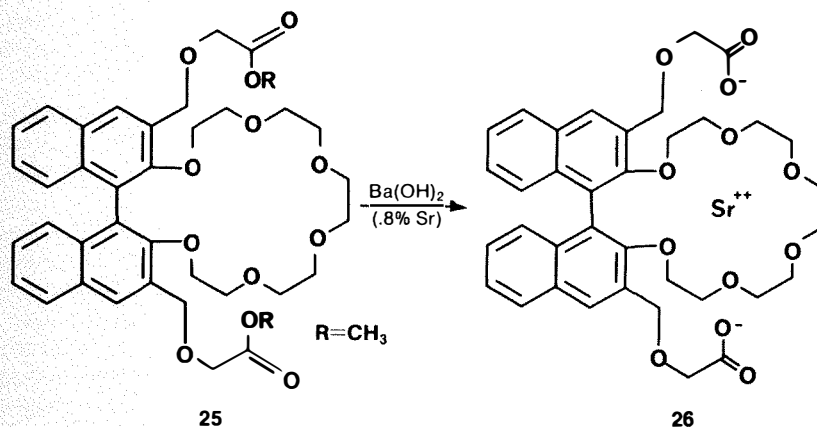
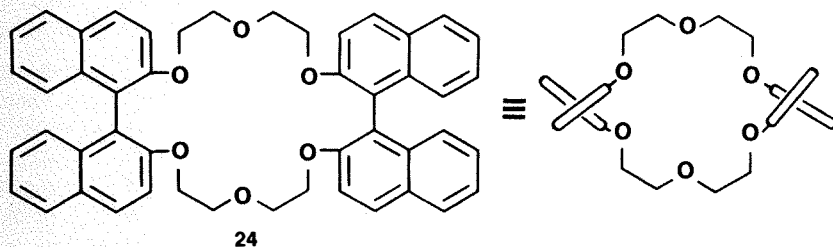
In a somewhat different application of the complexation of crown ethers, Cram and coworkers^{27,81} have designed optically active crown ethers, such as the dibinaphthyl crown ether (24), which extract alkyl ammonium salts (such as phenethylammonium hexafluorophosphate) from water into chloroform. The optically pure *S,S* crown ether was found to prefer the *R*-enantiomer of phenethylamine over the *S* enantiomer by a ratio of *ca.* 2:1. Because of this chiral recognition, effective partial resolutions of amines can be achieved on a preparative scale in separatory funnels.

Cram also reports that the related optically active diacid binaphthyl-20-crown-6 (25) has a great specificity for Sr⁺⁺ ions, even in the presence of a large excess of Ba⁺⁺ ions. For example, hydrolysis of the diester of 25 with barium hydroxide containing 0.8% Sr⁺⁺ as an impurity gives a complex (26) where the Sr⁺⁺ had been scavenged from the Ba(OH)₂ solution.

Optically pure diacid crown *S*-25 was found to preferentially complex *S*-valine from a racemic mixture by a ratio of 1:3.

This same chiral recognition approach has recently been extended by Stoddart and coworkers⁸² who synthesized a series of chiral 18-crown-6 ligands based on optically active diols. Selective extraction-complexation with the 18-crown-6 ligand (27) was observed with enantiomeric amines (as their salts).

The "chiral recognition" achieved by formation of diastereomeric complexes apparently depends largely on complementary steric relationships. Where the "fit" between a chiral ammonium salt and a chiral crown ether is good for one amine enantiomer and poor for its antipode, the selectivity of the crown ether will be high and so will the chiral recognition. As might be expected, a broad range of enantiomer selectivities has been reported. This procedure for partial resolution may be coupled with liquid chromatography to multiply the advantages of enantiomer



selectivity. In this way, Cram and coworkers have achieved total resolution of several amines.

Toxicology

Relatively little toxicity data is available on the crown ethers despite the many structures which have been prepared. This is particularly surprising in light of the cation binding properties of these systems and the biological implications thereof. Pedersen⁴⁸ reports that dicyclohexyl-18-crown-6 exhibits an approximate lethal dose (ALD) by ingestion (in rats) of 300 mg/kg. The compound is both a skin and eye irritant and exhibits a somewhat higher toxicity (ALD 130 mg/kg) by skin absorption. Sublethal doses appeared to be non-cumulative.

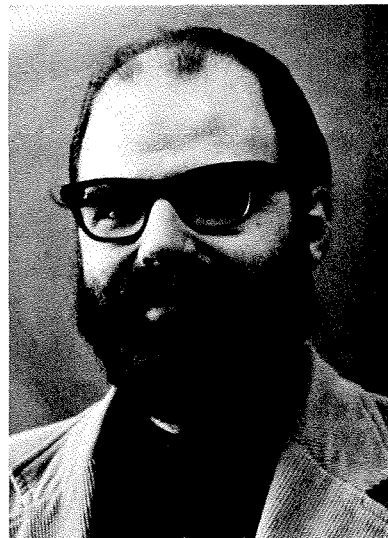
The cyclic tetramer of ethylene oxide (EO-4, 12-crown-4) has been found by Leong and coworkers⁸³ to exhibit considerable biological activity. This molecule exhibited deleterious effects on inhalation by rats, and higher homologs showed CNS activity. *It is clear that these and all new crown ethers should be handled with all due caution and respect.*

Conclusion and Prognosis

The report by Pedersen in 1967 that macrocyclic polyethers are effective complexing agents for numerous substrates and his preparation of many of these "crown" molecules has engendered considerable scientific activity during the last eight years. The complexation phenomenon is intrinsically linked to the template effect which allows these large ring com-



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H. Dupont Durst obtained the B.S. (1965) and M.S. (1967) in Biochemistry at Louisiana State University. He obtained the Ph.D. in Chemistry at the University of Minnesota in 1970. After graduation he went to the Department of Chemistry at the State University of New York at Buffalo where he is pursuing research on bio-organic model systems and synthetic methods.

pounds to be prepared in good yields at extraordinarily high concentration.

The crown ethers now seem to be firmly entrenched as phase-transfer catalysts and reagents to influence ionic reactions. They allow for enhanced rates, reactivity, economy, and convenience. For these and as yet unreported reasons, crown ether chemistry will continue to be important in the foreseeable future.

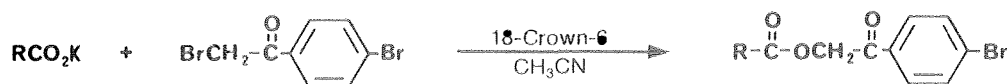
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Crown Ethers in Trace Fatty Acid Analysis

The use of 18-crown-6 and dicyclohexyl-18-crown-6 to catalyze the nearly quantitative formation (>97%) of *p*-bromophenacyl esters of fatty acids (C₁ to C₂₀) in aqueous and non-aqueous media has been recently reported.¹ The uv-absorbing *p*-bromophenacyl esters enable the detection of very small quantities of fatty acids (1-50ng) by high pressure liquid chromatography. The excellent yield of ester derivatives is not surprising in view of the report of the high nucleophilicity of the acetate anion in the presence of 18-crown-6.²



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Polymeric Reagents

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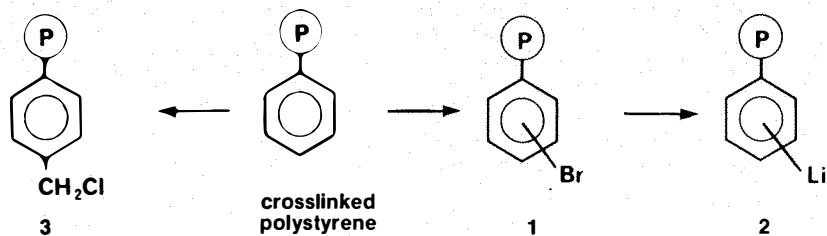
Historically, ion exchange resins can be considered as the earliest examples of polymeric reagents.¹ However, the use of insoluble polymers as supports for the synthesis of peptides² signalled the first growing interests in the unique advantages of functionalized polymers as reagents in organic synthesis. Simplification of the reaction work-up and product isolation are examples of the advantages of polymeric reagents most frequently cited in the literature,³ but the absence of volatility of noxious substances bound to polymers, together with the potential of recycling many polymeric reagents, present important environmental considerations which have received little attention.⁴ Additionally, there is evidence that low levels of functionalization, increased polymer crosslinking or the development of electronic charges near the backbone lead to restricted interaction of polymer functional groups, thus permitting certain reactions to proceed on polymers under conditions simulating an environment of high dilution.^{4,5} Matrix isolation provides a means of limiting unwanted intermolecular reactions or conducting a selective transformation of one group of a symmetrical difunctional molecule.^{4,6} Lastly, phase separation of two functionalized insoluble polymers suspended in a common medium has recently been utilized as an ingenious mechanistic probe for the detection of reaction intermediates whereby an intermediate of limited lifetime is liberated from one solid phase and trapped on the second solid phase.⁷

In recent years, insoluble polymeric reagents have been developed for the oxidation of alcohols,⁴ reduction of aldehydes, ketones and halides,⁸ acylation

of acids⁹ and the formation of halides from alcohols.¹⁰ In addition, there are reports of polymerically-bound tosyl azide,¹¹ hydrogenation catalysts,¹² peracids,¹³ ylide reagents,¹⁴ carbodiimides,¹⁵ and photosensitizers for the generation of singlet oxygen.¹⁶ Polystyrene crosslinked with varying amounts of divinylbenzene has been almost exclusively the polymer of choice for functionalization. The early limitations of both solvent and temperature-dependent swelling of microreticular polystyrene¹⁷ gels have been significantly reduced with the introduction of macroreticular polystyrenes.¹⁸ The two most common routes to functionalized crosslinked polystyrenes have involved the use of a lithiated polymer **2** prepared from brominated polystyrene **1**, or the chloromethylation product of polystyrene (**3**). Conclusions re-

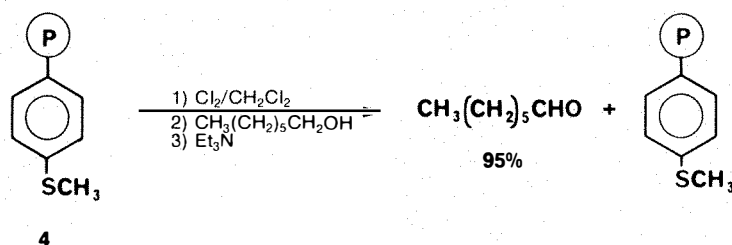
care, however, since the chloromethylation step is known to lead to increased crosslinking in the form of methylene bridges.¹⁹

The recent introduction of a polymeric thioanisole reagent **4** for the oxidation of saturated alcohols to aldehydes in high yield provides an excellent example of the potential environmental advantages of polymeric reagents;⁴ not only are the noxious odors of a monomeric sulfur reagent avoided, but the polymer can be recovered simply by filtration and reused, after washing, without the need of chemical regeneration. Aldehydes of high purity (>97%) are isolated from the reaction mixture merely by evaporating the washed and dried filtrate. The inevitable shortage of raw materials in the future may be lessened



garding the matrix-isolation of polymer-bound functional groups introduced *via* the latter intermediate must be made with

by the application of reusable reagents. In addition, use of the thioanisole reagent **4** containing a low concentration of methyl-

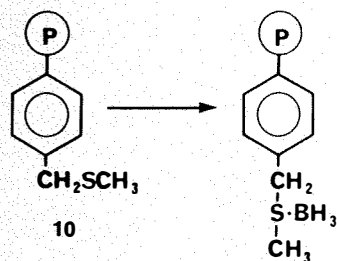


thio groups (0.66 mmol/g) provides a matrix-isolated environment for the selective oxidation of diols, such as 1,7-heptanediol (**5**) to the monoaldehyde **6**. However, significant amounts of starting material are recovered under the conditions required for optimum selectivity.

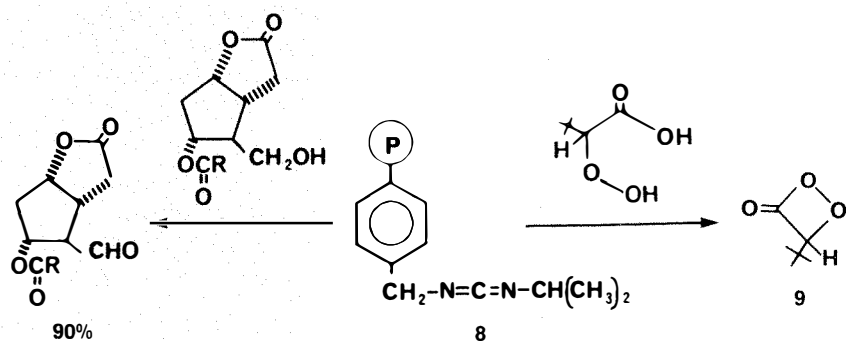
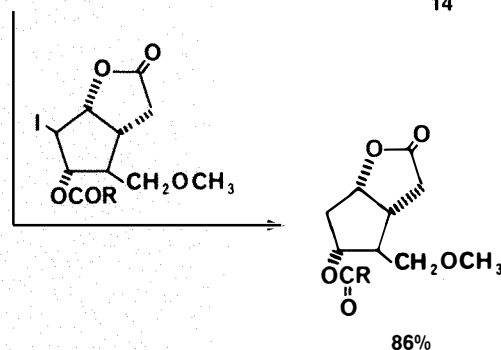
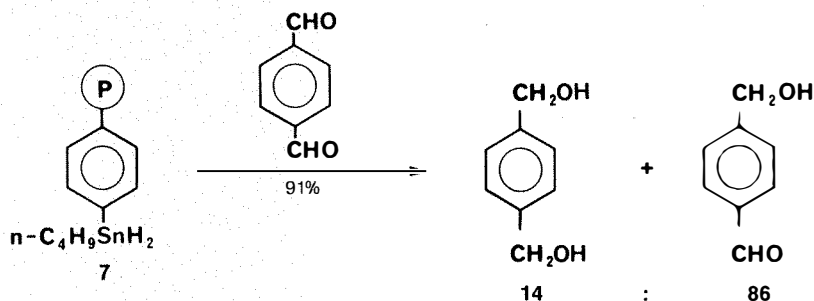
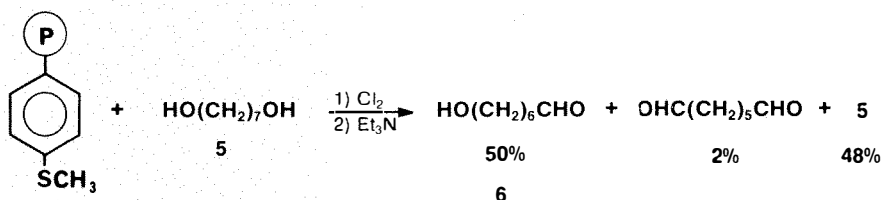
A general hydride reducing reagent has been developed⁸ utilizing a tin dihydride moiety. The polymeric reagent **7** is capable of reducing aldehydes, ketones and halides in high yields. Reduction of halides proceeds under mild conditions, and the product can be isolated in high purity simply by filtering the reaction mixture and evaporating the solvent. The often encountered difficulty of separating noxious tin by-products from reaction products is completely avoided by the use of a polymeric form of the reagent. Matrix-isolated reduction of a symmetrical dialdehyde such as terephthalaldehyde, with the polymeric hydride **7** results in moderately selective reduction of only one carbonyl group in high yield.

The advantages of a simplified reaction work-up and product isolation are best demonstrated by the polymeric carbodiimide reagent **8** which functions extremely effectively in the Moffatt oxidation of alcohols,^{15^b} as well as in the formation of anhydrides^{15^a} or lactones from appropriate carboxylic acids. The separation of urea by-products from carbodiimide-initiated reactions is frequently a major problem in organic synthesis. Professor Waldemar Adam and co-workers (University of Puerto Rico) encountered difficulties in separating the labile peroxy lactone **9** from dicyclohexylurea which was formed as a by-product in the lactonization with dicyclohexylcarbodiimide. Use of the insoluble polymer **8** however, permitted the lactonization to proceed smoothly in high yield with no isolation or purification problems.²⁰

The use of insoluble polymers to stabilize labile reagents is one application which deserves more attention.²¹ As an example, the thioether polymer **10** forms a stable complex with borane (~2 mmol/g),



which still functions effectively in typical hydroboration and reduction reactions.²² The insoluble reagent provides a solid



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source of borane which is easy to handle and store, although care must be taken to protect the reagent from air and moisture. Complete removal of the borane can be accomplished by application of reduced pressure.

Interestingly, the thioether polymer **10** has been found to behave like dimethyl sulfide in its ability to reduce hydroperoxides. The polymer **10** is capable of inhibiting the formation of peroxides in ethers such as diethyl and diisopropyl ethers, with an effectiveness equal to commercial stabilizers when used at a concentration of one gram per liter.²³ The reagent thus provides a simple means of stabilizing purified ether solvents against peroxide formation without contamination.²⁴ The solvent can be separated from the inhibitor by simple mechanical methods.

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Lab Notes. . .cont'd from page 2

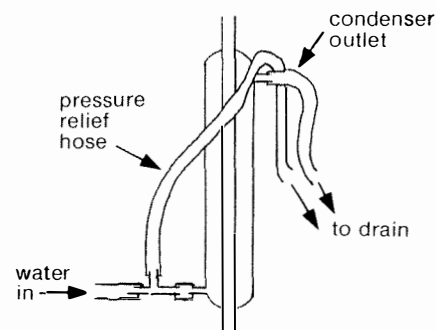
silicate glass. Anhydrous glycerol also has a refractive index very close to that of borosilicate glass. Thus, borosilicates will seem to disappear when immersed in either of the systems above, while the outline of other types will remain visible. This fast, easy test is often of value when one is considering repairs in the lab, particularly if the glass is not branded or otherwise identified.

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Mayo Foundation
Rochester, Minnesota 55901

Dear Sirs:

In "Lab Notes," *Aldrichimica Acta*, **8**, 26 (1975), Stan Davis described the use of a pressure relief valve to solve the problem of erratic water pressure during overnight or weekend refluxing. The following alternate solution eliminates the use of excessive amounts of water.

Connect a "T" tube to the inlet hose such that one end of the "T" leads to the condenser and the other to a hose which is draped over the outlet of the condenser



(this hose may be secured with a rubber band). The water pressure is adjusted so that water flow from the pressure relief hose stops, thereby allowing an adequate flow through the condenser. Any increase in water pressure will be alleviated by the relief hose. If a higher flow rate through the condenser is desired, the pressure relief hose may be raised higher above the outlet of the condenser. This simple system is fully adaptable to all types of condensers.

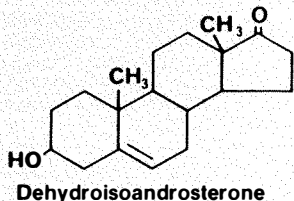
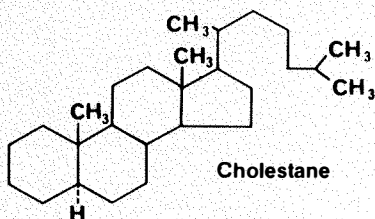
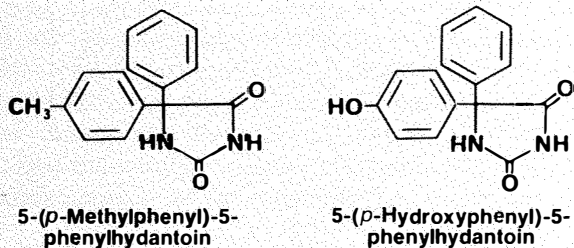
Peter M. Wovkulich
Department of Chemistry
Rice University
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Any interesting shortcut or laboratory hint you'd like to share with ACTA readers? Send it to Aldrich (attn: Lab Notes) and if we publish it, you will receive a handsome red and white ceramic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

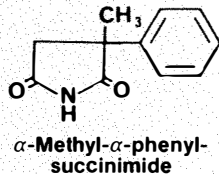
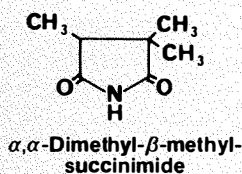
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Drug Detection Standards

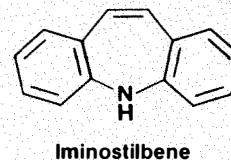
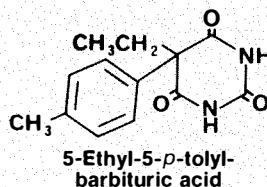
Rapid, accurate, and sensitive methods of assay for anticonvulsant levels in blood, serum, plasma, or urine of patients undergoing single- or multiple- drug therapy are very important in allowing the physician to establish drug dosage. Gc seems to offer the best method for simultaneous drug determination, to which purpose Aldrich offers several compounds as internal standards or markers.



5-(*p*-Methylphenyl)-5-phenylhydantoin (MPPH)^{1,2} and 5-(*p*-hydroxyphenyl)-5-phenylhydantoin (HPPH),^{3,4} a metabolite of 5,5-diphenylhydantoin (DPH), are widely used standards for the determination of DPH. Cholestane⁵ and dehydroisoandrosterone⁶ have also been used as internal standards for DPH assays.



α,α -Dimethyl- β -methylsuccinimide^{7,8} is a useful internal standard for ethosuximide (α -methyl- α -ethylsuccinimide), while α -methyl- α -phenylsuccinimide (normethsuximide),^{9,10} a major metabolite of methsuximide (*N*-methyl-2-methyl-2-phenylsuccinimide), is a standard in the assay of that drug.



5-Ethyl-5-*p*-tolylbarbituric acid^{1,11} is useful as an internal standard in the assay of barbiturates. Carbamazepine may be assayed using its metabolite, iminostilbene, as the internal standard.^{12,13}

Tetramethylammonium hydroxide⁸ and diazomethane¹⁴ are used to prepare methylated derivatives for gc analysis.

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Aldrichimica Acta

Volume 9, Number 2, 1976



Permeation Chromatography Using Enzacryl® Gel. See page 23.
Selective Reduction of α,β -Unsaturated Carbonyls. See page 31.

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About Our Cover:

When our chemist-collector first saw this haunting painting (oil on canvas, 39 1/4 x 32 3/4 inches) it was attributed to Aert de Gelder, and the Venetian-looking column on the right had been over-painted, probably to be able to call the painting *David and Bathsheba*. However, the figure on the left is not David, but a Roman statue of a Dacian king. That statue, formerly in the Palazzo Farnese, is now in the Museum in Naples. Our chemist thinks — but is by no means certain — that the painting depicts *Esther* in the courtyard of King Ahasuerus. Our chemist-collector would welcome other suggestions.

There is a Jewish legend (*Babylonian Talmud, Megillah 15b*) that when Esther came to the court of the King (*Esther 5, 1*) and reached the chamber of the idols, the Divine Presence left her and she quoted the 22nd *Psalms*, "My God, my God, why hast thou forsaken me?", the same *Psalms* quoted by Jesus in the agony of the crucifixion (*St. Matthew 27, 46*). If indeed it is *Esther in the Courtyard*, then the statue represents an idol, and the winged beast on the column a symbol of the Orient.

The painting had been fully signed and dated 1666, but the signature has been altered to resemble that of Aert de Gelder, whose work it certainly is not. It is probably by another Rembrandt student, Lambert Doomer (1624-1700), who is much better known for his landscape drawings than his rare Biblical paintings.

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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.

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Lab Notes

Dear Sirs:

The extraction of an organic compound from a viscous aqueous phase containing a suspended inorganic compound, such as magnesium hydroxide or chromium hydroxide, is difficult. Even if the suspended solids can be removed by filtration or centrifugation, some of the desired organic compound could be lost by being trapped within the suspended solids. Such a problem can be solved by doing the extraction in a Morton flask which also can be used as the reaction vessel. The indented sides of the flask and an overhead stirrer run at a fairly high rate effect thorough mixing of the aqueous phase and the extraction solvent. To minimize transfers, the Morton flask is equipped with a wide-bore Teflon® stopcock which is attached to the flask by a ball joint to provide a more flexible and hence less easily broken outlet. In the reaction which I ran, chromium hydroxide was very thoroughly dispersed in the thick aqueous phase so that only occasional blockage of the stopcock occurred. This extraction approach is a rather tedious batch method; however, it is worth the effort if other extraction methods have failed.

Le Roy W. Haynes
Department of Chemistry
The College of Wooster
Wooster, Ohio 44691

Gentlemen:

We have found a convenient method for handling small sublimable samples for mass spectral analysis. The crude mixture is introduced into a melting point capillary and placed in a Meltemp®. The heat is set at a convenient temperature and the material is allowed to sublime up the tube. In most cases, the solid deposits just above the point where the capillary is in contact with the Meltemp®. The tube is removed and broken at a point just under the sublimed material. The portion of the capillary containing the pure material can then be placed directly into the mass spectra sampling compartment. Using this method, we have been able to purify and obtain mass spectra on submilligram samples.

Thomas R. Nelsen
New York State Agricultural Expt. Station
Cornell University
Geneva, New York 14456

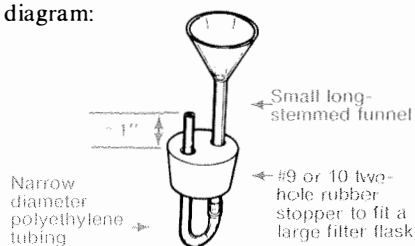
Gentlemen:

When carrying out operations involving liquids in a glove bag, one has to exercise great care to prevent moving the entire bag and spilling any liquids. This problem can be eliminated by using a lead brick sawed into quarters, each piece wrapped in a paper sack bound by tape or rubber band, and placing one in each corner of the dry bag. Before moving the dry bag, however, you must remember to "get the lead out."

Jon Howdeshell, Ph.D.
Laramie Chemical Company
P.O. Box 3611
Laramie, Wyoming 82071

Dear Sir:

An inexpensive uv/vis 1 cm cell washer can be prepared according to the following diagram:

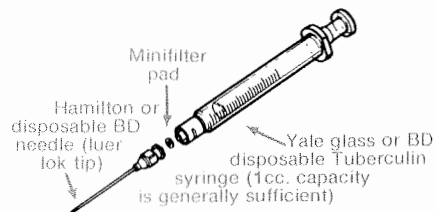


Install the completed cell washer on a one-liter or two-liter filter flask connected to a vacuum line. Set the cell over the protruding polyethylene tubing, turn on the vacuum, and pour the solvent of your choice into the funnel. After rinsing, leave the vacuum on to air-dry the cell. This design can be adapted for use with nmr tubes.

Brian Warner
Graduate Student
Department of Chemistry
Washington State University
Pullman, Washington 99163

Dear Sirs:

Frequently, it is necessary to remove solid material from small volumes of solutions to be analyzed by nmr spectroscopy or other sensitive instrumental



technique. The above diagram indicates a quick, efficient no-mess procedure for such small-scale "suction-filtrations." For larger quantities of solid, or for removing decolorizing carbon, the liquid may be introduced into the plunger end of the syringe. Six or more minifilter pads may be cut from a half-inch penicillin assay pad

with a small cork borer, and stored in a sample vial. No. 740-E (Schleicher & Schuell Co.) or equivalent penicillin assay pad is of adequate weight and porosity.

P.J. Macaulay
Department of Chemistry
Mount Allison University
Sackville, New Brunswick E0A 3C0
Canada

Dear Sir,

The work-up of lithium aluminum hydride reductions, particularly large-scale ones (1 to 10 moles), is not always a straightforward operation. Often gels and emulsions are obtained and these may seriously affect the yield and/or purity of the isolated product.

I wish to bring to your attention a method of work-up which affords a high recovery of the product even in the reduction of the carbomethoxy group of some complex indole alkaloids. The procedure is straightforward, relatively "foolproof" and simple.

Sodium sulfate, used as a drying agent in the laboratory, is saved and recrystallized from hot water. The Glauber's salt ($\text{Na}_2\text{SO}_4 \cdot 10\text{H}_2\text{O}$) so obtained is used in the work-up procedure described below. In this way one can obtain "double mileage" out of the sodium sulfate with an obvious saving in cost over the commonly used Rochelle salt.

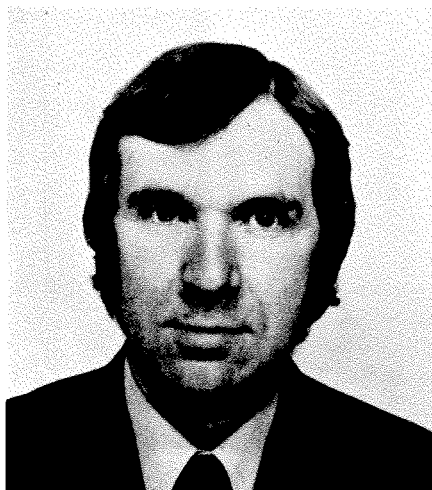
Glauber's salt is added with stirring to the reaction mixture (slowly at first because the reaction is exothermic) until hydrogen evolution ceases. A slight excess is added and the reaction mixture is stirred for an additional 10 minutes. A white granular precipitate is obtained which can be filtered easily under suction. The filter cake is returned to the flask and extracted twice with hot solvent. The combined organic filtrate is evaporated to yield the reduction product mixture. Product recoveries of >90% are routine and quantitative recoveries are not uncommon in the cases so far investigated.

Adi M. Treasurywala
Departement de Chimie
Université de Sherbrooke
Sherbrooke, Quebec J1K 2R1
Canada

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

Permeation Chromatography of Organic Solutes Using Enzacryl[®] Gel Packings

Roger Epton
Koch-Light Laboratories Ltd.
Colnbrook, Buckinghamshire
England



INTRODUCTION

Permeation chromatography, otherwise known as gel chromatography or gel filtration, has wrought great changes in biological chemistry and polymer science over the last decade. However, relatively few traditional organic chemists make use of the technique despite its predictability, speed and value in handling labile molecules. This is not a matter of mere conservatism. Organic species often differ dramatically in solubility properties and the would-be permeation chromatographer requires a wide range of elution solvents at his disposal. This raises serious problems in the selection of suitable chromatographic packings. The popular packings used in biological chemistry are intended primarily for use in water or aqueous buffers. In most common organic solvents, such supports do not undergo gelation and, consequently, are inapplicable. The permeation supports used in polymer science have a molecular weight fractionation range too high to be of use to

the organic chemist or are applicable in only a limited number of organic solvents.

Enzacryl[®] Gel^{1,2} has been developed specifically to meet the needs of the organic permeation chromatographer. Its most important feature is that it is applicable both in water and a range of common organic solvents together with an almost infinite variety of mixed-solvent systems. We have recently made Enzacryl Gel available in five grades, designated K0, K1, K2, K4 and K10, each covering a different molecular weight fractionation range.³ There are few organic species which cannot be chromatographed on one or another of these supports.

ENZACRYL GEL STRUCTURE

Chemically, Enzacryl Gel consists of a space network of poly(*N*-acryloylmorpholine) chains whose movement, relative to one another, is constrained by cross-linking (Fig. 1). The support is prepared by

free radical polymerization in aqueous solution. This is dispersed as droplets in liquid paraffin containing suitable surfactants. As a result, Enzacryl Gel is produced in the form of discrete beads. These are washed rigorously and graded according to size by elutriation techniques.

It will be apparent that the molecular weight fractionation range of a given Enzacryl Gel packing will be related closely to pore size and pore size distribution within the poly(*N*-acryloylmorpholine) network. The mean pore size is predetermined largely by the total monomer concentration and the ratio of monomer to cross-linker in the aqueous polymerization mixture. However, it is important to realize that useful secondary variations in mean pore size and molecular weight fractionation range of Enzacryl Gel networks may be obtained as a result of swelling variation in the different solvents used for permeation chromatography.

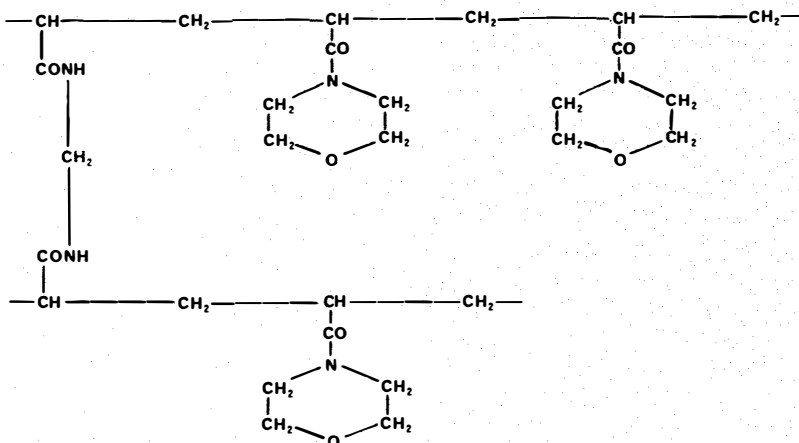


Figure 1 Cross-linked poly(*N*-acryloylmorpholine) — Enzacryl Gel.

Enzacryl Gel of very low mean pore size is obtained by carrying out the preparative polymerization at high total monomer concentration. Enzacryl Gel K0 has the lowest mean pore size of the five packings offered and is ideal for the permeation separation of small organic molecules in water and polar organic solvents, such as chloroform, dimethylformamide and pyridine (Fig. 2). The similarity in the molecular weight fractionation range of Enzacryl Gel K0 in each of these solvents is remarkable. Typical hydrophilic organic molecules such as alcohols, simple aliphatic aldehydes, ketones, ethers, amines, nitro compounds and saccharides are separated readily using water as solvent. With the exception of saccharides, all these species, together with their more hydrophobic homologs and aromatic equivalents, may be fractionated easily in the three organic solvents alongside simple aliphatic and aromatic hydrocarbons.

It is interesting to note that bead-polymerized, cross-linked poly(*N*-acryloylmorpholine) networks of much lower mean pore size and exclusion limit than Enzacryl Gel K0 can be prepared. We have found that, in practice, these supports offer little improvement in separating efficiency for small molecules. In permeation chromatography, the entire chromatographic fractionation profile emerges from the column within a volume of eluent corresponding to that filling the pores within the gel particles. Gel packings of extremely low pore size consist largely of polymer and so the total pore volume is low. This results in a very short elution profile.

The swelling properties of a given grade of Enzacryl Gel vary considerably from solvent to solvent. Pore size depends to some extent on swelling and in those solvents, such as tetrahydrofuran and methanol, in which swelling is only moderate, it is necessary to use Enzacryl Gel K1 or Enzacryl Gel K2 to obtain comparable molecular weight fractionation ranges. Excellent separations are possible in these solvents.

COLUMN CALIBRATION AND GEL PARAMETERS

The permeation behavior of an organic molecule, elution volume V_e , on a given column packing, may be characterized by calculating either the Wheaton and Baumann⁴ absolute distribution coefficient, K_d , or the less definitive but more accessible Laurent and Killander⁵ distribution coefficient, K_{av} . Both K_d and K_{av} are independent of the shape, volume and packing density variation within the gel bed. The coefficient K_d is calculated from

the relationship

$$K_d = \frac{V_e - V_o}{V_i} = \frac{V_e - V_o}{V_s - V_o} \quad (1)$$

where V_o is the column void volume as estimated by elution of a totally excluded solute and V_i is the cumulative internal bead volume available to a totally included solute or molecule of solvent, elution volume V_s .

The coefficient K_{av} is calculated from the equation

$$K_{av} = \frac{V_e - V_o}{V_t - V_o} \quad (2)$$

where V_t is the total bed volume for the column.

The advantage of the Wheaton and Baumann distribution coefficient, K_d , is that it is simply a statement of the fraction of the solvent accessible volume within the gel which is available to a given solute. Thus, its value varies between zero, for a solute too large to permeate the gel beads, to unity, for solutes able to penetrate the gel at random in a manner similar to the solvent. It can be a simple matter to superimpose a scale of K_d values on a given permeation profile (Fig. 2). The only obstacle to the universal use of K_d to define

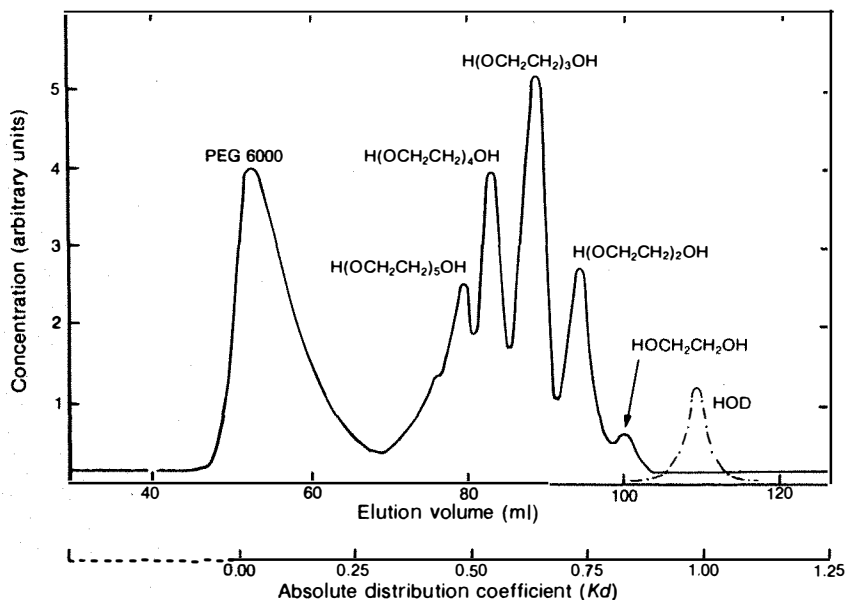


Figure 2 Fractionation of polyethylene glycol 200 on fine grade Enzacryl Gel K0 using water as solvent (bed volume 100 x 1.5ml). Enzacryl Gel may also be used to fractionate polyethylene glycols in chloroform, dimethylformamide and pyridine.

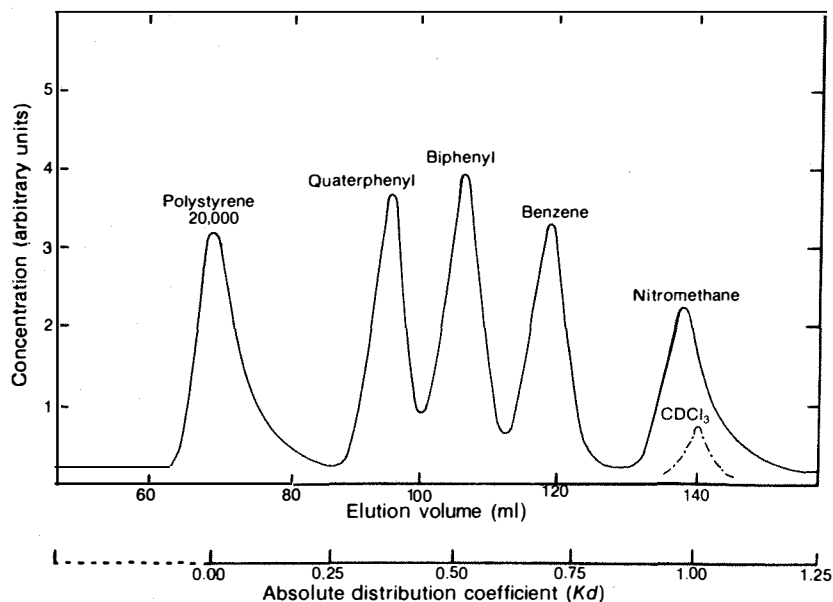


Figure 2b Fractionation of some aromatic solutes on medium grade Enzacryl Gel K1 in chloroform (bed volume 90 x 1.5ml).

elution behavior is the difficulty, in the case of a number of column packings, of determining the parameter V_i .

In the case of Enzacryl Gel, we have been most fortunate in that we have been able to use K_d values throughout our work. This has greatly assisted us in making useful comparisons of results obtained in different solvents over a long period (Fig. 3). An important advantage of Enzacryl Gel over

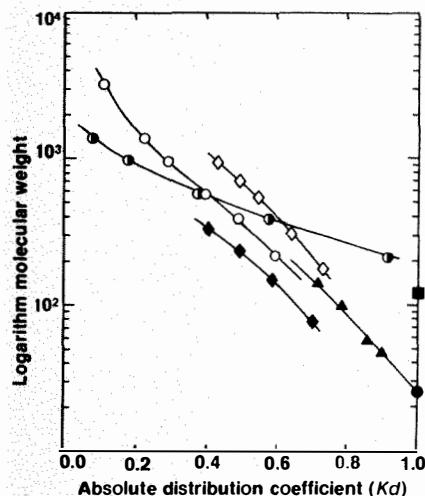


Figure 3. Comparison of logarithm molecular weight vs. K_d plots for various solutes on Enzacryl Gel K1: (a) Chloroform chromatography of polydisperse polyethylene glycols (●), condensed aromatic hydrocarbons (◆) and $CDCl_3$ (■); (b) Aqueous chromatography of polydisperse polyethylene glycols (○), discrete polyethylene glycol oligomers (▲), saccharides (◇) and D_2O (○). (Adapted from R. Epton, C. Holloway and J.V. McLaren, refs. 1 and 2).

all other supports used in aqueous permeation chromatography (gel filtration) is that the gel network contains very few labile protons. Consequently, it is possible to calculate exactly the cumulative internal bead volume, V_i , by subtraction of the void volume, V_o , from the elution volume, V_s , of the solvent. The latter corresponds to the elution volume of a sample of isotopically labelled solvent. This can be detected in column effluents by differential refractometry, mass spectrometry or, where appropriate, liquid scintillation counting.⁶

It is worth mentioning that, in aqueous permeation chromatography with the popular cross-linked dextran and cross-linked polyacrylamide packings, V_i cannot be determined easily from elution studies with D_2O or T_2O . This is because, to these molecules, the many labile protons of the polymer network behave as an extension of the mobile phase. Thus, the Laurent and Killander distribution coefficient, K_{av} , is used widely for these packings because K_d is difficult to obtain. A serious disadvantage of K_{av} is that it does not approach unity for small solutes. Moreover, the limiting value of K_{av} varies from gel to gel. This is a

consequence of the column packing volume, V_m , being implicit in the denominator ($V_i - V_o = V_i + V_m$) of equation 2.

THIN LAYER PERMEATION CHROMATOGRAPHY

In the course of our program of research, we have tried to prepare a series of poly(*N*-acryloylmorpholine) gel networks which would cover the widest possible molecular weight fractionation range.⁶ During polymerization, the two parameters which most affect molecular weight fractionation range are the overall aqueous dilution of monomers and the molar ratio of *N*-acryloylmorpholine to the cross-linker, *N,N'*-methylene diacrylamide. As indicated earlier, it was a relatively simple matter to prepare networks of very low mean pore size simply by reducing the overall aqueous dilution of monomers. However, to prepare networks of high mean pore size and molecular weight exclusion limit proved much more difficult and it became apparent that we would need to characterize systematically a wide range of networks in order to achieve this. Characterization using column chromatography would have been a major undertaking necessitating bead gradation by aqueous elutriation, column packing, and tedious sequential elution of standards. Consequently, we resorted to thin layer permeation chromatography in order to expedite our work.

Thin layer permeation chromatography is carried out most easily in water. This was fortuitous because selection of this solvent for chromatography enabled us to simplify the washing procedures for the various gel networks and equilibrate them directly with the buffer to be used for the chromatographic evaluation procedure. Nevertheless, we needed to overcome two major problems. The first was the difficulty in monitoring the migration of solutes during the development of the thin layer

plates. We overcame this obstacle by applying a procion dyeing technique⁷ to obtain a series of soluble, colored proteins for use as standards (Table I). The second difficulty was to relate migration distance

Table I
Thin layer standards

Dyed protein	Molecular weight
Insulin	(6,000) ^a 12,000 ^b
Ribonuclease	13,600 27,200 ^b 40,800 ^c
Chymotrypsinogen	25,000
Ovalbumin	45,000 90,000 ^b
Transferrin	67,000 134,000 ^b
Albumin	67,000 134,000 ^b 201,000 ^c
Fibrinogen	335,000
Urease	490,000
β -Galactosidase	520,000
Thyroglobulin	670,000

to the Wheaton and Baumann distribution coefficient, K_d , for each standard used. The solution to this problem lay in the derivation of a suitable relationship⁸

$$K_d = \frac{d_s[d-d_c]}{d_c[d_o-d_s]} \quad (3)$$

where d_c is the migration distance of the given standard, d_s is the migration distance of the solvent and d_o is the migration distance of the solute which is totally excluded from the gel. To determine d_s , it was necessary to use T_2O/TOH elution data. Tritium was detected by removing samples of gel from the thin layer plate and measuring the radioactivity by liquid scintillation counting.

Thin layer data was used to obtain K_d values for a series of gel networks prepared at steadily increasing monomer dilution with the mole ratio of *N*-acryloylmorpho-

Table II
Gel nomenclature for poly(*N*-acryloylmorpholine) networks synthesized at increasing monomer dilution and increasing *N*-acryloylmorpholine to cross-linker ratio.

Aqueous dilution (ml/g of monomer) in polymerization	Molar ratio of <i>N</i> -acryloylmorpholine/ <i>N,N'</i> -methylene diacrylamide				
	5/1	10/1	20/1	40/1	80/1
2.8	-	K2(2.9)	-	-	-
5.7	-	K3(5.1)	-	-	-
11.4	J4(K10),(9.7)	K4(12.1)	L4(12.4)	M4(17.4)	N4(20.6)
14.9	-	K5(14.9)	-	-	-

Equilibrium volume of 0.5M NaCl/0.05M phosphate buffer (pH 8.5) per gram of cross-linked poly(*N*-acryloylmorpholine) prior to the thin layer evaluation is given in parentheses.

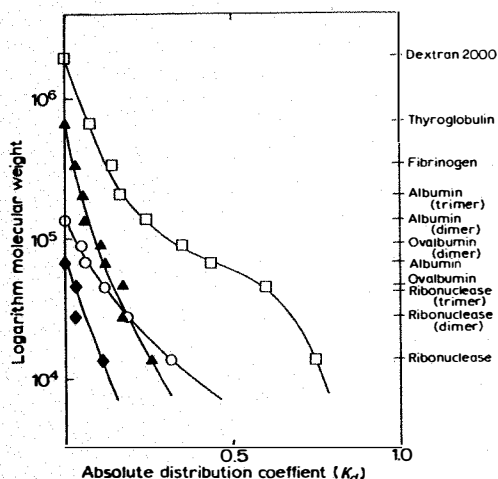


Figure 4. Logarithm molecular weight vs. K_d plots for gel networks K2(\blacklozenge), K3(\circ), K4(\blacktriangle) and K5(\square) synthesized at progressively increasing monomer dilution. (From R. Epton, S.R. Holding and J.V. McLaren, ref. 6).

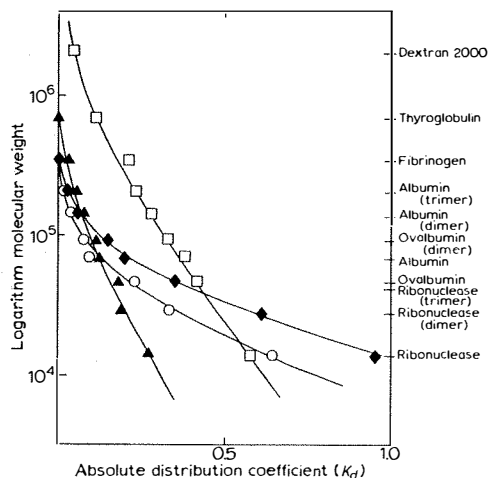


Figure 5. Logarithm molecular weight vs. K_d plots for gel networks J4(K10) (\square), K4(\blacktriangle), L4(\circ) and N4(\blacklozenge) synthesized with progressively increasing mole ratio of *N*-acryloylmorpholine to cross-linker. (From R. Epton, S.R. Holding and J.V. McLaren, ref. 6).

line to *N,N'*-methylene diacrylamide kept constant and for a series of networks prepared at constant monomer dilution but with steadily increasing mole ratio of monomer to cross-linker (Table 2). It is clear from the logarithm molecular weight vs. K_d plots (Fig. 4) for the first series (networks K₂, K₃, K₄ and K₅) that increase in network volume is accompanied by an increase in K_d and an overall increase in molecular weight exclusion limit. On the other hand, increase in K_d with network volume only holds at constant or high monomer to cross-linker ratio. This may be inferred from the logarithm molecular weight vs. K_d plots (Fig. 5) for the second series. Molecular weight exclusion limit progressively diminishes across the series J4(K10), K4, L4 even though the network volume is increasing.

The immediate practical value of these studies was to enable us to select network J4 as the most suitable for the fractionation of large molecules. Later, network J4 was made commercially available as a support for thin layer application and was renamed Enzacryl Gel K10.

STABILITY AND DERIVATIZATION OF ENZACRYL GEL

Because Enzacryl Gel is a completely synthetic carrier, it is not easily degraded by microbial attack. Furthermore, it is relatively stable to extremes of pH.⁹ Thus, with 1M HCl at 25°, no hydrolysis of the matrix could be detected after 9 days. With 1M NaOH at 25°, only 0.21 milliequivalents of carboxylate was produced per gram of Enzacryl Gel (dry weight) over the same period. To achieve a reasonable rate of degradation of Enzacryl Gel K2 with 1M NaOH, it was necessary to raise

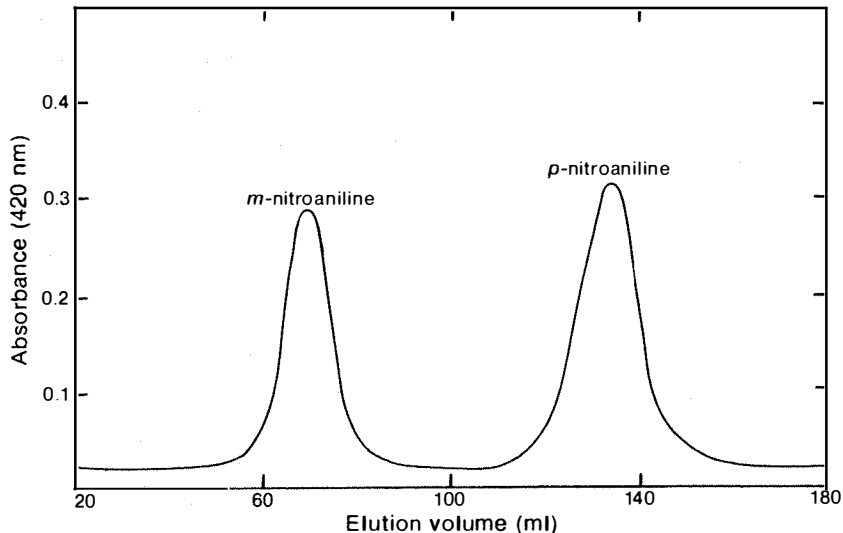


Figure 6 Separation of nitroaniline isomers by cation exchange on Enzacryl CO₂H using 2% aqueous acetic acid as eluent. (From R. Epton, S.R. Holding and J.V. McLaren, ref. 9).

the temperature to 100°. Under these conditions, it took 12-15 hours to produce approximately 1 milliequivalent of carboxylate groups per gram. The hydrolysis product was designated Enzacryl® CO₂H and performs usefully as a cation exchanger (Figs. 6 & 7).

We have also prepared an anion exchanger from Enzacryl Gel K2 by reaction with *N,N*-diethylethylenediamine in dry ethylene glycol at 175°. The titration curve (Fig. 7) for the diethylaminoethyl-substituted product, Enzacryl® DEAE, is ideal and almost exactly complementary to that for Enzacryl CO₂H. Superb anion exchange separations are possible as exemplified by the separation of adenosine 5'-monophosphate (AMP), adenosine 5'-di-

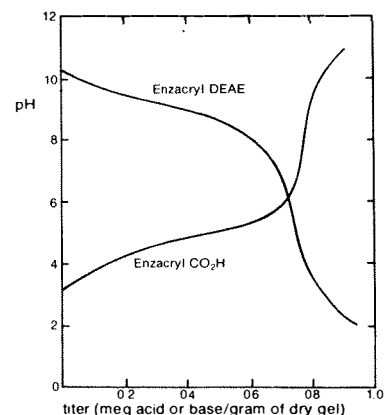


Figure 7. Titration curves for the ion exchangers Enzacryl CO₂H and Enzacryl DEAE. (From R. Epton, C. Holloway and J.V. McLaren, ref. 9).

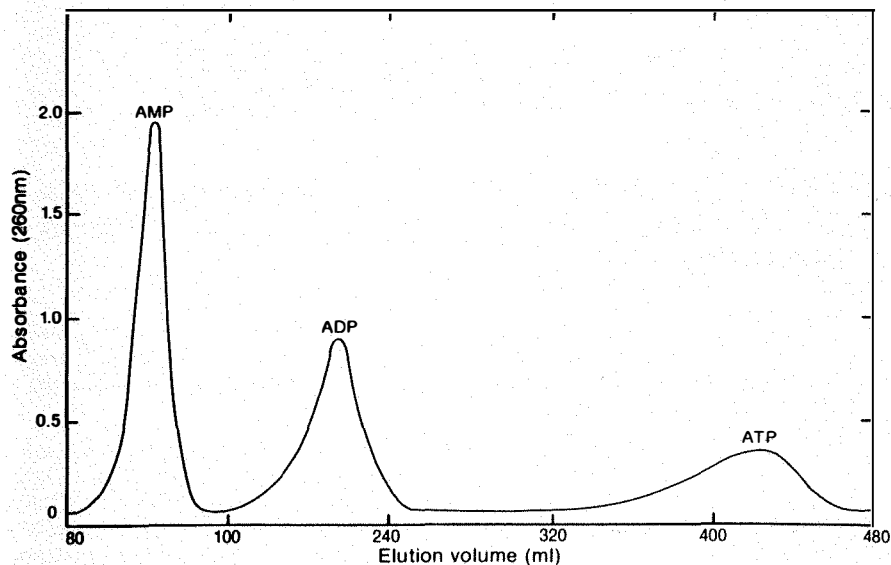


Figure 8 Separation of adenosine 5'-monophosphate (AMP), adenosine 5'-diphosphate (ADP) and adenosine 5'-triphosphate (ATP) on Enzacryl Gel DEAE using 0.1M Tris-HCl buffer, pH 8.3, as eluent. (From R. Epton, C. Holloway and J.V. McLaren, ref. 9)

phosphate (ADP) and adenosine 5'-triphosphate (ATP) (Fig. 8).

CONCLUDING REMARKS

Cross-linked poly(*N*-acryloylmorpholine) (Enzacryl Gel) has unique gelation properties which make it an almost universally applicable support for permeation chromatography. Its comparative stability to microbial and chemical attack is most advantageous and we have by no means ex-

hausted the development potential of these supports. Currently, composite networks of polymers are under investigation. Enzacryl CO₂H and Enzacryl DEAE offer intriguing possibilities for application as ion exchangers in mixed and non-aqueous solvents while other functional derivatives of poly(*N*-acryloylmorpholine) may well prove useful as solid (gel) phase reagents.

References:

- 1) R. Epton, C. Holloway, and J.V. McLaren, *J. Appl. Polym. Sci.*, **18**, 179 (1974).
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- 9) R. Epton, C. Holloway, and J. V. McLaren, *J. Chromatogr.*, **117**, 245 (1976).

About the Author

Dr. Roger Epton received his B.Sc. in 1961 from the University of Liverpool, U.K., and his Ph.D. in 1969 from the University of Birmingham, U.K. He was made a Fellow of the Royal Institute of Chemistry in 1974. He is actively engaged in directing research on gel filtration and GPC, immobilized enzymes, metallocenes and the chemistry of semisynthetic antibiotics.

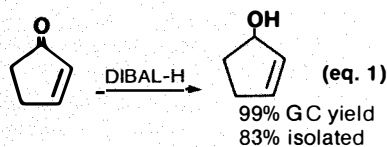
Currently he is a Reader in Bioorganic and Polymer Chemistry at Wolverhampton Polytechnic, U.K.

Selective Reduction of the Carbonyl Group in α,β -Unsaturated Aldehydes and Ketones

Clinton F. Lane
Aldrich-Boranes, Inc.
Milwaukee, Wisconsin 53233

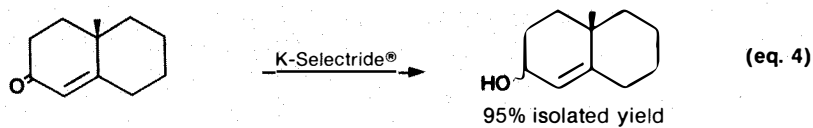
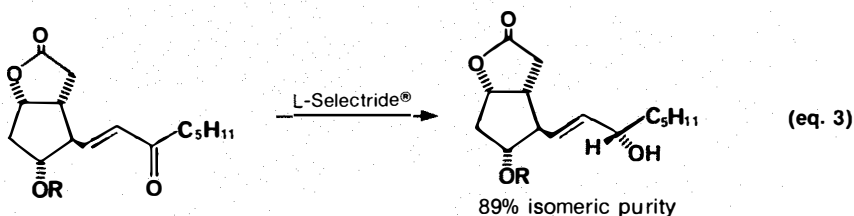
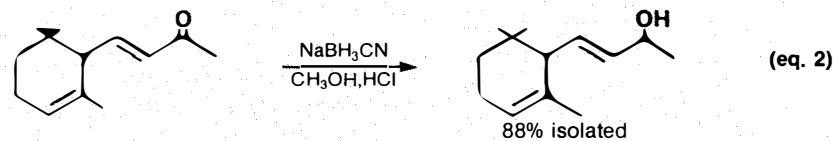
The reduction of α,β -unsaturated aldehydes and ketones with hydride reagents often results in a mixture of products.¹ Frequently, the desired allylic alcohol is contaminated with varying amounts of saturated alcohol or saturated ketone. For example, a detailed investigation of the reduction of conjugated aldehydes and ketones with sodium borohydride showed that the reaction invariably leads to substantial amounts of fully saturated alcohol products.² Superior results were obtained with lithium aluminum hydride (LAH).² However, LAH reduction of 2-cyclopentenones, which are known to be highly susceptible to conjugate addition, results in substantial saturation of the carbon-carbon double bond.³

The failure to achieve clean reduction of α,β -unsaturated aldehydes and ketones with either sodium borohydride or LAH led to the examination of various other hydride reducing agents. Brown and Hess found that, for the reduction of 2-cyclopentenones, aluminum hydride is clearly more selective than either LAH, lithium trimethoxyaluminumhydride, or lithium tri-*t*-butoxyaluminumhydride.³ Later, Masamune and coworkers found that diisobutylaluminum hydride (DIBAL-H) gives higher yields and cleaner reductions than does aluminum hydride.⁴ The excellent results achieved for the reduction of 2-cyclopentenone provide a specific example (eq. 1).



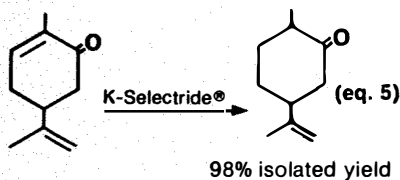
Unfortunately, Masamune reported only DIBAL-H reduction of 2-cycloalkenones. When DIBAL-H is used for the reduction of certain acyclic 2-enones, substantial amounts of saturated ketones are obtained upon hydrolysis.⁵ Also, DIBAL-H is a relatively powerful reducing agent which will reduce many other functional groups in the same molecule. For example, DIBAL-H readily reduces acids, esters, amides, epoxides, acetals, and nitriles.

Hutchins and Kandasamy recently reported that sodium cyanoborohydride in acidic media can be used for the clean conversion of acyclic conjugated aldehydes and ketones to the corresponding allylic alcohols.⁶ The reduction of α -ionone is an interesting example (eq. 2). However, sodium cyanoborohydride reduction of cyclic enones gives mixtures of allylic and saturated alcohols.⁶



The stereoselective reduction of cyclic ketones is one of the most important uses of our Selectride® reagents (lithium or potassium tri-*sec*.-butylborohydride).⁷ These highly hindered trialkylborohydrides were also used by Corey and coworkers for the stereoselective synthesis of a prostaglandin allylic alcohol (eq. 3).⁸ Likewise, β -substituted cyclohexenones are cleanly converted to the corresponding allylic alcohols (eq. 4).⁹ However, when Ganem tried a similar reduction of a 2-cyclohexenone, which was unsubstituted at the β -vinylic position, exclusive 1,4-reduction was observed.⁹ This reduction with K-Selectride® produces the saturated ketone in near quantitative yield (eq. 5).

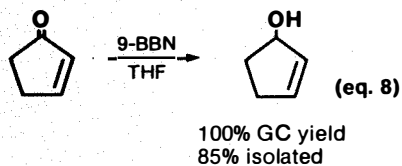
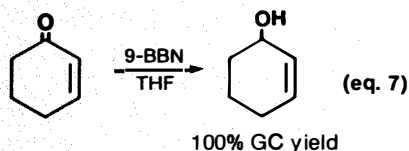
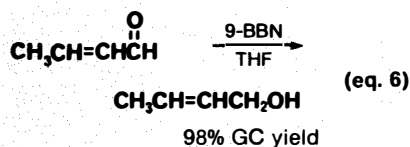
Most of the above problems and difficulties associated with the selective reduction of the carbonyl group in α,β -unsaturated aldehydes and ketones have



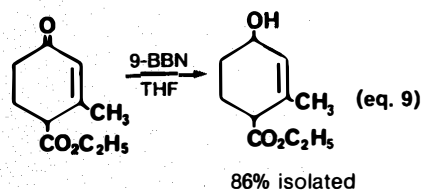
now been overcome. Krishnamurthy and Brown recently reported that 9-borabicyclo[3.3.1]nonane (9-BBN) in



tetrahydrofuran (THF) reduces 2-enones cleanly to the corresponding allylic alcohols.¹⁰ Equations 6-8 provide some simple examples and illustrate the excellent selectivity that is possible with 9-BBN.



A detailed investigation¹¹ of the reactivity of various representative functional groups toward 9-BBN/THF indicates that this reduction of 2-enones can tolerate the presence of a large variety of sensitive functional groups. Specific examples include carboxylic acid, ester, amide, epoxide, oxime, nitrile, nitro, azo, azoxy, halogen, sulfide, disulfide, sulfoxide, sulfone, and tosylate groups.¹¹ The following selective reduction of a 2-enone in the presence of an ester group provides an interesting example (eq. 9).¹⁰



Although DIBAL-H, NaBH₃CN, or the Selectrides[®] may prove satisfactory for specific cases, in general, 9-BBN/THF appears to be the reducing agent of choice for the conversion of conjugated aldehydes and ketones to allylic alcohols.¹²

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Phase-Transfer Catalysis in Organic Synthesis. See page 35.
Recent Advances in Synthetic Pyrethroids. See page 49.

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Table of Contents:

Lab Notes	34
Applications of Phase-Transfer Catalysis in Organic Synthesis	35
MEM Chloride	46
Custom Glassware	46
BOC-ON	47
New Listings	48
Recent Advances in Synthetic Pyrethroids	49
Potpourri	52

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This being our bicentennial year, it seemed fitting to ask our chemist-collector to feature an American painting on our Acta cover. He chose this sensitive portrait (oil on canvas, 18 $\frac{1}{2}$ x 14 $\frac{1}{2}$ inches) by one of America's most prolific painters, Thomas Sully (1783-1872). The painting is monogrammed and dated 1828, and our chemist-collector believes that it may be a self-portrait which the artist painted for his sister.

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Applications of Phase-Transfer Catalysis in Organic Synthesis



Organic chemists are frequently faced with synthetic routes which involve the reaction between water-soluble reagents and water-insoluble organic compounds. Traditionally, this problem has been resolved by the use of an appropriate mutual solvent, such as dimethylformamide, 1-methyl-2-pyrrolidone, dimethyl sulfoxide, or hexamethylphosphoric triamide.¹ There are disadvantages, however, in the use of these dipolar aprotic solvents, especially in their application on an industrial scale, as they are both expensive and difficult to recover. Their use at elevated temperatures may also give rise to complicated side reactions. Alternatively, a water-miscible cosolvent, such as ethanol or dioxane, may be added to the organic phase in order to promote the solubility of the organic compound, but such procedures are not universally applicable. The rate of the heterogeneous two-phase reaction may also be increased by rapid agita-

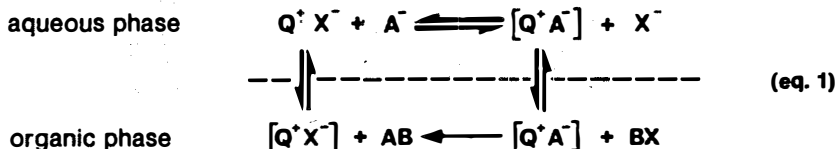
tion, which increases interfacial contact between the two phases. Such a procedure is not always successful, however, as illustrated by the failure of 1-bromooctane to react with aqueous sodium cyanide under vigorous stirring at 100° for two weeks, the only reaction being the hydrolysis of the cyanide to give sodium formate. The rate of the interfacial reaction may be enhanced by the use of surfactants which disperse the organic compound in the aqueous phase through micellar formation. Such reactions are characterized by the linear dependence of the reaction rate upon the rate of stirring and discontinuity behavior in the dependence of the reaction rate upon the surfactant concentration, due to changes in the micelle size.²

During the past few years, due largely to the pioneering work of Brändström, Starks and Makosza,* increasing interest has been centered upon phase-transfer catalysis,

also sometimes referred to as "ion-pair partition" or "extractive methylation," as a solution to the problem posed by heterogeneous systems.⁴ An increase in the reaction rate for such heterogeneous systems is brought about by the addition of catalytic amounts of an agent which transfers the water-soluble reactant across the interface into the organic phase where a homogeneous reaction can take place rapidly. Thus, in the reaction involving the water-

soluble nucleophile, A⁻ (eq. 1), the addition of the phase-transfer catalyst, Q⁺X⁻, causes the transfer of the nucleophile as an ion-pair [Q⁺A⁻] into the organic phase where it reacts with the organic reagent, BX. Migration of the cationic catalyst back to the aqueous phase completes the cycle, which continues until equilibrium has been reached or until all of either the nucleophile, A⁻, or the organic compound, BX, has been consumed.

The success of the catalytic effect depends to a large extent upon the high partition coefficient of the ion-pair [Q⁺A⁻] between the aqueous and organic phases, compared with the corresponding value for the ion-pair [Q⁺X⁻]. Where the leaving group, e.g., Y⁻, from the organic compound is not the same as the anion associated with the phase-transfer catalyst, a third partition coefficient for the ion-pair [Q⁺Y⁻] is significant.⁵ As the reaction rate is



directly dependent upon the partition coefficient for the ion-pairs between the two phases, it is solvent-dependent. The most commonly used organic solvents are methylene chloride, chloroform and *o*-dichlorobenzene and it has been generally observed that the reaction rate enhancement is greater with the more polar solvents. Quaternary ammonium and phosphonium salts are excellent phase-transfer catalysts and it has been found that salts having the larger and more symmetrical cations, e.g., tetrabutylammonium, methyltrioctylammonium, and tetra-

* The technique is by no means new, however, and examples of the procedure were reported as long ago as 1926.³

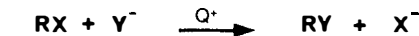
butylphosphonium salts, are the most effective.^{6,7} Early suggestions that these reagents behave as surfactants have been discounted,^{6,7} although the more linear ammonium salts, *e.g.*, cetyltrimethylammonium salts, are known to be micellar catalysts. Crown ethers also serve as efficient phase-transfer catalysts and their activity has been reviewed in earlier issues of *Aldrichimica Acta*.⁸

The versatility, simplicity and speed of phase-transfer-catalyzed reactions make them particularly attractive synthetic procedures. Relatively few kinetic data are available but it appears that reactions induced by phase-transfer catalysis proceed to completion more rapidly than do the corresponding "classical" reactions conducted in a homogeneous medium, while the addition of a phase-transfer catalyst to a heterogeneous system has been observed to produce reaction rate increases of the order of 10⁴ to 10⁹. In addition, many reactions which hitherto required anhydrous solvents may now be carried out in the presence of water.

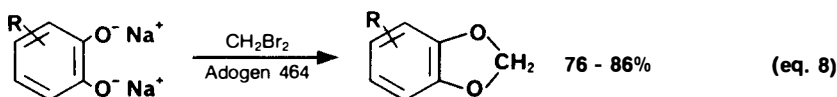
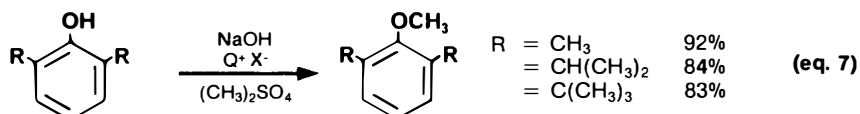
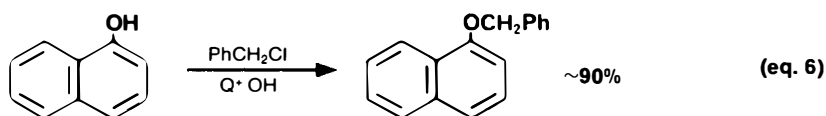
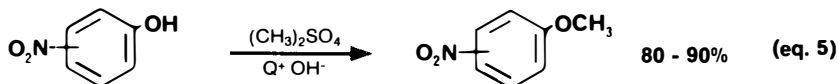
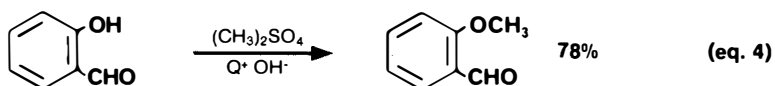
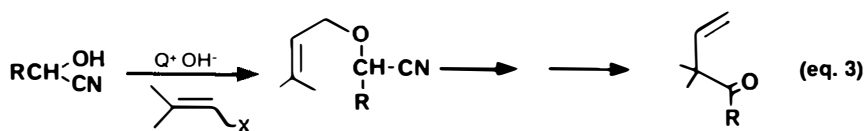
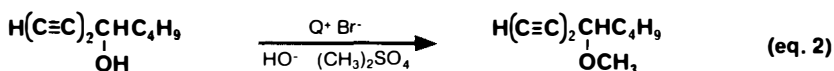
Experimentally, the reactions are very easy to perform. The reagents, appropriately dissolved in water or an organic solvent, are shaken or stirred in the presence of a catalytic amount of, for example, tetrabutylammonium hydrogen sulfate, at room temperature or, if necessary, under reflux conditions. The course of the reactions, which may be complete within a matter of several minutes, may be followed easily by TLC or GLC analysis of the organic layer and the product is readily isolated by separation of the organic phase and evaporation. In many instances the yields are in excess of 90% and, if considered expedient for economic reasons, the catalyst may be recovered and recycled.

NUCLEOPHILIC SUBSTITUTION REACTIONS:

Using phase-transfer catalysis, S_N2 reactions become perfectly simple and straightforward. Examples have been cited in the literature for reactions of alkyl chlorides and bromides with the



nucleophiles Y = F,⁹ Cl,^{6a} Br,^{6a,10} CN,^{6,11-14} NCO,^{6a} HO,^{6a} alkyl-O,^{15,16} aryl-O,^{3,17,18} aryl-S and alkyl-S,^{7,19,20} RCO₂,^{6a,21-26} and NO₂.^{6a} In the majority of cases the reaction times are short when 1-10% catalyst is used and the yields are frequently almost quantitative. Nucleophilic substitution of alkyl iodides, however, requires the use of greater-than-catalytic amounts of the quaternary ammonium salts, due to the high solubility of the quaternary ammonium iodides in organic solvents. Similarly,



quaternary ammonium tosylates and mesylates are extremely soluble in organic solvents and, although examples of the nucleophilic displacement of tosyloxy and mesyloxy groups have been reported,²⁷⁻²⁹ almost equimolar quantities of the catalyst and substrates must be used. Kinetic studies³⁰ have suggested that the nucleophilicity of the non-solvated halide ions, produced upon dissolution of the quaternary ammonium salts in organic solvents, follows the order F > Cl > Br > I. However, the conversion of chloroalkanes into the corresponding fluoro compounds requires high temperatures and prolonged reaction times and may be accompanied by elimination reactions.⁹ The method of choice for the preparation of fluoroalkanes appears to be by the displacement of an alkyl or aryl sulfonyloxy group.²⁷⁻²⁹ It is obvious that reactions which normally require anhydrous conditions or the use of strong bases, such as alkoxides, amides or carbanions, can now be accomplished in the presence of water. In addition to the Williamson-type synthesis of alkyl ethers from alkyl halides, the phase-transfer-catalyzed methylation of alcohols with dimethyl sulfate has been reported.³¹ Among the examples cited is the O-

methylation of acetylenic alcohols, which occurs without alkylation of the terminal acetylenic group (eq. 2).

The alkylation of cyanohydrins under phase-transfer-catalyzed conditions has been utilized in the synthesis of unsaturated ketones (eq. 3).³²

The phase-transfer-catalyzed O-alkylation of phenols generally proceeds in yields in excess of 80% and the procedure is particularly attractive for cases where the classical methods give trouble as, for example, in the alkylation of resonance-stabilized phenoxide anions (eq. 4, 5, 6). Moreover, it has been noted that the reaction is virtually insensitive to steric effects (eq. 7).¹⁸

Although dichloromethane is frequently used as the organic solvent, it has been found that it will react with phenols in the presence of benzyltriethylammonium salts and solid potassium hydroxide to form di(aryloxy)methanes.³³ Similarly, methylenedioxy derivatives, which are usually difficult to prepare by conventional methods, have been obtained in good yield *via* the reaction of the disodium salts of catechols with dibromomethane in the presence of Adogen 464 [CH₃(C₈-C₁₀)₃N⁺Cl⁻] (eq. 8).³⁴

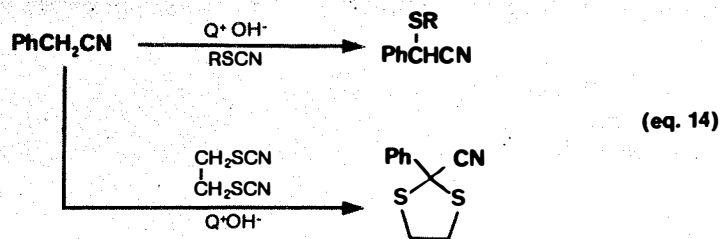
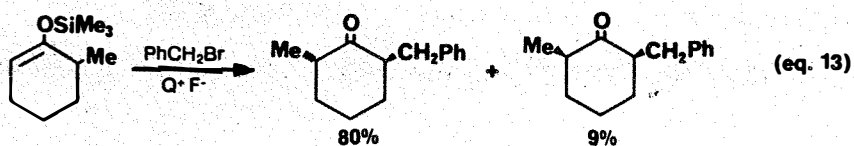
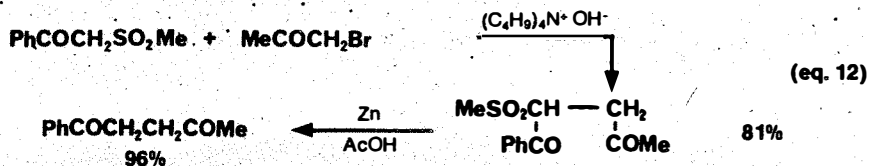
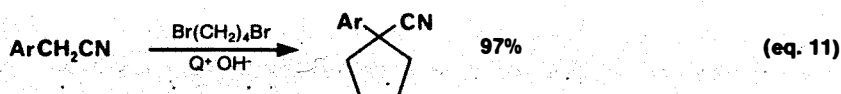
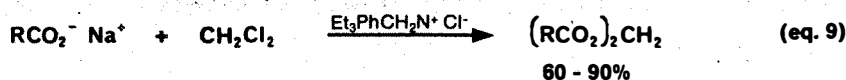
Thiols also react with dichloromethane to give the corresponding dithioethers.¹⁹ The reactions of the dihalogenomethanes are, however, generally slower than the corresponding reactions involving monohalogenoalkanes.

Esterification of carboxylic acids proceeds rapidly under phase-transfer conditions and may be applied to the synthesis of sterically hindered esters.³⁵ In the absence of other alkylating agents, carboxylic acids react slowly with dichloromethane to give methylene diesters (eq. 9).²⁶

Sulfones have been synthesized by the alkylation of sodium arylsulfonates in the presence of tetrabutylammonium bromide³⁶ and mixed dialkyl phosphates by the reaction of bis(tetraalkylammonium) monoalkyl phosphates with alkyl halides.³⁷ Phosphorylation of alcohols has also been carried out by means of the phase-transfer-catalyzed reaction with dialkyl phosphites in the presence of either tetrabutylammonium bromide or benzyltriethylammonium chloride.³⁸ The phase-transfer-catalyzed two-phase system has also been applied to the corresponding Atherton-Todd phosphorylation of amines,³⁹ and *tert*-butyl phosphorochloridate and the analogous bromine derivative have been synthesized by the reaction of the phosphite with the appropriate tetrahalogenomethane under basic conditions in the presence of benzyltriethylammonium chloride.⁴⁰ Attempts to prepare other dialkyl phosphorobromidates failed. The heterogeneous reaction of bromoalkanes with silver nitrate to yield alkyl nitrates is accelerated by the presence of tetraethylammonium salts.⁴¹

An important application of phase-transfer-catalyzed two-phase reactions is the formation of carbanions in the presence of water. The reaction of compounds containing acidic C-H groups with quaternary ammonium hydroxides, generated from the ammonium salts with sodium hydroxide, yields the corresponding quaternary ammonium salts of the carbanion, which, in certain instances, have been isolated.^{42,43} The salts are soluble in dichloromethane and react readily with alkylating agents.^{6,42-75} Reaction with an excess of the alkylating agent frequently yields the dialkylated product,^{43,49-51,55,60} while dihalogenoalkanes react with the quaternary ammonium salts to give cycloalkanes (eq. 10, 11).^{51,56,62,63,67,76}

The phase-transfer-catalyzed reaction of β -keto sulfones with bromoacetone provides a convenient route to γ -dicarbonyl compounds (eq. 12).⁷⁷



In virtually all cases where there are alternative sites for alkylation of the carbanion as, for example, in the reactions of β -dicarbonyl compounds, the C-alkylated products predominate. Only in reactions in which there is a possibility of steric hindrance between the alkylating agent and the carbanionic system is there any evidence of O-alkylation. In such reactions the rate of alkylation is extremely slow and yields of the O-alkylated product are small.^{55,63,68} The C-arylation of the quaternary ammonium salts of the carbanions by activated halogenobenzenes has also been reported to proceed in good yields.⁷⁸ In contrast, acylation of β -dicarbonyl compounds under phase-transfer conditions has been found to produce the O-acylated derivatives in yields in excess of 75%.⁷⁵

An interesting variation of the alkylation of quaternary ammonium enolates, generated by proton extraction from the ketone, is the displacement of a trimethylsilyl group from silyl enol ethers by quaternary ammonium fluorides in the presence of an alkylating agent (eq. 13).⁷² Such reactions have been shown to be regiospecific, monoalkylation occurring at the least substituted α -C atom. (The cleavage of silyl enol ethers by quaternary ammonium

fluorides⁷⁹ appears to be superior to procedures using potassium fluoride.)

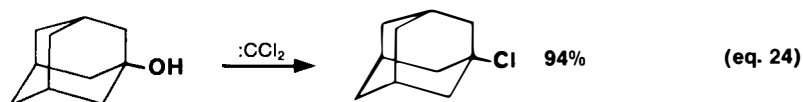
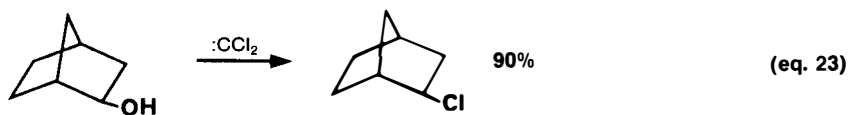
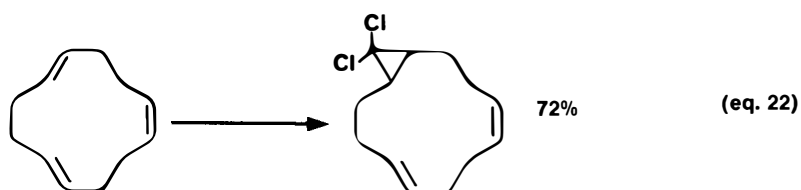
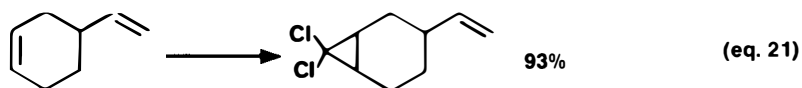
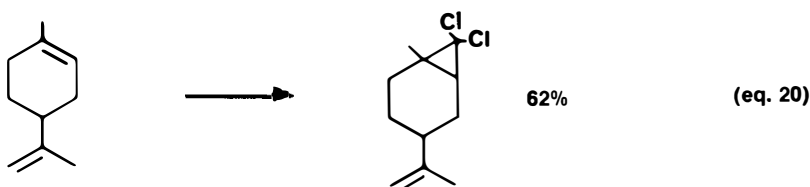
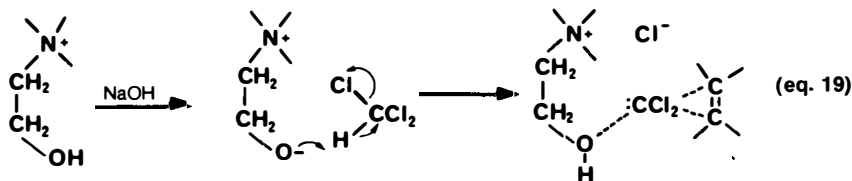
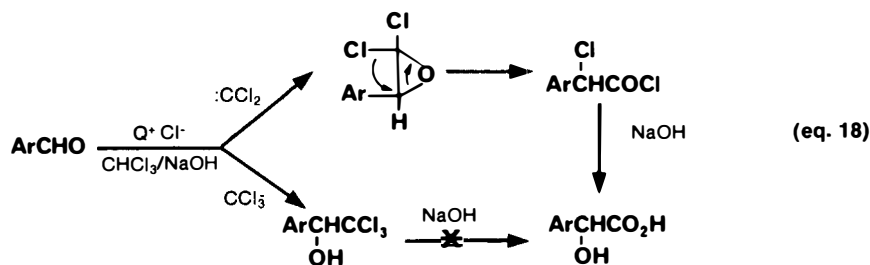
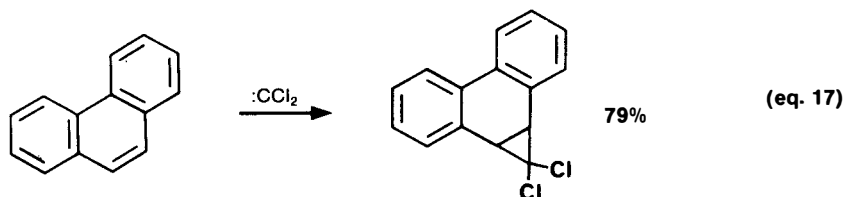
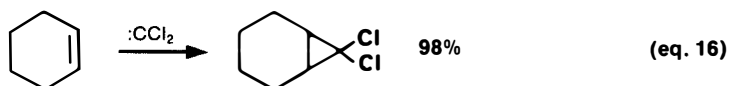
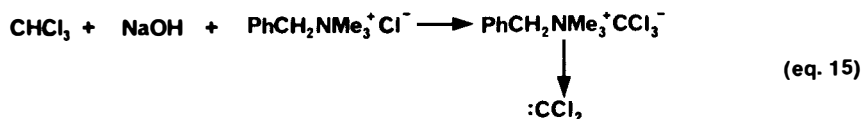
The asymmetric alkylation of ketones using chiral quaternary ammonium salts has met with only limited success.⁸⁰

Carbanions, generated under phase-transfer conditions, react with organic thiocyanates to give thioethers.⁸¹ Thioketals have been synthesized by a similar route (eq. 14).⁸¹

Reissert compounds, derived from isoquinoline, have been alkylated at the 1-position under the influence of quaternary ammonium bases.⁸²

FORMATION OF CARBENES:

Perhaps the most impressive use so far made of phase-transfer catalysts is in the generation of carbenes. The dihalogeno-carbenes can be generated readily under very mild conditions and can be utilized as standard reagents.^{6,9,81,83-132} Thus, a very wide range of dichlorocyclopropane derivatives have been synthesized from dichlorocarbenes, generated from the reaction of chloroform and aqueous sodium hydroxide in the presence of a quaternary ammonium salt (usually benzyltriethylammonium chloride) (eq. 15, 16, 17).



The corresponding production of dibromocarbene from bromoform is generally poor and good yields of the dibromocyclopropanes are obtained only by the use of an excess of bromoform and prolonged reaction time.^{85, 101, 102, 107, 123, 124, 126-128} Bromofluorocarbene,¹²⁹ chlorofluorocarbene,^{129, 131} and fluoroiodocarbene¹³⁰ have been generated by similar procedures and the method appears to be particularly effective for the production of diiodocarbene.¹³² It has been shown, however, that monohalogenocarbenes cannot be generated in the two-phase system.⁴ The stronger electron-withdrawing effect of a cyano group, however, allows the formation of monocyanocarbene under the mildly basic conditions.^{133, 134}

As indicated above, the dihalogenocarbenes are generated in the organic phase *via* the trihalogenomethyl anion. It has been assumed that the reaction of carbenes with alkenes produces the cyclopropane derivatives, whereas reactions involving the trihalogenomethyl anion generally yield open-chain products. The mechanism of the phase-transfer-catalyzed addition reactions, however, appears to depend upon the electronic character of the unsaturated system.^{96, 135, 136} The conversion of aryl aldehydes into mandelic acids has been shown to proceed *via* the carbene and not through nucleophilic attack by the anion upon the carbonyl group (eq. 18).¹²⁵

Dichlorocarbene, when generated in the presence of tetraalkylammonium salts, generally reacts at all available unsaturated sites of a polyalkene.⁸⁹ However, when β -hydroxyethylammonium salts are used to generate the carbene, selective addition of the carbene to only one site occurs.¹¹⁹ It has been suggested that a complex (eq. 19) is formed between the hydroxyalkylammonium ion and the carbene and, although it has been shown that β -hydroxyethylammonium salts greatly enhance the rate of *S*_N2 reactions,^{137, 138} the formation of the complex presumably reduces the reactivity of the carbene. The addition reactions appear to occur invariably at the more reactive highly substituted unsaturated sites (eq. 20, 21), but it is not immediately obvious why the *trans* alkenic bond is more readily attacked than the *cis* bond in the cyclododeca-1,5,9-triene system (eq. 22). The use of a chiral β -hydroxyethylammonium salt appears to result in some asymmetric induction in the reaction.

When dichlorocarbenes are generated in the presence of an alcohol, the normal deoxygenation reaction occurs with the formation of the corresponding chloroalkane *via* the carbonium ion intermediate (eq. 23, 24).^{87, 96}

1,2-Diols react with dichlorocarbene, generated under phase-transfer conditions, to yield ketones and alkenes, possibly by the mechanisms shown in eq. 25.¹¹⁰

Amides are dehydrated efficiently to give nitriles in a two-phase system (eq. 26, 27). Yields vary from *ca.* 10 to 90%.^{104,109}

The use of a phase-transfer catalyst represents a major improvement upon the classical Hofmann carbylamine reaction for the synthesis of isonitriles (eq. 28).^{90,91}

Under similar conditions secondary amines yield formamido derivatives (eq. 29)¹¹⁵ and tertiary amines react with C-N cleavage (eq. 30).¹⁰⁵

The aziridines, produced from the reaction of imines with dichlorocarbene, rearrange under the basic phase-transfer conditions to yield α -chloroacetamides (eq. 31).¹¹⁸

The ring expansion of indoles into 3-halogenoquinolines proceeds cleanly and in moderate yields under phase-transfer-catalyzed conditions.¹³⁹

Phase-transfer catalysts have also been used to prepare vinylidene carbenes from 3-chloroprop-1-ynes and from 1-chloro-prop-1-ynes.¹⁴⁰⁻¹⁴³ 1-Halogenoallenes react in a similar manner.¹⁴⁰ In the presence of alkenes the expected reaction to give vinylidene cyclopropanes occurs (eq. 32),¹⁴⁰⁻¹⁴² but in an interesting rearrangement reaction which involves N-N cleavage, dimethylvinylidene carbene reacts with azobenzene to give a benzimidazole derivative (eq. 33).¹⁴³

N- β -Hydroxyethyl-N-nitrosoacetamides yield vinylidene carbenes under basic conditions in the presence of quaternary ammonium salts (eq. 34).¹⁴⁴⁻¹⁴⁶

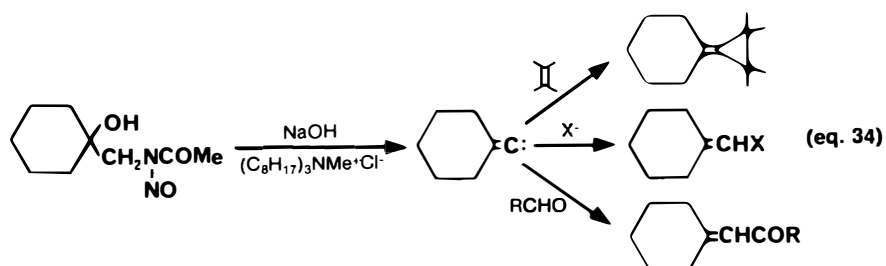
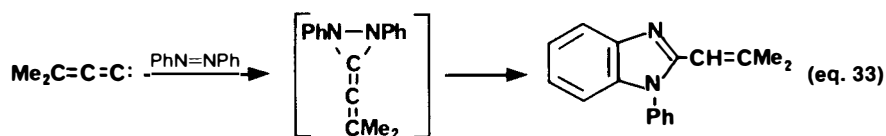
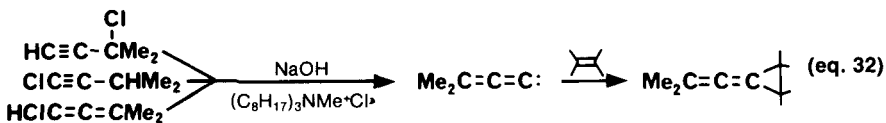
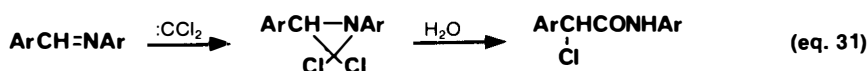
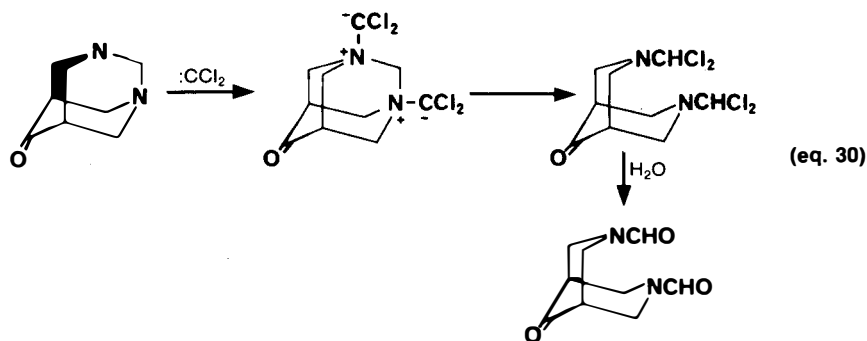
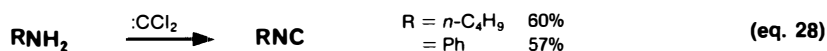
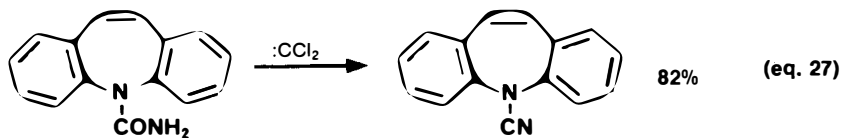
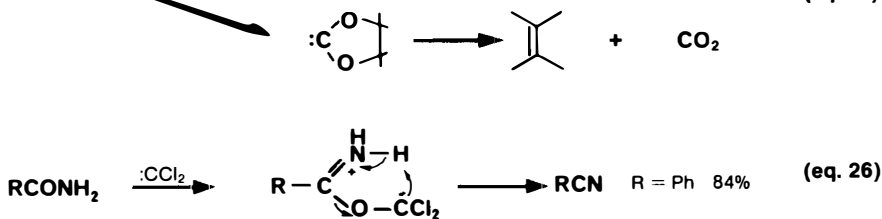
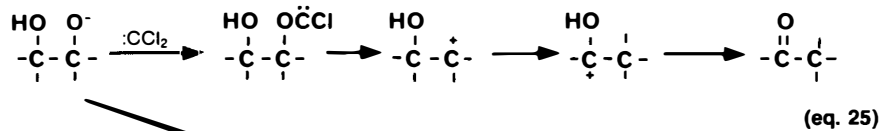
N-ALKYLATION REACTIONS:

The phase-transfer-catalyzed alkylation of acidic NH-compounds proceeds cleanly and, in the majority of cases, in excellent yield. The alkylation of acetanilide and of phthalimide generally requires reaction temperatures of between 60 and 100°, ^{147,148} while pyrroles and indoles react exothermically with primary and secondary alkyl halides.¹⁴⁹⁻¹⁵¹ Alkylation with tertiary alkyl halides fails,¹⁵⁰ presumably due to a preferential elimination reaction.

The alkylation of 1,4-dihydropyridines under phase-transfer conditions has also been reported.¹⁵²

OXIDATION REACTIONS:

In the presence of quaternary ammonium and phosphonium salts, permanganate ions are transferred efficiently into benzene ("purple benzene") and they



oxidize terminal alkenes in the organic phase to give carboxylic acids having one carbon atom less than the alkene.^{64,153,154} Non-terminal alkenes are oxidized to 1,2-diols under strongly alkaline conditions in dichloromethane.¹⁵⁵ Diols, which are highly soluble in water, are oxidized with C-C cleavage to dicarboxylic acids in the aqueous phase of the two-phase system. Benzonitrile, benzyl alcohol and stilbene are oxidized by tetrabutylammonium permanganate in benzene to give benzoic acid¹⁵⁵ in yields in excess of 90%.

Quaternary ammonium perchlorates have been prepared and used as oxidizing agents in chloroform.¹⁵⁶

REDUCTION REACTIONS:

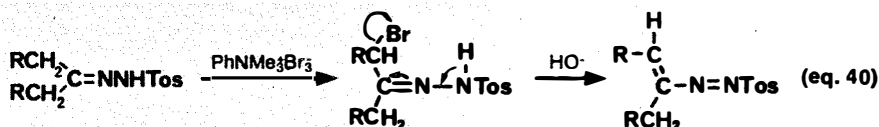
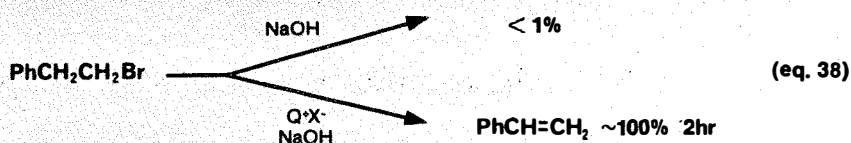
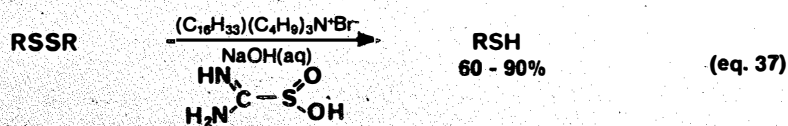
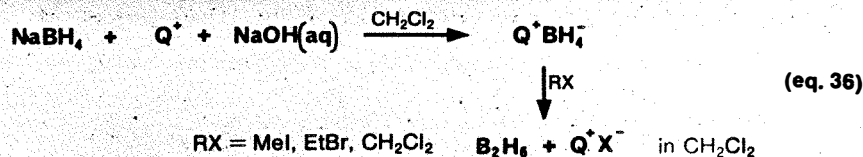
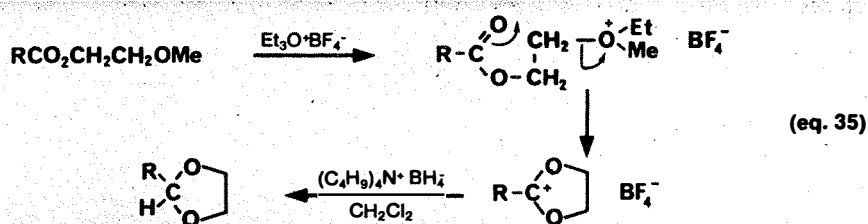
The rate of reduction of ketones to the corresponding alcohols with sodium borohydride is greatly enhanced in a two-phase system by the addition of quaternary ammonium salts.^{64,157,158} Tetraalkylammonium borohydrides can be extracted almost quantitatively into dichloromethane from an aqueous sodium hydroxide solution of sodium borohydride upon the addition of the tetraalkylammonium salt. Evaporation of the organic phase yields the solid ammonium borohydride,^{5,159,160} which, in spite of its low reactivity, has been used extensively for reductions in organic solvents.

The reagent has been used, for example, in the synthesis of 1,3-dioxolanes from 2-methoxyethyl carboxylates (eq. 35).¹⁶¹

Attempts to induce asymmetric reduction of ketones by the use of chiral quaternary ammonium salts have met with varied success.^{157,158} The degree of asymmetric induction depends upon the structure of the ketone and is enhanced by a high concentration of catalyst.

In general it has been assumed that diborane can be generated and used only in ethers. It is possible, however, to produce diborane in dichloromethane through the reaction of tetrabutylammonium borohydride with alkyl halides (eq. 36). The diborane so produced is as versatile and, in many respects, more reactive than that generated by classical procedures. Thus, in addition to the normal reduction of nitriles, aldehydes and ketones to amines, primary and secondary alcohols respectively, it has been found that esters are also reduced to give alcohols. Hydroboration of alkenes in dichloromethane and the subsequent almost quantitative conversion into alkyl alcohols by the addition of sodium hydroxide and hydrogen peroxide is extremely simple.

Tetrabutylammonium cyanoboro-



hydride has been prepared and used for the reduction of alkyl iodides and bromides at room temperature.¹⁶²

Dialkyl disulfides are reduced to thiols in high yield by formamidinesulfonic acid in the presence of cetyltributylammonium bromide and aqueous sodium hydroxide (eq. 37).¹⁶³

ELIMINATION REACTIONS:

The rate of elimination of halogen acids from halogenoalkanes is dramatically increased by the addition of a phase-transfer reagent, particularly when the products are conjugated (eq. 38).⁴ A phase-transfer catalyst has also been used in the preparation of dichloroacetylene from tetrachloroethylene.¹⁶⁴

The reaction of 1,2-dibromoalkanes with sodium iodide in the presence of sodium thiosulfate and methyltrioctylammonium chloride proceeds easily to give the alkenes in 85-95% yield (eq. 39).¹⁶⁵

Trimethyl(phenyl)ammonium perbromide brominates tosylhydrazones which, under basic conditions, eliminate HBr with

the formation of tosylazo derivatives (eq. 40).¹⁶⁶

The elimination of triphenylsilane from 2-triphenylsilylalk-1-enes to give allenes has been found to be catalyzed by quaternary ammonium fluorides.¹⁶⁷

ADDITION REACTIONS:

Tetraethylammonium bromide catalyzes the addition of ethylene oxide to aldehydes and ketones to form 1,3-dioxolanes.¹⁶⁸ It has been postulated that tetraethylammonium β -bromoethoxide is formed, which acts as a nucleophile in the initial step of the reactions. The same intermediate is involved in the phase-transfer-catalyzed reaction of ethylene oxide with alkyl halides in the formation of β -halogenoethyl ethers.¹⁶⁹ Highly reactive sulfur ylides have been formed in the presence of water and have been employed in the synthesis of oxiranes through their reaction with aldehydes and ketones (eq. 41).^{170,171} Both trimethylsulfonium iodide and trimethylloxosulfonium iodide are converted into the sulfur ylides in dichloromethane by aqueous sodium hydroxide in

the presence of tetrabutylammonium salts. A six-membered ring by-product is produced in the reaction of benzaldehyde with trimethyloxosulfonium iodide (eq. 42) and a similar 2:1 cyclized adduct results from the base-catalyzed reaction of benzaldehyde with dimethyl sulfone (eq. 43).¹⁷² In none of the reactions is there any evidence of a Cannizzaro reaction in the case of benzaldehyde, or of aldol condensation products from other aldehydes.

α,β -Unsaturated ketones yield cyclopropyl ketones in high yield in their reaction with the ylide derived from trimethyloxosulfonium iodide under the phase-transfer conditions (eq. 44).¹⁷⁰

Utilization of chiral β -hydroxyethyl quaternary ammonium salts results in the enantioselective ring closure in the formation of the oxiranes from aldehydes and the ylide derived from trimethylsulfonium iodide.¹⁷¹

Oxiranes have also been prepared via the phase-transfer-catalyzed reaction of chloromethylsulfones and aldehydes or ketones.¹⁷³ It was assumed that a carbanionic intermediate is involved in the reaction, but it is possible that a carbene is generated. The sulfonyloxiranes, which hitherto had been assumed to be of limited stability, may be isolated under the mild phase-transfer conditions (eq. 45).

The Michael addition reaction to α,β -unsaturated ketones and esters is catalyzed by tetrabutylammonium cyanide (eq. 46).¹² In the carbohydrate field, it has been observed that the use of phase-transfer catalysis favors the formation of the thermodynamically less stable isomer in the addition of carbanions to nitroalkenes (eq. 47).¹⁷⁴

The catalyzed addition of phenylacetonitrile to acetylenes under basic conditions has also been reported (eq. 48).^{175,176}

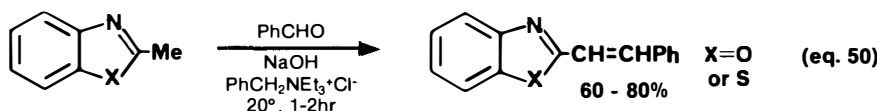
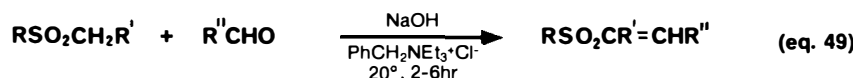
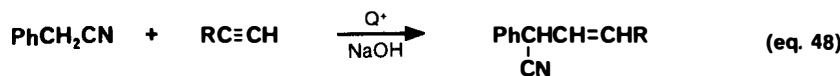
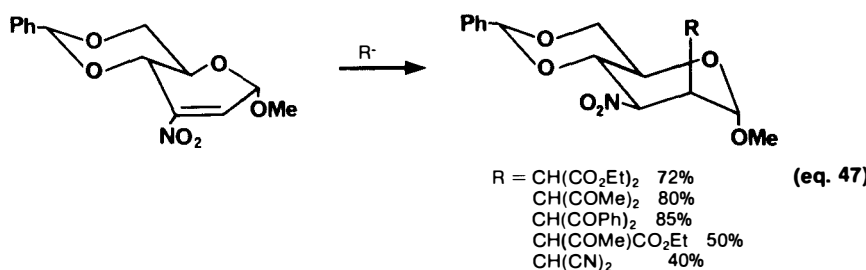
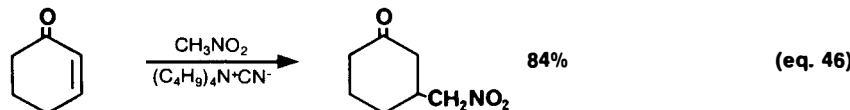
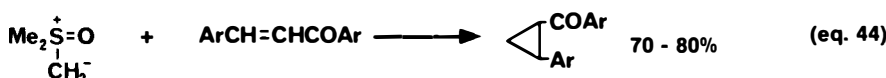
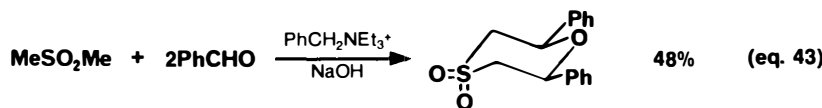
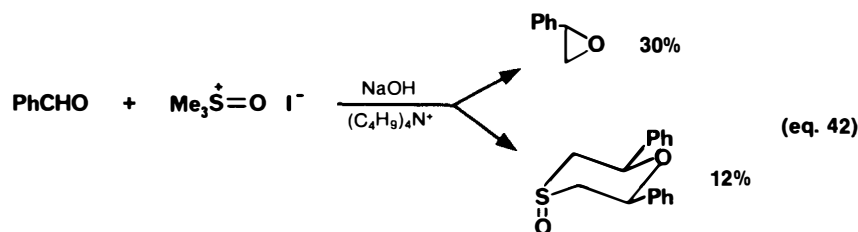
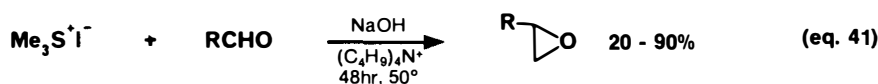
CONDENSATION REACTIONS:

The benzoin condensation of benzaldehyde may be effected by tetrabutylammonium cyanide under considerably milder conditions than those used in the classical procedures.^{12,177} The reaction may be carried out in water in the absence of an organic phase.

The base-catalyzed condensation of aldehydes with sulfones to give α,β -unsaturated sulfones (eq. 49)¹⁷⁸ and the synthesis of 2-styrylbenzazoles (eq. 50)¹⁷⁹ have been shown to be catalyzed by benzyltriethylammonium chloride.

WITTIG AND WITTIG-HORNER REACTIONS:

Application of phase-transfer catalysis permits the generation of phosphoranes and



phosphonate anions by aqueous sodium hydroxide without recourse to strong bases or anhydrous solvents. Quaternary ammonium salts have been used^{52,180-182} but, as phosphonates and, in particular, phosphonium salts are excellent phase-transfer catalysts, it is possible to conduct both the

Wittig and the Wittig-Horner reactions in two-phase systems without the addition of a catalyst.¹⁸³⁻¹⁸⁷ Although the yields obtained with and without a quaternary ammonium salt are comparable, the rates of the reactions at room temperature are invariably slower when a catalyst is not used.

In the preparation of α,β -unsaturated sulfides ($R = SPh$, $R' = Ph$, $R'' = H$) it has been noted that the $E : Z$ isomer ratio depends upon the catalyst used, being higher with the more efficient catalysts (eq. 51).^{52,181} In the absence of an added catalyst the tetraethyl bis-phosphonate reacts with benzaldehyde to give exclusively the E -isomer (eq. 52).¹⁸⁷

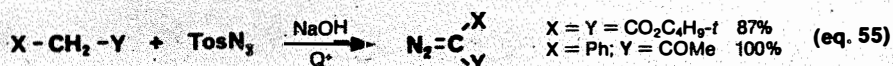
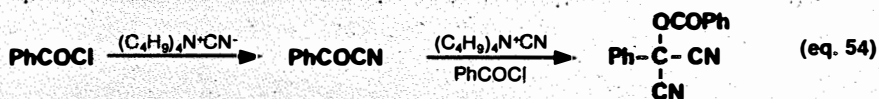
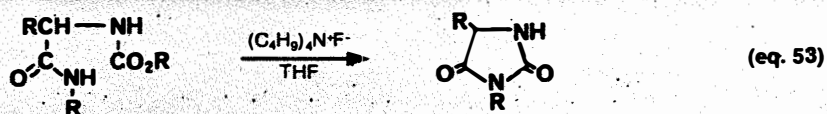
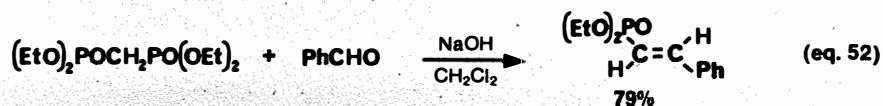
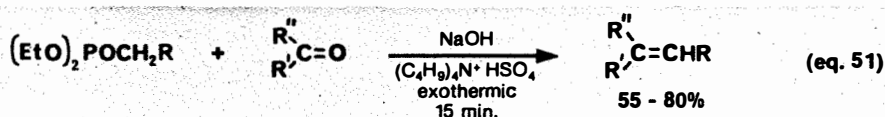
MISCELLANEOUS REACTIONS:

The hydrolysis of carboxylic esters by aqueous sodium hydroxide is aided by the addition of quaternary ammonium salts.^{64,188,189} The rate enhancement is most significant in the hydrolysis of low molecular weight esters. Thus, for example, although dimethyl adipate is inert to 50% aqueous sodium hydroxide at room temperature over a period of several hours, the addition of a catalytic amount of tri(hexadecyl)methylammonium chloride produces an exothermic reaction and hydrolysis is complete in 30 min.⁶⁴ The catalytic effect is less powerful in the hydrolysis of long-chain carboxylic esters, due possibly to the formation of strong ion-pairs between the quaternary ammonium ion and the carboxylate anion, which are highly soluble in the organic phase. Hydrolysis tends to stop after 35% reaction, but further addition of catalyst does not produce any appreciable continuation of the reaction.⁶⁴ It is apparent that quaternary ammonium hydroxides are stronger bases than they are nucleophiles in organic solvents, as they rapidly generate the carbanion from ethyl acetoacetate without any significant hydrolysis of the ester group. Use is made of the reactivity of the non-solvated fluoride ion in the catalytic effect of tetrabutylammonium fluoride in the synthesis of hydantoins (eq. 53).¹⁹⁰

Tetrabutylammonium azide has been employed in the Curtius rearrangement reaction for the preparation of acyl azides in toluene¹⁹¹ and, in a similar reaction, the moisture-sensitive aroyl cyanides have been synthesized in *ca.* 60% yield from aroyl chlorides and tetrabutylammonium cyanide in dichloromethane.¹⁹² A further reaction can occur between the aroyl cyanide and the reactive cyanide ion to yield a higher molecular weight by-product (eq. 54).

The synthesis of α -diazoalkanes is improved by the addition of quaternary ammonium salts (eq. 55).¹⁹³

Quaternary ammonium salts have also been utilized in D/H exchange reactions⁶⁴ and, in place of ion-exchange resins, in the conversion of iodides into chlorides.¹⁹⁴



EVALUATION OF CATALYSTS:

In early studies, Makosza examined the catalytic activity of different quaternary ammonium salts in the ethylation of benzyl cyanide.⁴ It is evident that the benzyltriethylammonium ion is more effective than the more symmetrical tetraethylammonium ion.^{67,195} Similarly, the efficiency of alkyltriethylammonium ions, $[\text{Me}(\text{CH}_2)_n\text{NEt}_3]^+$ in the catalytic elimination of hydrogen bromide from 2-phenylethyl bromide increases to a maximum when $n = 5$, but falls off only slightly through to $n = 11$,⁴ while the maximum activity with alkyltrimethylammonium ions was found with the butyl derivative.¹⁹⁶

As indicated in the Introduction, the rate of reaction depends to a great extent upon the ability of the quaternary ammonium ion to transfer the reactive anionic species into the organic phase as an ion-pair and is therefore dependent, not only upon the structure of the ammonium ion, but also upon the anion. Consequently, no one catalyst can be said to be universally the most effective. Thus, for example, the activities of different catalysts upon the generation of carbenes,¹²² SN_2 reactions,⁷ and the transfer of the permanganate anion into organic solvents¹⁵⁵ have been examined. It is generally accepted that benzyltriethylammonium chloride is the catalyst of choice for carbene reactions, whereas methyltriocetylammonium chloride and tetrabutylammonium hydrogen sulfate are the most effective for the other two reactions, respectively. These three salts are the most commonly employed phase-transfer catalysts and they are commercially available. Other quaternary ammonium

salts are frequently used, however, as are phosphonium salts. Although the selected kinetic data presented in the Table show phosphonium salts to be as efficient as many ammonium salts in SN_2 reactions, they are less frequently used, due to their susceptibility to decomposition, particularly under basic conditions, and to their proneness to side reactions.

Second-Order Rate Constants for the Reaction of Thiophenoxide with 1-Bromooctane in Benzene:Water⁷

Catalyst (0.00137 mol)	$k \times 10^3 \text{ M}^{-1}\text{sec}^{-1}$
$\text{Me}_4\text{N}^+\text{Br}^-$	<0.0016
$\text{PhCH}_2\text{NEt}_3^+\text{Br}^-$	<0.0016
$\text{C}_{16}\text{H}_{33}\text{NMe}_3^+\text{Br}^-$	0.15
$\text{C}_{16}\text{H}_{33}\text{NEt}_3^+\text{Br}^-$	0.48
$(\text{C}_4\text{H}_9)_4\text{N}^+\text{Br}^-$	5.2
$(\text{C}_8\text{H}_{17})_3\text{NMe}^+\text{Cl}^-$	31.0
$\text{Ph}_3\text{PMe}^+\text{Br}^-$	1.7
$\text{C}_{16}\text{H}_{33}\text{PEt}_3^+\text{Br}^-$	1.8
$\text{Ph}_4\text{P}^+\text{Br}^-$	2.5
$(\text{C}_4\text{H}_9)_4\text{P}^+\text{Cl}^-$	37.0
$(\text{C}_8\text{H}_{17})_3\text{PET}^+\text{Br}^-$	37.0

Recently, renewed interest has been shown in the catalytic effect of tertiary amines as catalysts for two-phase systems but, in general, they are less effective than the quaternary ammonium salts.^{15,113,197,198}

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Recent Advances in Synthetic Pyrethroids

Alfred Bader

How is great research achieved?

Perhaps a systematic study of how research is carried out in various countries is just not possible, as it would require intimate knowledge of so many research groups. Even today, when great research is being done so openly by many academic research teams, often in the same or adjacent buildings — R.B. Woodward's or E.J. Corey's groups at Harvard, for example — there has not been a systematic study of how this differs from country to country, from industrial to academic laboratories, or even from one professor's laboratory in the same building to the next. One can come close to understanding how academic research was done fifty to a hundred years ago by reading those wonderfully informative obituaries of great chemists that appeared in the *Berichte*. Also, some autobiographies, such as "Aus meinem Leben" by Richard Willstätter, are most informative. Today, however, chemists write much less personally: too many heed that most foolish of sayings that time is money. Time is the one commodity that money cannot buy, and we are so busy "doing" chemistry that we seldom reflect how it could be done best.

Naturally, as a supplier of building blocks for organic chemical research, we are most interested in how research is being done, and most suggestions for our new compounds have come from great research laboratories around the world. Thus, we were very interested in meeting, and discussing research in general and his research in particular, with Dr. Michael Elliott of the Rothamsted Experimental Station in Harpenden, Hertfordshire, England, whose work is likely to change the world's

agriculture as fundamentally and more lastingly than the chlorinated hydrocarbons such as DDT have done earlier.

Dr. Elliott, born in London in 1924, educated at University College at Southampton and King's College, University of London (Ph.D. and D. Sc.), is a most approachable chemist, and when I called him from London recently, he readily invited me to his laboratories in Harpenden, and he subsequently visited Aldrich for a day to discuss our interest in providing building blocks for synthetic pyrethroids. (Fig. 1 shows Dr. Elliott with Dr. Irwin Klundt and Mr. Charles Pouchert of Aldrich.)

Dr. Elliott's interest in the chemistry of pyrethrins started when he was a student with Professor Stanley Harper, with whom

he moved from Southampton to London. From London, Dr. Elliott went directly to the Rothamsted Experimental Station where work on pyrethrins had been guided by Dr. Frederick Tattersfield and Dr. Charles Potter, who had realized the great importance of a stable supply of insects to the studies of structure-activity relationships, and who had built a multidisciplinary team at the Experimental Station. Today the team associated with Dr. Elliott includes organic chemists Dr. Norman F. Janes (Fig. 2) and Dr. David A. Pulman (Fig. 3), an electrophysiologist, Mr. Paul Burt, and entomologists Dr. Andrew W. Farnham and Mr. Paul H. Needham. This team works in modest, cluttered laboratories, much like university laboratories built in the thirties, and one gets no inkling

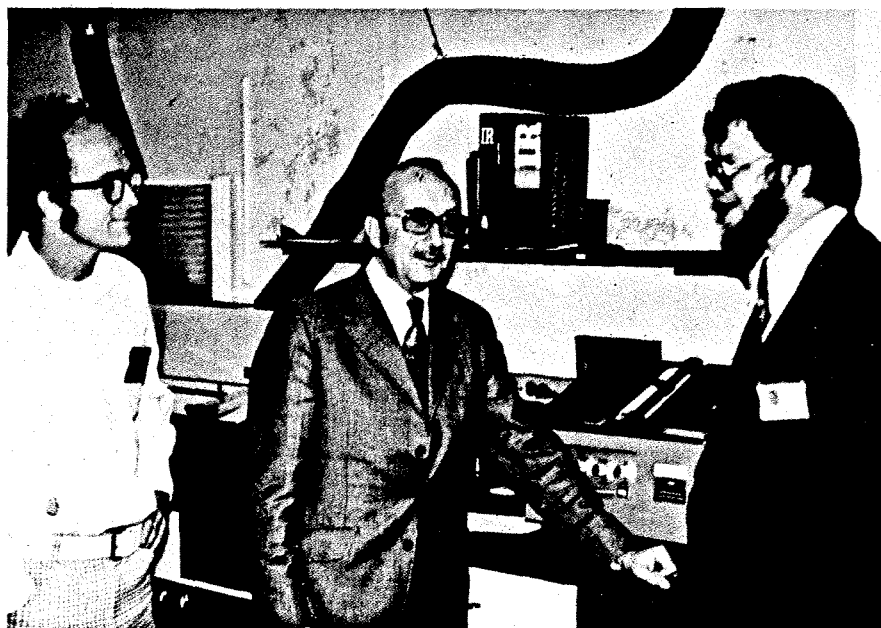


Fig. 1. From left to right, Mr. Pouchert, Dr. Elliott and Dr. Klundt.

from discussions with these modest scientists that they are doing fundamental work on which the giants of the world's chemical industry — ICI, Roussel-Uclaf, FMC, Sumitomo and others — are spending millions in efforts to commercialize these inventions.

Naturally, my first question to Dr. Elliott was how he believed his research differs in method from that in the laboratories of the industrial giants. The Rothamsted research on pyrethroids has been supported by the National Research Development Corporation which has patented the active compounds and has licensed these to the companies mentioned, and so Dr. Elliott has been able to compare their research efforts with those of his own team. In some of the laboratories of the chemical giants, one group of chemists makes the new compounds. These are then computer-coded and eventually — often months later — fed to insects by scientists

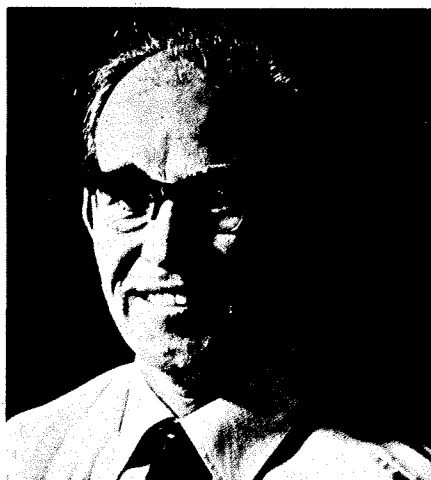
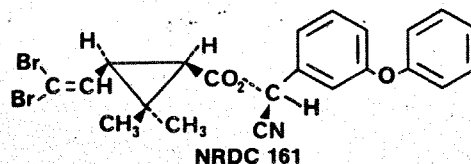
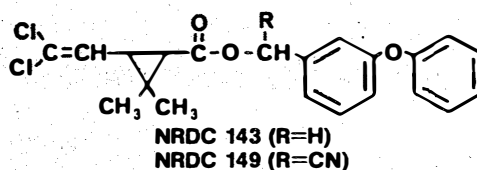
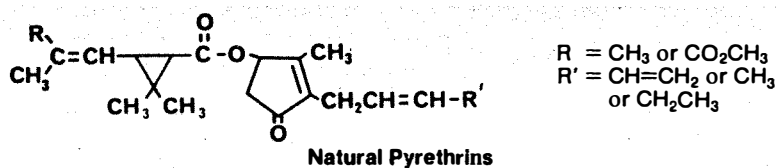


Fig. 2. Dr. Norman F. Janes

who may not even know the chemists who made the chemicals, and it may be months later before the synthetic chemists get the neatly tabulated test results. All this is often impersonal and always time-consuming. At Rothamsted, a compound synthesized in the morning is sometimes tested for its insecticidal activity the same afternoon, by scientists working in proximity. They know and talk to each other, and have only one aim — to produce quickly the most active, least toxic compound of the series being studied to establish fundamental structure-activity relationships. Clearly it is easier to find active compounds in such an environment.

The natural pyrethrins are the active insecticidal ingredients of pyrethrum flowers. Their chemistry has been carefully reviewed;^{1a-d} they are esters of cyclopropanecarboxylic acids and alkenylcyclopentenolones.



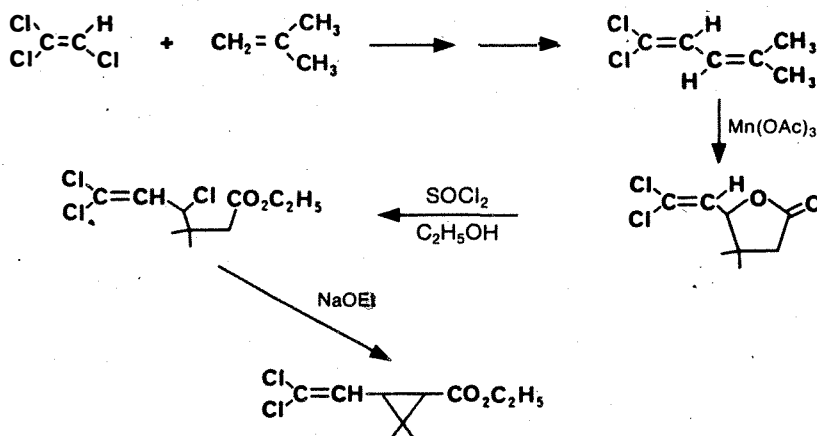
Until relatively recently, the interest in the pyrethrins as insecticides was greatly overshadowed by the interest in the chlorinated hydrocarbons, phosphates and carbamates, because these are generally much more easily made and more stable than the pyrethrins. The pyrethrins, however, have the great advantages of being biodegradable, much less volatile, and harmless to mammals, and so the environmentalists' concern about DDT, Aldrin, Dieldrin, etc., has shifted interest to the synthetic pyrethroids which have been studied by Dr. Elliott and his co-workers since the sixties. Many hundreds of analogs of the natural pyrethrins have been made, and the relationship between structure and activity has been studied in detail.²

To date, the three most promising compounds are NRDC 143, NRDC 149 and NRDC 161.

All three compounds appear very difficult to prepare, and their facile preparations are the result of work by some of the ablest chemists in the world's giant chemical companies.

The acid moiety was the more difficult to synthesize, and Professor Ralph A. Raphael of Cambridge University electrified this September's symposium on synthetic pyrethroids in San Francisco when he described the as yet unpublished preparation from trichloroethylene and isobutylene, developed by Dr. Peter Cleare at ICI. Trichloroethylene and isobutylene are condensed to 1,1-dichloro-4-methyl-1,3-pentadiene which is then converted to a lactone with manganic acetate. When this is treated with thionyl chloride and ethanol, it yields an ester which can be cyclized to the key cyclopropanecarboxylic ester required for NRDC 143.

FMC chemists reported a parallel synthesis of this ester at the same symposium. It proceeds *via* the same dichloromethylpentadiene, which is converted to the ester with ethyl diazoacetate. FMC reported raw materials cost by this route to be low, only about \$2.50/lb, but the cost of a plant to handle ethyl diazoacetate safely is likely to be much higher than that for the ICI process.



m-Phenoxybenzyl alcohol and *m*-phenoxybenzaldehyde are much more easily made, but how best to do this on the hundreds-of-tons scale that may be needed? We understand that an air-oxidation process from *m*-phenoxytoluene, which is readily available from phenol and *m*-cresol, has been developed. Also *m*-phenoxytoluene can be halogenated and hydrolyzed to *m*-phenoxybenzyl alcohol which can be easily oxidized to the aldehyde. Alternately, the benzal halide can be converted to the aldehyde directly. These methods, however, involve a raw material cost estimated at \$5-6 per lb of alcohol or aldehyde, which may be too high for economic feasibility.

Aldrich became interested in *m*-phenoxybenzyl alcohol when we were asked to study the reduction by hydroboration of *m*-phenoxybenzoic acid, easily made by the oxidation of *m*-phenoxytoluene. We had no problem scaling up the hydroboration and made several hundred pounds of the alcohol. However, it became clear that this process could not compete economically with the alternate routes.

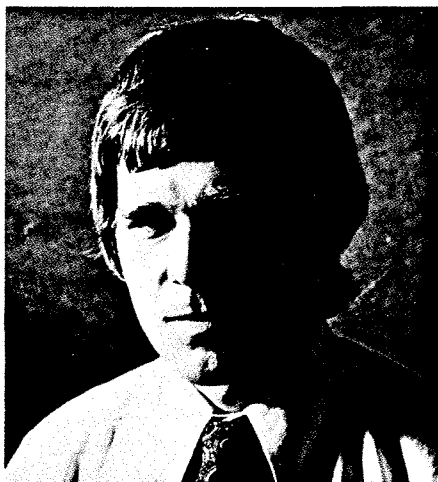


Fig. 3. Dr. David A. Pulman

Shortly after completion of this work, we found a much better synthesis of *m*-phenoxybenzyl alcohol *via* the aldehyde. This uses neither *m*-phenoxytoluene nor the acid, and has an intrinsically lower raw material cost than the syntheses from *m*-phenoxytoluene. Just at that time, attention focused on NRDC 161, the ester of the cyanohydrin of the aldehyde, so the aldehyde itself became important. We believe that we have a more economical synthesis of the aldehyde than any involving the oxidation of *m*-phenoxybenzyl alcohol and, in fact, the most economical preparation of the alcohol may be *via* the reduction of the aldehyde made by our method.

We at Aldrich do not have any large-scale equipment and certainly could not

make many tons ourselves. However, some time ago I discussed the industrial production of the aldehyde with one of my best friends, Bert Van Deun, at Janssen Pharmaceutica in Belgium. The Janssen engineers then scaled up the process using specific technology developed within the company, and so we have licensed Janssen to prepare the aldehyde, and hope that they will be able to fill much of the demand.

Naturally, we were most interested to learn what the contributions of the NRDC licensees have been. As we understand the situation, it is as follows: ICI may have made the greatest synthetic efforts, particularly towards NRDC 143, culminating in Dr. Cleare's work discussed. Shell appears to have concentrated on new structures, and FMC with ICI (U.S.), the licensees in the Western Hemisphere, have emphasized studies of biological activity. Roussel-Uclaf has developed elegant syntheses of chrysanthemic acid, either *via* a sulfone³ derived from isoprene, and β,β -dimethylacrylic acid (which may explain why we have sold many tons of this recently) or *via* addition of this sulfone to an isopropylidene malonate ester.⁴ All the most active compounds are resolved, optically active isomers; for example, the (+)-*trans*-chrysanthemates and analogs are active while the (-)-*trans*-isomers are virtually inactive. Thus, resolution is very important, and the best methods appear to have been developed by chemists at Roussel-Uclaf.⁵ Sumitomo's contributions have been both in synthetic innovations and of new structures. They have prepared the esters *via* the triethylamine salt of *m*-phenoxybenzyl bromide without isolation of the alcohol. Also, they have shown⁶ that the cyclopropane moiety is not essential to activity: 'Sumicidin,' S5602, is the *p*-chloro- α -isopropylphenylacetate of the cyanohydrin of *m*-phenoxybenzaldehyde.

Just how active these synthetic pyrethroids are in comparison with the older insecticides can be seen from this table.⁷

	Relative toxicity to	
	house flies	mustard beetles
Parathion	37	7
DDT	4-15	11
Dieldrin	35	4-10
NRDC 161	2300	1600

This much greater insecticidal activity, coupled with their low mammalian toxicity and biodegradability, makes it appear likely that these pyrethroids will become important insecticides in the future.⁸

Because of my interest in art, I am often asked how I believe motivation between great artists and great chemists differs. The great chemists often achieve greatness

because they want to be the first to reach a difficult goal: R.B. Woodward must have known that if he did not synthesize quinine or strychnine and Vitamin B₁₂, *someone else would*. A great artist paints because he knows that if he does not create this great work, no one else will. If Rembrandt had not painted that marvellous "Return of the Prodigal Son" now in the Hermitage, *no one else would have*. This rather pat answer falters when considering Dr. Elliott's work: would NRDC 161 really have been made without him and his team? Probably not, or at least not for a very long time: in the case of men like Elliott, the motivation of scientists and that of artists overlap.

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