REACTIONS OF POTASSIUM SALTS SOLUBILIZED BY 18-CROWN-6 AND MECHANISM OF NUCLEOPHILIC SUBSTITUTION ON 6-FLUORO-9-METHOXYMETHYLPURINE

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SUMMARY

The first portion of the work described in this thesis involved studies on the effects of 18-crown-6 on the solubility and reactivity of potassium salts in organic solvents. The discovery that the crown ether formed solid "complexes" with acetonitrile also led to a purification procedure for 18-crown-6.

Reactions of potassium fluoride and potassium acetate were mainly investigated. Although flame photometric studies showed that the crown ether enhanced the solubility of potassium fluoride in acetonitrile by only a factor of about ten, the solubility of potassium acetate found by nmr increased by a factor of 200 in the presence of 0.14 M crown.

With only catalytic quantities of 18-crown-6 in the solution, reactive substrates substrates such as benzyl bromide, 2,4-dinitrochlorobenzene and acetyl chloride gave high yields of the corresponding fluorides. Although reaction times were too long to be practical with only catalytic amounts of crown ether, primary alkyl bromides could be converted to the corresponding fluorides in high yields by reaction with potassium fluoride in molten crown ether/acetonitrile complex. Secondary bromides produced predomi-

nantly olefinic products.

Potassium acetate dissolved in acetonitrile with catalytic amounts of crown ether reacted at room temperature with benzyl bromide to form the acetate in only one hour. Primary alkyl bromides were converted to the corresponding acetates in three hours at 83°. In the case of the secondary substrate, 2-bromooctane, 87% substitution product was observed.

The rate of displacement of the leaving group from primary alkyl substrates with both potassium fluoride and potassium acetate followed the order bromide > tosylate > chloride. Furthermore, reactions with potassium fluoride occurred more rapidly in acetonitrile than in benzene.

Reactions of potassium acetate, fluoride and chloride were carried out with 2-chloro-2-methylcyclohexanone. With potassium acetate, substitution products were obtained almost exclusively. Potassium fluoride reacted to form a mixture of 2-methylcyclohexenone and the tertiary fluoride, 2-fluoro-2-methylcyclohexanone. Potassium chloride, in catalytic amounts, produced the highest yield of elimination product.

The second portion of this work was a mechanistic study of the reaction of 6-fluoro-9-methoxymethylpurine with

piperidine-N-h and -N-d in isooctane and with piperidine-N-h in benzene for comparison with other studies done on similar chloropurines. The kinetics were followed by means of ultraviolet spectrophotometry. The results of this study indicated that the addition-elimination, or Bunnett, mechanism readily accounted for the observations.

Plots of the second-order rate constant k_{obs} vs. concentration of piperidine were linear. In isooctane, no change in these lines was observed in going from 10° to 25° to 40°. Only a slight temperature effect was found for the reaction in benzene.

A change from piperidine-N-h to piperidine-N-d slowed the catalysis step of the reaction noticeably. The kinetic isotope effect of about 1.4 was termed a primary effect resulting from the breaking of the N-H bond in the rate-determining step of the reaction.

Additives were tested for their effect on the reaction rate in order to understand the catalysis step of the mechanism. Ketones, ethers and tertiary amines had no effect upon the rate. Alcohols and secondary amines, however, increased the rate. Thus it was concluded that a proton bound to an electronegative atom was necessary for catalysis. The lactam 2-azacyclononanone produced a large

rate acceleration. From this observation, a bifunctional catalysis was postulated. This idea was further strengthened by a Hammett study of the catalysis step using substituted benzyl alcohols. The small positive ρ value of +0.17 showed that bifunctional catalysis with a slight emphasis on the acid nature of the catalyst was occurring.

In comparisons with the analogous chloropurines, it was found that (1) the same catalysts were effective, although no isotope effect was found in the chloro cases; (2) the relative order of halogen mobility was the usual fluorine greater than chlorine; (3) the catalyzed step was more significant in the fluoro case; and (4) the same trends were observed in going from isooctane to benzene.

CHAPTER 1

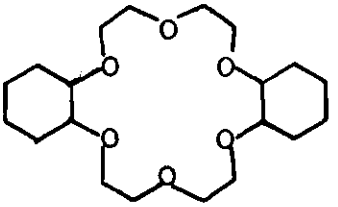
HISTORICAL BACKGROUND

The Chemistry of Crown Ethers

The chemistry of crown ethers began with the accidental discovery by C. J. Pedersen of one member of this class of macrocyclic polyethers. In a series of papers,[1-7] Pedersen gave these compounds their trivial "crown" nomenclature, synthesized many members of the family, and determined their properties and complexing abilities. The most unique attribute of this class of neutral molecules is the ability to form stable complexes with many metal cations, most notably the alkali metal cations. Many authors have published new or improved syntheses of crown-type compounds[8-14] and evidence for other crown complexes of various sorts.[9,15-23]

The "crown" names are formed by giving (1) the number and kind of hydrocarbon rings, if any; (2) the total number of atoms in the polyether ring; (3) the class name, crown; and (4) the number of oxygen atoms in the polyether ring. For example, structure 1 has the systematic name

2,5,8,15,18,21-hexaoxatricyclo[20.4.0.$0^{9,14}$]hexacosane, but is termed dicyclohexyl-18-crown-6 by trivial nomenclature. Likewise, structure 2 has the systematic name 1,4,7,10,13,



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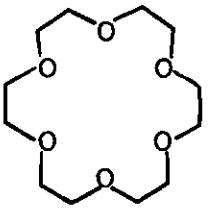

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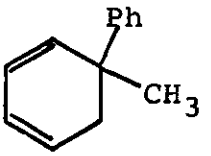
16-hexaoxacyclooctadecane, but will be called 18-crown-6 throughout this thesis.

Much effort has been devoted toward elucidating the interactions of crown ethers with metal cations. Many of these complexes can be isolated as stable, crystalline solids, and numerous papers deal with x-ray crystallographic determinations of their structures.[24-35] Interactions in solution have been investigated by spectrophotometry[36,47] (especially with fluorenyl salts[37-41]), potentiometry,[42] solvent partition equilibria,[43] calorimetry,[44-46] nmr,[48-51] esr[52-53] and conductance measurements.[54] Considerable attention has been given to this family of compounds as model carriers in biological ion transport systems.[55-60] D. J. Cram has synthesized novel chiral crown ethers and used them to selectively complex one enantiomer of a pair.[61-65]

Crown ethers have also been incorporated into polymer chains and their complexing abilities evaluated.[66-69] Effects on electrode processes have been reported.[70-72] Use of the cation-binding properties of various crowns has produced ion-selective electrodes,[73,74] extraction techniques for cesium[75-77] and carboxylic acids,[78] and a solid electrolyte device.[79]

To date, little use has been made of the unique complexing properties of the crown ethers in organic synthesis. Most of the work has been done exploring their effects as addends in reactions. Typically, it has been assumed that this will increase dissociation of ion pairs and thereby modify the course of a reaction. Thus, the crowns were used solely to increase dissociation and thereby test postulated mechanisms.

An interesting effect has been demonstrated by Staley[80] in reactions of 5-methyl-5-phenyl-1,3-cyclohexadiene (structure 3) with metal amides in liquid ammonia.



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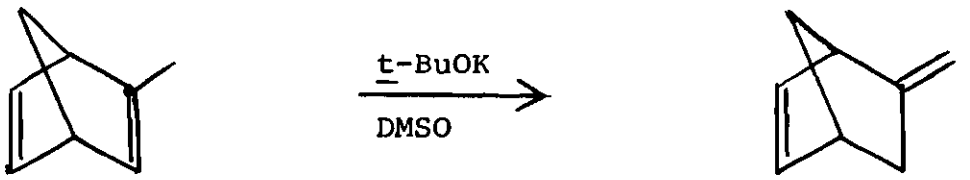
Product distributions were determined for lithium, sodium, potassium and cesium amides and for potassium amide in the

presence of dicyclohexyl-18-crown-6. The product yields of the last reaction resembled those obtained using lithium amide and were quite different from those obtained with potassium amide alone.

Cram[81,82] has studied the effects of added dicyclohexyl-18-crown-6 on the rates and stereochemical course of potassium alkoxide catalyzed carbanion-generating reactions in alcoholic solvents. It was found that potassium t-butoxide in t-butanol showed a much greater kinetic basicity in the presence of the crown than when alone.

Maskornick[83] has shown the exceptional complexing ability of 18-crown-6 by determining the rate of isomerization of 2-methylbicyclo(2.2.1)hepta-2,5-diene (structure 4) to 5-methylenebicyclo(2.2.1)hept-2-ene (structure 5) by potassium t-butoxide in DMSO. At low concentrations (ca.



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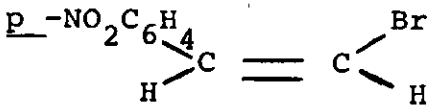
0.1 M) of potassium t-butoxide, the reaction showed variable order base dependence, approaching first order at high dilution, while at higher concentrations, zero order base

dependence was observed. In the presence of the linear polyether tetraglyme, similar results were found. For added cyclic 18-crown-6, however, the kinetics followed first order base dependence from 0.01 M to 0.33 M potassium t-butoxide. The results were interpreted to mean that at low concentration in DMSO alone some solvent-separated ions are present, while at higher concentration, ionic aggregation began to appear. With the crown, solvent-separated ions were maintained to a higher level of base concentration. This demonstrates that this crown can dramatically improve the activity of potassium salts even in highly solvating media.

Crown ethers have also been used in elimination reactions. Several authors[84-86] have added dicyclohexyl-18-crown-6 to increase solvent separated ion pairs in solution and thereby test hypotheses concerning the effect of association of the base in such reactions. In each case, the expected behavior was observed.

An interesting extension of this type of investigation has recently been reported.[87] In this work, potassium fluoride solubilized by dicyclohexyl-18-crown-6 in acetonitrile, DMF and ethylene glycol mono-n-butyl ether (Butyl Cellosolve) was used to form acetylenes from structure 6.

The results depended upon the nature of the solvent. In acetonitrile, no reaction occurred without crown, while



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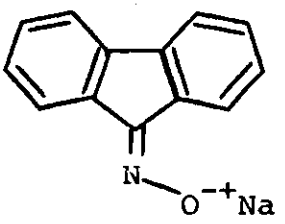
with crown 53 to 71% conversion was reported at 80° in 60-90 minutes. In DMF and Butyl Cellosolve, however, the results were not so dramatic, although yields did increase in the presence of crown ether by a factor of two to four. This represents a novel use of the crown ether, in that in its absence the base used, potassium fluoride, shows very little solubility in the reaction medium acetonitrile.

Nucleophilic substitution reactions have also seen the use of crown ethers. The reaction[88] of sodium 9-fluorenone oximate (structure 7) with methyl iodide in 33.5% acetonitrile and 66.5% t-butanol gives alkylation at both



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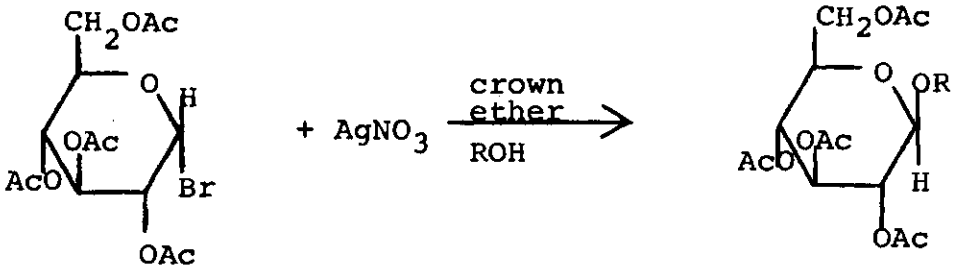
oxygen and nitrogen. This ratio of oxygen to nitrogen alkylation as well as spectral changes in the reactant

solution and rate of reaction indicate whether the salt is associated. Addition of dibenzo-18-crown-6 to the reaction causes a spectral shift to longer wavelength, increased rates of reaction and higher fractions of oxygen alkylation indicative of increased dissociation of the salt in solution.

Another group[89] has investigated the alkylation of potassium phenoxide with butyl bromide in dioxane with various linear and cyclic ethers and DMSO as additives. A series of unsaturated and saturated crown ethers, dibenzo- or dicyclohexyl-3n-crown-n (n = 4,5,6 and 8) were used. All of the crown ethers were superior in increasing the reactivity of potassium phenoxide to the other additives. In the cyclic series, the saturated members showed superior complexing ability (based upon phenoxide reactivity) to the corresponding unsaturated members. Ring size likewise played a role, with complexing ability being at a maximum with the 18-crown-6 ethers. These results reaffirm similar findings of Pedersen concerning complexation of potassium.

Formation of glucosides has also been investigated utilizing dibenzo-18-crown-6. Reaction of acetobromoglucose 8 with silver nitrate dissolved in an alcohol, which serves as both solvent and nucleophile, produces the gluco-

side in 43 to 81% yield at room temperature in one to five



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minutes. Yields depended upon the alcohol used.

Increased reactivity of potassium t-butoxide in nucleophilic displacements on fluoronitrobenzenes in t-butanol has also been demonstrated.[91]

Other reports are available concerning the effects of crown ethers as additives in the bromination of stilbene in chloroform[92] and the reduction of ketones with sodium borohydride in aromatic solvents.[93]

All of the preceding papers have effectively demonstrated the complexing powers of the crown ether family. However, most have used the crowns to increase dissociation of salts which are already soluble in the reaction medium. Only a few papers have been published to date in which these macrocycles have been used to solubilize salts in solvents in which they are not inherently soluble.

The earliest such report was one of the original Pedersen papers[2] in which potassium hydroxide in toluene

with dicyclohexyl-18-crown-6 was used to saponify sterically hindered esters such as t-butyl 2,4,6-trimethylbenzoate. (This report has since been modified.)[94]

Phenyl potassium has been generated in solution by dissolving potassium phenylazoformate ($PhN = NCO_2K$) in THF with the aid of dicyclohexyl-18-crown-6. Heating this solution to reflux temperature gave benzene and potassium benzoate as products, indicative of the presence of phenyl potassium.

Another use of the crown in synthesis involves solubilizing potassium permanganate in benzene and use of the solution as an oxidizing agent for olefins, alcohols, aldehydes, and alkylbenzenes.[96] Without the crown ether, potassium permanganate shows no detectable solubility in benzene, and no reaction occurs with organic substrates. Furthermore, the crown ether may be used in catalytic quantities. Isolated yields are high, generally 90-100%, and the conditions are mild (25°) and neutral.

Sam and Simmons have also reported both displacement and elimination reactions with dicyclohexyl-18-crown-6.[94] Reaction of potassium bromide and iodide with n-butyl brosylate in acetone at 25.0° gave second-order rate constants for production of the corresponding n-butyl halide

which were slightly greater than those obtained for reaction with the predominantly dissociated n-Bu_4N^+ halides. Furthermore the potassium iodide complex can be used as a base, yielding only 2-octene when allowed to react with 2-bromooctane in DMF.

A surprising nucleophilic aromatic substitution was also reported by these authors. When the complex of dicyclohexyl-18-crown-6 with potassium hydroxide was prepared by Pedersen's solvent exchange method,[2] it was determined that only 11% of the anions in the toluene solution were actually OH^-. The main anion was OCH_3^- formed from reaction of the potassium hydroxide with the methanol used in the solvent exchange procedure. However, reaction of this solution with o-dichlorobenzene at 90° for 16 hr gave a 40-50% yield of o-chloroanisole.

We[97] have already published one communication partially covering our work with potassium fluoride displacements. Using these procedures,[98] Durst[99] has prepared p-bromophenacyl esters in very high yield using potassium salts of organic acids solubilized in acetonitrile or benzene with either dicyclohexyl-18-crown-6 or 18-crown-6.

Although no comprehensive reviews have been published to date on the crown ethers, the Pedersen papers[1-7]

(particularly reference 7) and partial reviews by Izatt,[100,101] Cram,[65] Smid,[40] Lehn[102] and Truter[35] provide surveys of specific areas of this field.

CHAPTER II

EXPERIMENTAL, 18-CROWN-6

All boiling points and melting points reported herein are uncorrected and all temperatures are in degrees centigrade. Glpc work was done on a Varian Model 90P equipped with a thermal conductivity detector and using helium carrier gas. Infrared spectra were obtained as thin liquid films (neat) or as potassium bromide pellets on a Perkin-Elmer 237B grating infrared spectrophotometer with the 1601.4 cm^{-1} absorption of polystyrene as a reference. Nmr data were obtained on either a Varian A60D or a Varian T60 spectrometer. Mass spectra were determined with either a Varian M66 or a Hitachi Perkin-Elmer RMU-7L instrument. All exact mass determinations were run on the Hitachi. The potassium fluoride solubility studies were done with a Coleman Model 21 flame photometer.

Chemicals

Acetonitrile (Fisher) was used without further purification. Benzene (Fisher) was distilled from sodium (3 g per liter), bp 80.1° (740 mm) [lit[103] bp 80.1° (760 mm)].

Potassium fluoride (Allied Chemical or ROC/RIC), potassium acetate (Baker) and potassium chloride (Baker), used in the reactions involving 18-crown-6, were all dried at least 12 hours in an oven at 120° and finely powdered in a hot mortar before use.

1,4,7,10,13,16-Hexaoxacyclooctadecane (18-Crown-6)

18-Crown-6 was prepared by the method of Cram and Gokel.[104] A three-liter, three-neck flask equipped with a mechanical stirrer and water-cooled bearing, a reflux condenser, and a 500 ml dropping funnel, was charged with 133 g triethylene glycol (Matheson, Coleman and Bell, 0.75 mole) in 500 ml THF (Fisher). Potassium hydroxide (109 g, Fisher, 85% pellets) was dissolved in 60 ml distilled water and added in one portion to the stirred glycol solution. After 20 minutes stirring at ambient temperature (the solution darkens), a solution of 140 g 1,8-dichloro-3,6-dioxaoctane (Eastman practical, 0.75 mole) in 100 ml THF was added in a thin stream to the stirred reaction mixture. When addition was complete, the solution was refluxed for 15 hr. After this time, the bulk of the solvent was removed on a rotary evaporator. The residual oil and solid was stirred for 30 min with 500 ml methylene chloride, filtered under vacuum and dried over $MgSO_4$. This solution was filtered

under vacuum , concentrated on the rotary evaporator, and distilled under vacuum. After a forerun boiling at 25-130° (0.2 mm), crude crown ether (71.5 g, 36%) was collected, bp 130-157° (0.2 mm). This material was purified by the acetonitrile complex method. To 50 g of the semi-solid crude in a 250 ml Erlenmeyer flask was added 125 ml acetonitrile (Fisher). The resulting slurry was heated until solution was effected. A magnetic stirring bar was added, and the top was equipped with a Drierite drying tube. As the solution slowly cooled to room temperature, vigorous agitation produced fine, white crystals of the crown ether/acetonitrile complex. After reaching room temperature, the flask was cooled with stirring in an ice/acetone bath to complete precipitation. The mixture was quickly filtered under vacuum and the hygroscopic crystals were transferred to a round-bottom flask. This flask was equipped with a magnetic stirrer, a vacuum take-off, and a heating mantle. The acetonitrile was removed over a period of two to three hr under 0.5 to 0.1 mm pump vacuum and low (ca.40°) heat. The pure, colorless crown ether (25 g, 50% yield)which crystallized on standing showed no ions above 265 in the mass spectrum and no significant hydroxyl absorption in the 3500 cm^{-1} region of the ir spectrum. The pure crown ether

melted at 36.5-38° [lit[105] mp 39-40°], showed only a singlet at δ 3.52 in the nmr (CCl_4, internal TMS), had ir absorptions (neat) at 2875 (alkane C-H), 1450 and 1350 (alkane C-H), and 1120 cm^{-1} (ether C-O), and showed a mass spectrum having m/e 265 and 264 and abundant fragments at 89, 87, 59, 45, 44, 34, 31 and 28. The crown ether/acetonitrile complex used for purification is a hygroscopic white solid: mp 63.5-65.5° with nmr peaks (CH_2Cl_2, internal TMS) at δ 3.60 (singlet, crown protons) and at 2.00 (singlet, CH_3CN). Integration indicates a 2:3, crown: acetonitrile complex. If the crystals are allowed to grow slowly, integration of the nmr spectrum shows a 1:2 complex, mp 72-75°.

2-Chloro-2-methylcyclohexanone[106]

A two-liter, three-necked flask fitted with a mechanical stirrer with a water-cooled bearing, a 500 ml pressure-equalizing dropping funnel and a gas outlet tube, was charged with a solution of 112 g 2-methylcyclohexanone (Aldrich, 1.0 mole) in 500 ml dry carbon tetrachloride (Fisher). A solution of 90 ml of sulfuryl chloride (Eastman, practical, 1.1 mole) in 150 ml dry carbon tetrachloride was added over a period of 1.5 hr to the stirred solution. The reaction flask was cooled by a water bath at room temperature. After the addition was complete, stirring was

continued for two hours. The reaction mixture was then washed successively with three 150 ml portions of distilled water, two 100 ml portions of saturated sodium bicarbonate, and one 100 ml portion of saturated sodium chloride. The organic phase was dried ($MgSO_4$), filtered under vacuum, and the bulk of the solvent was removed by distillation through a 15 cm Vigreux column at atmospheric pressure. The yellow crude was distilled, bp 50-52° (2 mm) [lit[106] bp 94-96° (27 mm)]. A yield of 117 g (80%) of the colorless product was obtained.

n-Hexyl Tosylate

This compound was prepared by a standard procedure from the literature.[107] A 500 ml three-necked flask , equipped with an internal thermometer, magnetic stirrer, and a rubber sleeve,was charged with 100 ml pyridine (Fisher) and 12.5 ml n-hexanol (Eastman, 0.10 mole). This solution was cooled to -10° with an ice and acetone bath. p-Toluenesulfonyl chloride (Eastman, 28.0 g, 0.15 mole) was slowly added at 0° to -10° through the rubber sleeve over a period of one hour. After addition was complete, the reaction mixture was stirred one hour at 0° and then placed into a freezer for two days. The reaction mixture was poured onto a slurry of 200 ml of ice and concentrated HCl. The dark oil

which formed on top of the aqueous layer was dissolved in ether and the aqueous layer was extracted with two 200-ml portions of ether. The combined ether layers were washed with two 100-ml portions of cold 1:1 concentrated HCl, then two 100-ml portions of water. The ether layer was dried (K_2CO_3 and Na_2SO_4), filtered, and the ether was removed on a rotary evaporator. The resulting oil, 11.1 g (43%) showed nmr peaks (CCl_4, external TMS) at δ 7.3 (4H multiplet, ArH), at 3.7 (2H triplet, CH_2O), at 2.2 (3H singlet, $ArCH_3$) and at 1.6-0.4 (11 H multiplet, aliphatic CH).

Reactions Using 18-Crown-6

Potassium Fluoride Reactions

Benzyl Fluoride. A 100-ml round-bottomed flask equipped with a magnetic stirrer, reflux condenser and Drierite drying tube was charged with a solution of 25.97 g benzyl bromide (Eastman, 0.152 mole, 3.04 M) diluted with acetonitrile to the mark in a 50.0-ml volumetric flask. To this solution was added 4.10 g 18-crown-6 (0.0155 mole, 0. 3 M) and 17.90 g anhydrous potassium fluoride (ROC/RIC, 0.308 mole). The stirred mixture was refluxed for 20 hr. After this period of time, only a trace of benzyl bromide could be detected by glpc (3% SE 30, 5' x 1/4", 90°). The reaction was filtered under vacuum, the salts were washed with

two small portions of acetonitrile, and a sample of the solution was taken for glpc analysis. By glpc (1-bromohexane as internal standard, 3% SE 30, 5' x 1/4', 88°), the yield of benzyl fluoride was 14.7 g (88%). The filtered solution was distilled at atmospheric pressure through a 15 cm Vigreux column to remove the acetonitrile, then ca. 0.1 g anhydrous KF was added, the Vigreux column was removed, and distillation was continued under aspirator vacuum to give 11.49 g (69%) of benzyl fluoride: bp 38-40° (17 mm) [lit[103] bp 40° (14 mm)]; infrared absorptions (neat) at 3040 cm^{-1} (aromatic CH), and at 1590 and 1500 cm^{-1} (aromatic C = C); nmr peaks (neat, internal TMS) at δ 7.19 (5H singlet, ArH) and at 5.15 (2H doublet, J = 48 cps, $-CH_2F$); and mass spectrum m/e 110 (M^+) and abundant fragments at 109, 91, 83, 63, 51, 39 and 28. The glpc retention time, infrared and nmr of this compound were identical to those obtained for an authentic sample of benzyl fluoride (Pierce Chemical Company). In the absence of the crown ether, negligible amounts of benzyl fluoride were formed under the same reaction conditions.

α-Fluoroacetophenone. A 100-ml round-bottomed flask equipped with a magnetic stirrer and a ground-glass stopper was charged with 16.10 g α-bromoacetophenone (East-

man, 0.0809 mole, 1.1 M), 4.50 g 18-crown-6 (0.017 mole, 0.24 M), 70 ml acetonitrile (Fisher) and 9.0 g anhydrous potassium fluoride (ROC/RIC, 0.16 mole). The reaction was stirred at room temperature for 88 hr. During this time, the color of the reaction mixture became progressively darker, reaching a deep red-brown at completion. The reaction was monitored by following the disappearance of the $-CH_2Br$ singlet in the nmr spectrum. When the reaction was complete, the mixture was filtered under vacuum, the precipitate was washed with three portions of acetonitrile, and the filtrate was analyzed by glpc (3% SE 30, 5' x 1/4", 100°, 1-bromohexane as internal standard). By this method, the yield of α-fluoroacetophenone was 34%. The filtrate was concentrated by distillation under aspirator vacuum and distilled under pump vacuum giving 2.99 g (27%) of α-fluoroacetophenone: bp 52-55° (0.1 mm) [lit[108] bp 65-70° (0.1 mm)]; infrared absorption (neat) at 1690 cm^{-1} (C = O); nmr peaks (CCl_4, internal TMS) at δ 8.1-7.2 (5 H multiplet, ArH) and at 5.46 (2H doublet, J = 47 cps, $-CH_2F$); and mass spectrum m/e 138 (M^+) and abundant fragments at 105, 77, 51 and 50 [lit[109] infrared absorption (CCl_4) at 1710 cm^{-1}; nmr peaks (CCl_4, internal TMS) at δ 6.19 (J = 46 cps)]. No further attempt was made to improve yields. A large quantity of dark tar

remained in the distillation flask.

2,4-Dinitrofluorobenzene. A 100-ml round-bottomed flask equipped with a magnetic stirrer, reflux condenser and a calcium chloride drying tube was charged with 17.314 g 2,4-dinitrochlorobenzene (Eastman, 0.855 mole, 1.71 M) and 0.706 g 18-crown-6 (0.00267 mole, 0.0534 M) in enough acetonitrile to make exactly 50.0 ml of solution. To this was added 10.0 g anhydrous potassium fluoride (ROC/RIC, 0.17 mole). The stirred reaction was refluxed for 21 hr. Monitoring was done by glpc (3% SE 30, 5' x 1/4', 156°). By glpc analysis (o-dichlorobenzene as internal standard), the yield of 2,4-dinitrofluorobenzene was 95%. The reaction mixture was filtered under vacuum and the solvent was removed by distillation at atmospheric pressure. The product was distilled under vacuum giving 14.48 g (91%) 2,4-dinitrofluorobenzene as a pale yellow liquid: bp 99-101° (0.2 mm) [lit[103] 178° (25 mm)]; infrared absorptions (neat) were identical to those of a known sample (PCR); nmr peaks (acetone-d_6, internal TMS) at δ 9.2-8.4 (multiplet) and at 7.90 (triplet, J = 9 cps) and mass spectrum m/e at 186 (M^+) and abundant fragments at 94, 93, and 30. The infrared, nmr and glpc retention time were identical to those of the known compound (PCR). In the absence of crown ether, negli-

gible formation of 2,4-dinitrofluorobenzene was observed under the same conditions.

Immediately upon mixing the reactants for this preparation, a dark, red-brown color formed. On dilution with more acetonitrile, this solution showed λ max of 425 and 375 nm. Reaction of 2,4-dinitrofluorobenzene with a solution of 18-crown-6, acetonitrile and potassium fluoride showed the same peaks. This colored product was assumed to be some type of σ-anionic (Meisenheimer) complex.

Acetyl Fluoride. A heavy-walled glass ampoule was charged with 2.0 ml acetyl chloride (Allied Chemical, 0.028 mole, 7.0 M), 2.0 ml stock 0.27 M 18-crown-6 in acetonitrile (0.00054 mole, 0.14 M), and 2.53 g anhydrous potassium fluoride (ROC/RIC, 0.0435 mole). The reaction mixture was vigorously agitated on a wrist-action shaker at room temperature and monitored by nmr. After 23 hr, the acetyl chloride singlet (δ 2.67) ahd disappeared, leaving the acetyl fluoride doublet (δ 2.3, J = 7 cps). Under identical conditions, the reaction in the absence of crown ether had gone to 10% acetyl fluoride after 167 hr.

1-Fluorooctane. A 25-ml round-bottomed flask equipped with a magnetic stirrer, reflux condenser and Drierite drying tube was charged with 2.5 ml 1-bromooctane

(Aldrich, 0.014 mole, 1.2 M), 10.0 ml of a 0.24 M stock solution of 18-crown-6 in acetonitrile (0.0024 mole, 0.19 M), and 1.65 g anhydrous potassium fluoride (Allied Chemical, 0.028 mole). The stirred solution was refluxed and monitored by glpc (3% SE 30, 5' x 1/4', 100°). After 115 hr about half of the 1-bromooctane had been converted to 1-fluorooctane and octene. Of the product mixture, ca.90% was 1-fluorooctane and ca. 10% was olefin. The 1-fluorooctane was identified by comparison of its glpc retention time and nmr spectrum in the reaction mixture with those of a known sample (Pierce Chemical Company). In the absence of crown ether, less than 5% of the reactant was converted to products under identical conditions.

The same reaction was also run in benzene solution with increased concentrations of both 18-crown-6 and 1-bromooctane. A 50-ml round-bottomed flask equipped with a magnetic stirrer, reflux condenser and Drierite drying tube was charged with 5.0 ml 1-bromooctane (Aldrich, 0.029 mole, 2.9 M), 5.0 ml of a 1.36 M stock solution of 18-crown-6 in dry benzene (0.0068 mole, 0.68 M) and 3.3 g anhydrous potassium fluoride (Allied Chemical, 0.057 mole). The stirred solution was refluxed and monitored by glpc (3% SE 30, 5' x 1/4", 103°). After 128 hr, about half of the 1-bro-

mooctane had been converted to 1-fluorooctane and olefin. Of the product mixture, about 90% was 1-fluorooctane (identified by its glpc retention time) and about 10% was olefin.

1-Fluorooctane. A 100-ml round-bottomed flask equipped with a magnetic stirrer, reflux condenser and calcium chloride drying tube was charged with 20.43 g 1-bromooctane (Aldrich, 0.106 mole), 16.08 g 18-crown-6 ether/acetonitrile complex (2:3 complex, ca. 0.05 mole 18-crown-6), and 18.8 g anhydrous potassium fluoride (ROC/RIC, 0.32 mole). The stirred reaction mixture was boiled under reflux (pot temperature 97°) for 22 hr. At the end of this time, no more 1-bromooctane could be detected by glpc (3% SE 30, 5' x 1/4", 101°). The reaction mixture was filtered under vacuum and the solid residue was washed with two 25 ml portions of hexane. This solid was then dissolved in 50 ml water and extracted with three 25 ml portions of hexane. The combined hexane solutions were dried ($MgSO_4$), filtered under vacuum, and analyzed by glpc (3% SE 30, 5' x 1/4", 80°, with 1-bromohexane internal standard). The yield of 1-fluorooctane was 86%, with olefin (indicated by nmr analysis) as the only other peak in the glpc. The hexane solution was distilled yielding 11.61 g (83%)1-fluorooctane: bp 142-145° (743 mm) [lit[103] 142-143° (760 mm)]; infrared ab-

sorption (neat) at 2925 cm^{-1} (broad, aliphatic CH) and no absorptions above 3000 cm^{-1} ; nmr peaks (neat, internal TMS) at δ 4.7 and 3.9 (1 H each, each a triplet, J = 48 cps) and at 2.2-0.6 (15 H, multiplet); and mass spectrum m/e (no M^+, highest mass was 112, M-HF) 70, 57, 56, 55, 43, 42, 41, 29. The infrared, nmr and glpc retention time data for this compound were identical with those of a known sample (Pierce Chemical Company).

1-Fluorohexane. To each of two 25-ml round-bottomed flasks equipped with a magnetic stirrer, reflux condenser and Drierite drying tube was added 4.3355 g 1-chlorohexane (Eastman, distilled prior to use, bp 132-133° (740 mm) [lit[103] 134.5° (760 mm)], 0.0359 mole, 2.40 M), or 5.9696 g 1-bromohexane (Eastman,0.0362 mole, 2.41 M), 10.0 ml of stock 0.195 M 18-crown-6 in acetonitrile (0.00195 mole, 0.130 M), and 5.0 g anhydrous potassium fluoride (Allied Chemical, 0.086 mole). The stirred solutions were refluxed and monitored by glpc (10% SE 30, 5' x 1/8', ca.50°) and by nmr. After 150 hr, less than 5% 1-fluorohexane had been formed from 1-chlorohexane, while ca. 30% 1-fluorohexane had been formed from 1-bromohexane. The product 1-fluorohexane was identified by its characteristic nmr in the reaction mixture and by comparison of its glpc retention time with a known

sample. The 18-crown-6 still appeared as a sharp singlet in the nmr of the reaction mixtures after 150 hr.

1-Fluorohexane. To each of two 25-ml round-bottomed flasks equipped with a magnetic stirrer, reflux condenser and Drierite drying tube was added, respectively, 4.3405 g 1-chlorohexane (Eastman, distilled prior to use, bp 132-133° (740 mm) [lit[103] 134.5° (760)], 0.0360 mole, 2.40 M) or 5.9436 g 1-bromohexane (Eastman, 0.0360 mole, 2.40 M), 10.0 ml stock 0.195 M 18-crown-6 in dry benzene (0.00195 mole, 0.130 M) and 4.5 g anhydrous potassium fluoride (Allied Chemical, 0.078 M). The stirred reaction mixtures were refluxed and monitored by glpc (10% SE 30, 5' x 1/8", ca. 50°) and nmr. After 300 hr, less than 1% 1-fluorohexane could be found by glpc in the 1-chlorohexane reaction mixture. Nmr showed no visible 1-fluorohexane. In this nmr spectrum, the crown ether was still a sharp singlet. The 1-bromohexane reaction had produced only ca. 5% 1-fluorohexane (by glpc) in this same time period. Again, the crown ether peak in the nmr was still a sharp singlet.

1-Fluorohexane. To each of three 25-ml round-bottomed flasks equipped with a magnetic stirrer, reflux condenser and Drierite drying tube was added, respectively, 4.336 g 1-chlorohexane (Eastman, distilled prior to use,

bp 132-133° (740 mm) [lit[103] 134.5° (760)], 0.0359 mole), 5.938 g 1-bromohexane (Eastman, 0.0360 mole), or 9.238 g n-hexyl tosylate (0.0361 mole), 4.63 g 18-crown-6/acetonitrile complex (2:3 complex, 0.0142 mole crown), and 6.05 g anhydrous potassium fluoride (Allied Chemical, 0.104 mole). The stirred reaction mixtures were refluxed (pot temperature 95°) for 20 hr. At the end of this time, the per cent 1-fluorohexane was determined by glpc and nmr. For the 1-bromo-, 1-tosylate, and 1-chlorohexane reactions, respectively, the per cent 1-fluorohexane present was 87%, 62%, and 24%. The product was identified by comparison of the nmr spectrum and glpc retention time with a known sample.

2-Fluorooctane. A 100-ml round-bottomed flask equipped with a magnetic stirrer, reflux condenser and Drierite drying tube was charged with 27.59 g 2-bromooctane (Eastman, 0.143 mole), 11.73 g 18-crown-6/acetonitrile complex (2:3 complex, 0.036 mole crown), and 17.0 g anhydrous potassium fluoride (ROC/RIC, 0.29 mole). The stirred solution was refluxed for 70 hr. After this time, the mixture was filtered under vacuum, and the solid residue was washed with about 50 ml of hexane. The filtrate was analyzed by glpc (3% SE 30, 5' x 1/4", 70°, 1-bromohexane as internal standard) and was found to contain 81% of a mixture of ole-

fins and 17% of the 2-fluorooctane. Distillation through a 15 cm Vigreux column gave 12.04 g of a mixture of the olefins and the 2-fluorooctane. This distillate was brominated by addition of bromine, dropwise with stirring, to the cooled product mixture. Distillation gave 1.42 g (7.5%) 2-fluorooctane:[110] bp 38-42° (17 mm) infrared absorption (neat) at 2920 and 2850 cm^{-1} (aliphatic CH) and no absorption above 3000 cm^{-1} ; nmr peaks (neat, internal TMS) at δ 5.05 and 4.25 (0.5 H each, each a multiplet, J = 50 cps, -CHF) and at 2.2-0.8 (16 H multiplet, aliphatic CH); and mass spectrum m/e 112 (M^+-HF) and abundant fragments at 70, 69, 57, 56, 55, 43, 42, 41, and 29.

The product olefins decolorized bromine instantaneously and showed the following properties: bp 124-126° (740 mm) [lit[103] bp 121° and 125° (760 mm)]; infrared absorption (neat) at 1640 cm^{-1} (weak, alkene); nmr peaks (neat, internal TMS) at δ 5.5 (multiplet, vinyl CH) and at 2.2-0.6 (multiplet, aliphatic CH); and mass spectrum m/e 112 (M^+) and abundant fragments at 70, 69, 57, 56, 55, 43, 42, 41, and 29.

2-Fluorooctane. A 25-ml round-bottomed flask equipped with a magnetic stirrer, reflux condenser and Drierite drying tube was charged with 5.0 ml 2-bromooctane

(Eastman 0.0284 mole, 2.8 M), 5.0 ml of a stock solution of 1.0 M 18-crown-6 in dry benzene (0.0050 mole, 0.50 M) and 3.30 g anhydrous potassium fluoride (Allied Chemical, 0.057 mole). The mixture was refluxed and vigorously stirred. After 240 hr, glpc analysis indicated that about half of the reactant had been converted to products and that the volatile product mixture contained ca. 32% 2-fluorooctane and ca. 68% of the 1- and 2-octenes.

2-Fluoro-2-methylcyclohexanone. A 100-ml round-bottomed flask equipped with a magnetic stirrer, reflux condenser and Drierite drying tube was charged with 10.0 g 2-chloro-2-methylcyclohexanone (0.068 mole, 2.8 M), 15 ml of stock 0.27 M 18-crown-6 in acetonitrile (0.0040 mole, 0.17 M) and 8.44 g anhydrous potassium fluoride (Baker, 0.145 mole). The stirred solution was refluxed for 100 hr. After four hours, the solution was yellow-green. Monitoring of the reaction was done by glpc (3% SE 30, 5' x 1/4", 100°).

When the reaction was complete, the dark brown mixture was filtered under vacuum, the salts were washed with three small portions of acetonitrile, and the filtrate was distilled under aspirator vacuum with a short-path distilling head to remove volatile products from the tarry resi-

due. The distillate was then redistilled through a 15 cm Vigreux column to give 1.93 g of a mixture of about equal amounts of two products, bp 63-72° (23 mm). The compound eluted second from the glpc was assumed to be 2-methylcyclohexenone based upon glpc comparison with the known compound.

The two products were separated by column chromatography with 150 g silica gel (Curtin, 100-200 mesh) in benzene yielding a column 54 x 2.5 cm. The first compound was eluted after 400 ml of benzene; the second after 1 l of solvent had been passed through. At this point, chloroform was used to elute all of the second compound (2-methylcyclohexenone).

The solution of the first eluted compound assumed to be 2-fluoro-2-methylcyclohexanone was distilled under aspirator vacuum. A small quantity of material was collected: bp ca. 59° (23 mm); infrared absorption (neat) at 1725 cm^{-1} (C = O); nmr peaks (CCl_4, internal TMS) at δ 3.0-0.9 (8H multiplet, aliphatic CH), and at 1.35 (3H doublet, J = 22 cps); and mass spectrum m/e 130.08138 (calculated for M^+, 130.07940) with abundant fragments at 86, 73, 55, and 43 [lit[111] bp 45° (15 mm); infrared absorption (CCl_4) at 1736 cm^{-1}; nmr peaks (CCl_4, internal TMS) at δ 1.37 (3 H doublet, J = 22cps)]. In the absence of the crown ether,

only a few per cent of the product compounds were formed under the same conditions and reaction time. No further attempt was made to increase product yields.

Attempted Preparation of Cyclohexyl Fluoride.A 25-ml round-bottomed flask equipped with a magnetic stirrer, reflux condenser and Drierite drying tube was charged with 4.0 ml cyclohexyl bromide (Eastman, 0.032 mole, 3.6 M), 5.0 ml of stock 0.27 M 18-crown-6 in acetonitrile (0.0014 mole, 0.15 M), and 4.30 g anhydrous potassium fluoride (Allied Chemical, 0.074 mole). The stirred solution was refluxed and monitored by glpc (3% SE 30, 5' x 1/4", 63°). After 104 hr, about half of the reactant had been converted to cyclohexene. No other products could be seen by either glpc or nmr. The product cyclohexene showed glpc retention time and nmr peaks in the vinyl region identical to those of a known sample. In the absence of crown ether, a reaction under the same conditions produced only a few per cent cyclohexene.

Attempted Preparation of o-Difluorobenzene. A small heavy-walled glass tube was charged with 1.5 g o-dichlorobenzene (Fisher, 0.0102 mole, 1.7 M), 5.0 ml of stock 0.24 M 18-crown-6 in acetonitrile (0.0012 mole, 0.2 M) and 1.2 g anhydrous potassium fluoride (Allied Chemical, 0.021 mole).

The tube was sealed and shaken with a wrist-action shaker in a 180° oil bath for 50 hr. After this time, the tube was opened and the reaction mixture analyzed by glpc (3% SE 30, 5' x 1/4', 65°). Only the o-dichlorobenzene peak was visible. By comparison with a known sample of o-difluorobenzene none of this compound was formed.

Potassium Acetate Reactions

Benzyl Acetate. A 100-ml round-bottomed flask equipped with a magnetic stirrer and reflux condenser was charged with 29.00 g benzyl bromide (Eastman, 0.0170 mole, 3.39 M), 1.4 g 18-crown-6 (0.0053 mole, 0.11 M) and enough acetonitrile (Fisher) to make exactly 50.0 ml of solution. To this was added 36.0 g anhydrous potassium acetate (Baker, 0.37 mole). The slightly exothermic reaction was stirred at ambient temperature and monitored by glpc (3% SE 30, 5' x 1/4', 120°). After 60 min, only benzyl acetate remained. The reaction mixture was filtered under vacuum and the remaining salts washed with ether. The combined filtrates were analyzed by glpc (1-bromohexane as internal standard) and shown to contain 24.0 g (95%) benzyl acetate. Nmr analysis likewise confirmed that only this product was present. The mixture was concentrated by distillation at atmospheric pressure through a 15 cm Vigreux column. The product was

washed with 25 ml saturated potassium chloride solution, and the aqueous phase was extracted with two 25-ml portions of ether. The organic layers were combined, dried ($MgSO_4$), and distilled giving 23.9 g (94%) benzyl acetate: bp 214-218° (740 mm) [lit[103] bp 215.5° (760 mm)]; infrared absorption (neat) at 1740 cm^{-1} (ester C = O); nmr peaks (neat, internal TMS) at δ 7.18 (5H singlet, ArH), at 4.95 (2 H singlet, $-CH_2OAc$), and at 1.80 (3 H singlet, CH_3CO-); and mass spectrum m/e, 150 (M^+), and abundant fragments at 108, 91, 90, 79, and 43. Comparison with commercial benzyl acetate (Baker) showed identical glpc retention time (3% SE 30, 5' x 1/4", 100°), nmr and ir.

Methylene Diacetate. A 100-ml round-bottomed flask equipped with a magnetic stirrer, reflux condenser and Drierite drying tube was charged with 87.10 g methylene chloride (Fisher, 1.03 mole, 16 M), 5.80 g 18-crown-6 (0.022 mole, 0.34 M) and 29.7 g anhydrous potassium acetate (Baker, 0.303 mole). The reaction mixture was refluxed for 94 hr (a convenient length of time). After this period of time, the mixture was filtered under vacuum, concentrated by distillation at atmospheric pressure through a 15 cm Vigreux column and distilled under aspirator vacuum to yield 15.84 g (79%) methylene diacetate: bp 70-72° (20 mm) [lit[103] bp

164.5° (760 mm)]; infrared absorption (neat) at 1760 cm^{-1} (ester C = O); nmr peaks (neat, internal TMS) at δ 5.71 (2 H singlet, CH_2) and at 2.05 (6H singlet, CH_3CO_2); and mass spectrum abundant fragments (no M^+) at m/e 103, 73, 61, 43 and 28. Only peaks for methylene diacetate were present in the nmr and glpc of the crude reaction mixture. No evidence for a significant amount of chloromethyl acetate was found.

n-Octyl Acetate. A 100-ml round-bottomed flask equipped with a magnetic stirrer, reflux condenser and Drierite drying tube was charged with a solution of 13.90 g 1-bromooctane (Aldrich, 99%, 0.0720 mole, 1.44 M), 1.35 g 18-crown-6 (0.0050 mole, 0.102 M) and enough acetonitrile (Fisher) to make exactly 50.0 ml. To this was added 15.30 g anhydrous potassium acetate (Baker, 0.16 mole). The mixture was stirred and refluxed for three hours. At this time, no 1-bromooctane was observed in the glpc (3% SE 30, 5' x 1/4", 90°). The reaction mixture was taken up with 50 ml ether and filtered under vacuum. The salts remaining on the filter were washed with three 10-ml portions of ether and the combined organic phases distilled yielding 11.94 g (96%) n-octyl acetate; bp 210-212° (740 mm) [lit[103] 210° (760 mm)] infrared absorption (neat) at 1740 cm^{-1} (ester

C = O); nmr peaks (neat, internal TMS) at δ 3.98 (2 H triplet, J = 6 cps, $-CH_2-OAc$), at 1.90 (3H singlet, CH_3-CO-), and at 1.8-0.6 (15 H multiplet with spikes at 1.3 and 0.9, aliphatic $-CH_2-$); and mass spectrum abundant fragments at m/e 112, 84, 83, 70, 69, 61, 57, 56, 55, 43, 42, and 41. By glpc and nmr, no olefinic product could be detected. When carried out at room temperature on a wrist-action shaker, this reaction required ca. 140 hr to reach completion. In the absence of 18-crown-6, less than 5% reaction occurred under the same conditions.

n-Hexyl Acetate. To each of three 10-ml volumetric flasks was added, respectively, 1.7313 g 1-chlorohexane (Eastman, 0.0144 mole), 2.7381 g 1-bromohexane (Eastman, 0.0144 mole), and 3.6946 g n-hexyl tosylate (0.0144 mole). To each flask was added 5.0 ml 0.199 M 18-crown-6 in acetonitrile (0.000994 mole) and enough acetonitrile to bring the volume in each flask to the mark. Thus, the concentration of each substrate was 1.44 M and of crown was 0.0994 M. These three solutions were transferred to vials and 3.3 g anhydrous potassium acetate (Baker, 0.034 mole) was added to each. The vials were shaken at room temperature on a wrist-action shaker. Disappearance of reactant and formation of the product acetate was followed by glpc (10% SE 30,

5' x 1/8", 53°). In the case of the tosylate, only the product peak could be observed at this low temperature. Qualitatively, the rate of formation of product followed the order -Br > -OTs > -Cl, with the bromide disappearing about four fimes as fast as the chloride. After 150 hr, only n-hexyl acetate was visible in the glpc of the 1-bromohexane reaction. No evidence for olefin was found in either the glpc or the nmr of the crude reaction mixture. This reaction was worked up by adding 100 ml carbon tetrachloride and 50 ml water to the reaction mixture. The organic layer was then further extracted with two 50 ml portions of saturated aqueous potassium chloride, dried ($MgSO_4$), filtered, and distilled through a 15/cm Vigreux column to give 1.00 g (50%) n-hexyl acetate; bp 155-170° (750 mm) [lit[103] bp 171.5° (760)]; infrared absorption (neat) at 1740 cm^{-1} (ester C = O);nmr peaks (neat, internal TMS) at δ 3.95 (2H triplet, $-CH_2OAc$), at 1.90 (3H singlet, CH_3CO), and at 1.8-0.6 (11 H multiplet, aliphatic CH); and mass spectrum, m/e 145 (M + 1), and abundant fragments at 85, 84, 83, 73, 69, 61, 58, 57, 56, 55, 54, 44, 43, 42, 39, 29, and 27.

Ethylene Acetate. A 100-ml round-bottomed flask equipped with a magnetic stirrer, reflux condenser and

Drierite drying tube was charged with 50.0 ml of a solution of 12.20 g 1,2-dibromoethane (Eastman, distilled prior to use, bp 130.5° (740 mm) [lit[103] 131.4° (760 mm)], 0.0649 mole, 1.3 M) and 1.37 g 18-crown-6 (0.00518 mole, 0.10 M) in acetonitrile. To this was added 26.10 g anhydrous potassium acetate (Baker, 0.266 mole). The reaction mixture was refluxed for 3.5 hr. During the course of the reaction, 2-bromoethyl acetate was observed as an intermediate by glpc analysis. After this period of time, the mixture was filtered under vacuum and analyzed by glpc (1-bromohexane internal standard, 3% SE 30, 5' x 1/4", 82°) and found to contain 90% of the diacetate. The solvent was removed from the filtered solution by distillation at atmospheric pressure through a 15 cm Vigreux column and the concentrated product was distilled under aspirator vacuum to give 7.14 g (75%) ethylene acetate: bp 88-91° (18 mm) [lit[103] bp 190° (760 mm)]; infrared absorption (neat) at 1730 cm^{-1} (ester CO); nmr peaks (neat, internal TMS) at δ 4.27 (4 H singlet, $-CH_2-$) and at 2.05 (6 H singlet, CH_3CO_2); and mass spectrum m/e 147 (M + 1) and abundant fragments at 116, 103, 86, 73, and 43.

2-Bromoethyl Acetate. A 100-ml round bottomed flask equipped with a magnetic stirrer, a reflux condenser, and a

Drierite drying tube was charged with 21.60 g 1,2-dibromoethane (Eastman, distilled prior to use, 0.115 mole, 1.9 M), 2.2 g 18-crown-6 (0.0083 mole, 0.12 M), 50.0 ml acetonitrile and 11.4 g anhydrous potassium acetate (Baker, 0.116 mole). the stirred solution was allowed to reflux for 2 hr. By glpc of the crude reaction mixture, both mono- and diacetate were present. Of this mixture of acetates, ca. 66% was 2-bromoethyl acetate and ca. 34% was ethylene acetate. The reaction mixture was filtered under vacuum, concentrated by distillation at atmospheric pressure through a 15 cm Vigreux column, and the product distilled under aspirator vacuum to give 5.86 g (31%) 2-bromoethyl acetate: bp 64-67° (21 mm) [lit[103] bp 162-163° (760 mm)]; infrared absorption (neat) at 1740 cm^{-1} (ester CO); nmr peaks (neat, internal TMS) at δ 4.40 (2 H triplet, CH_2), at 3.58 (2 H triplet, CH_2Br) and at 2.05 (3 H singlet, CH_3CO_2); and mass spectrum m/e at 166 and 168 (M^+) and abundant fragments at 108, 106, 87, 73 and 43.

2-Octyl Acetate. A 100-ml round-bottomed flask equipped with a magnetic stirrer, reflux condenser and calcium chloride drying tube was charged with a solution of 13.64 g 2-bromooctane (Eastman, 0.076 mole, 1.41 M), 1.40 g 18-crown-6 (0.0053 mole, 0.11 M) and enough acetonitrile to

produce exactly 50.0 ml. To this was added 19.5 g potassium acetate (Baker, 0.20 mole). The stirred solution was allowed to reflux for 20 hr. By glpc analysis (1-bromohexane internal standard, 3% SE 30, 5' x 1/4", 100°), the crude reaction mixture contained 87% 2-octyl acetate, ca. 10% olefinic products and about 3% of an unknown, the retention time of which was slightly less than that of 2-octyl acetate. After this time, the mixture was concentrated on a rotary evaporator, 50 ml of water was added and the yellow organic layer was separated. The aqueous layer was extracted with 50 ml ether and the combined organic layers were washed with one 25-ml portion of saturated aqueous potassium chloride. The organic layer was dried ($MgSO_4$), concentrated on a rotary evaporator, and distilled yielding 9.97 g (82%) 2-octyl acetate: bp 82-85° (17 mm) [lit[103] bp 194.5° (744 mm)]; infrared absorption (neat) at 1740 cm^{-1} (ester C = O); nmr peaks (neat, internal TMS) at δ 4.85 (1 H sextet, -CH-OAc), at 1.85 (3 H singlet, CH_3CO-), and at 1.8-0.6 (16 H multiplet, aliphatic CH); and mass spectrum m/e 173 (M + 1) and abundant fragments at 112, 97, 87, 84, 83, 71, 70, 69, 59, 58, 57, 56, 55, 43, 42, 41 and 28.

2- and 6-Acetoxy-2-methylcyclohexanone. A 100-ml round-bottomed flask equipped with a magnetic stirrer,re-

flux condenser and Drierite drying tube was charged with 14.8 g 2-chloro-2-methylcyclohexanone (0.101 mole, 2.9 M), 20 ml stock 0.27 M 18-crown-6 solution in acetonitrile (0.0054 mole, 0.15 M) and 20.5 g potassium acetate (Baker, 0.209 mole). The stirred solution was allowed to reflux for 1.5 hr and monitored by glpc (3% SE 30, 5' x 1/4', 103 °). After this time, the reaction mixture was filtered, the collected salts were washed with acetonitrile, and the filtrate dried ($MgSO_4$). After filtration to remove the $MgSO_4$, the solution was distilled through a 15 cm Vigreux column, bp 60-67° (0.15 mm) yielding 13.2 g (78%) of the acetate products. By glpc analysis of the crude solution, 2-methylcyclohexenone was present in less than 10% yield. The acetate products were redistilled through a 15 cm Vigreux column, bp 60-63°(0.3 mm). No separation of the three components seen in the glpc was effected. The highest boiling fraction was dissolved in a minimum amount of hot petroleum ether. The solution was cooled rapidly in a Dry Ice and acetone bath. On slow warming, needle-like crystals appeared. These were collected by filtration under vacuum while the liquid was still cold. After drying at room temperature *in vacuo*, the white needles, later shown to be *cis*-2-acetoxy-6-methylcyclohexanone, had the following pro-

perties: mp 52.5-53.5°; infrared absorptions (KBr pellet) at 1740 (ester C = O) and 1720 cm^{-1} (C = O); nmr peaks (CCl_4, internal TMS) at δ 5.10 (1 H broad multiplet, AcOCHCO) at 2.8-1.2 (7 H multiplet, aliphatic CH) at 2.04 (3 H singlet, CH_3CO) and at 1.02 (3 H doublet, J =6cps, CCH_3); and mass spectrum m/e 170 (M^+) and abundant fragments at 128, 81, 43, and 28. The yield was 0.28 g (2%). The glpc of these crystals showed only one peak which corresponded in retention time to the third eluted component, the major product.

Using the procedure of H. O. House and F. A. Richey,[112] a known mixture of the acetoxy ketones was prepared for comparison with the mixture obtained from the crown ether reaction. By glpc comparison (3% SE 30, 5' x 1/4", 101°), assignment of structures was made. Of the total quantity of isolated acetoxy ketones, ca. 30% (first eluted) was the tertiary acetoxy ketone, 2-acetoxy-2-methylcyclohexanone, ca. 10% (second eluted) was the less stable trans-2-acetoxy-6-methylcyclohexanone, and ca. 60% (third eluted) was the more stable cis-2-acetoxy-6-methylcyclohexanone. The nmr, ir and mass spectra and glpc retention time obtained for the cis isomer agree well with those of House and Richey.

The reaction of potassium acetate with 2-chloro-2-methylcyclohexanone was also carried out in refluxing acetonitrile without 18-crown-6. Over the same 1.5 hr reaction time, only traces of the acetoxy ketone products were formed.

Attempted Preparation of Cyclohexyl Acetate. A 25-ml round-bottomed flask equipped with a magnetic stirrer, reflux condenser and calcium chloride drying tube was charged with 3.1 ml cyclohexyl bromide (Eastman, 0.024 mole, 3.0 M), 5.0 ml of stock 0.27 M 18-crown-6 in acetonitrile (0.0014 mole, 0.18 M), and 3.0 g anhydrous potassium acetate (Baker, 0.031 mole). The stirred solution was refluxed for 100 hr. Glpc of the crude reaction mixture showed about 90% unreacted cyclohexyl bromide and about 10% cyclohexene. The entire reaction mixture was dissolved in 40 ml water and extracted with 40 ml ether. The ether layer was washed with 20 ml water, two 20-ml portions saturated aqueous sodium bicarbonate solution and two 20-ml portions of saturated aqueous sodium chloride. The ether solution was dried ($MgSO_4$) and distilled through a 15 cm Vigreux column. A small quantity of cyclohexene was collected: bp less than 95° (740 mm) [lit[103] bp 83° (760 mm)]; infrared absorptions (CCl_4) at 3030 cm^{-1} (olefin) and 1650 cm^{-1} (weak,

olefin); and nmr peaks (CCl_4, internal TMS) at δ 5.60 (2 H, vinyl) and at 2.1-1.3 (8 H, aliphatic H). The glpc retention time and nmr and ir spectra were identical to those of a known sample of cyclohexene.

2-Methylcyclohexenone. A 100-ml round-bottomed flask equipped with a magnetic stirrer, reflux condenser and Drierite drying tube was charged with 9.5 g 2-chloro-2-methylcyclohexanone (0.065 mole, 2.2 M), 20.0 ml of stock 0.27 M 18-crown-6 in acetonitrile (0.0054 mole, 0.2 M) and 0.14 g anhydrous potassium chloride (Baker, 0.0019 mole). The stirred solution was allowed to reflux for 21 hr and monitored by glpc (3% SE 30, 5' x 1/4", 100°). During the course of this reaction the solution turned from colorless to pink to red to red-brown. The reaction mixture was filtered under vacuum and distilled to give 3.6 g (51%) 2-methylcyclohexenone: bp 74-76° (23 mm) [lit[106] bp 83-85.5° (35 mm)]; infrared absorption (neat) at 1675 cm^{-1} (conjugated C = O); nmr peaks (neat, internal TMS) at δ 6.83 (1 H multiplet, vinyl H), at 2.1 (6 H multiplet, aliphatic H), and at 1.7 (3H singlet, $-CH_3$); ultraviolet λ_{max}^{EtOH} 235 nm (ε 10,100 [lit[106] λ_{max}^{alc} 234 nm (ε 9660-9680)]; and mass spectrum m/e110.07306 (calculated for M^+ 110.07316) and abundant fragments at 82, 54, 39, and 28.

In the absence of both 18-crown-6 and potassium chloride, reaction still occurred, though the time required to reach completion increased considerably.

Potassium Acrylate Reaction

Potassium Acrylate. A 1-l round-bottomed flask equipped with a magnetic stirrer, Y-tube, rubber sleeve and nitrogen bubbler was charged with 700 ml dry benzene and 20 ml acrylic acid (Eastman, 0.030 mole). To this solution under nitrogen was added slowly with stirring 25 g potassium t-butoxide (MSA, 0.22 mole) through the sleeve. The reaction mixture was stirred at room temperature for 15 hr. After this period of time, the mixture was filtered under vacuum and the thick paste was transferred directly into the next reaction vessel.

2-Bromoethyl Acrylate. A 500-ml round-bottomed flask equipped with a magnetic stirrer was charged with 300 ml acetonitrile, 40 ml 1,2-dibromoethane (Fisher, 0.46 mole), 7.6 g 18-crown-6 (0.029 mole), and the paste of potassium acrylate from the preceding reaction. The stoppered reaction mixture was stirred at room temperature for four days. After this time, the mixture was filtered under vacuum, concentrated on a rotary evaporator, and distilled to give 6.8 g (43% based on potassium t-butoxide used) 2-bromoethyl

acrylate: bp 36-37° (0.5 mm) [lit[113] bp 53° (5 mm)]; infrared absorptions (neat) at 1725 cm^{-1} (conjugated ester C = O) and at 1630 cm^{-1} (C = C); nmr peaks (neat, internal TMS) at δ 6.8-5.6 (3 H multiplet, vinyl H), at 4.25 (2H triplet, OCH_2) and at 3.58 (2 H triplet, CH_2Br); and mass spectrum m/e 181 and 179 (M^+) and abundant fragments at 109, 108, 107, 106, 99, 85, 72, 56, 55, 43, 28, 27 and 26.

Determination of Salt Concentrations in Solution

Potassium Fluoride

To determine the concentration of potassium fluoride in solutions of 18-crown-6 in benzene and acetonitrile, the concentration of potassium ion was found by flame photometry. Standard solutions for the calibration curve for the Coleman Model 21 flame photometer were prepared in 50.0 ml volumetric flasks by mixing 1.0 ml of stock 0.16 M 18-crown-6 in acetonitrile, various volumes of a solution of aqueous potassium fluoride (Allied Chemical) of known concentration, and enough distilled water to bring the total volume to the mark. A blank solution was also prepared in a 50.0 ml volumetric flask by diluting exactly 1.0 ml of stock 0.16 M crown in acetonitrile to the mark with distilled water. The flame photometer was adjusted to read zero scale divisions with the blank solution and 100 scale

divisions with the standard solution of highest concentration (ca. 1 x 10^{-3} M KF). The two other standard solutions were then run and a plot of scale divisions vs. concentration of potassium fluoride in solution was made. This linear plot was the calibration curve for the instrument.

A sample of potassium fluoride solubilized by 0.16 M 18-crown-6 in acetonitrile was prepared by stirring excess anhydrous potassium fluoride at room temperature for 1.5 hr with the same stock solution of crown ether in acetonitrile used to prepare the standard solutions. This mixture was then centrifuged and exactly 1.0 ml of the clear supernatant liquid was carefully removed. This sample was diluted to the mark with distilled water in a 50.0 ml volumetric flask.

To determine the solubility of potassium fluoride in acetonitrile without 18-crown-6, acetonitrile alone was also stirred 1.5 hr over excess anhydrous potassium fluoride. This mixture was likewise centrifuged and 1.0 ml of the clear supernatant liquid was diluted to 50.0 ml with distilled water.

The two unknown samples of potassium fluoride in acetonitrile (with and without crown ether) were run on the flame photometer and the concentration of potassium ion in

each was determined from the calibration curve. The solution containing no crown ether registered about zero scale divisions just as the blank solution did. From the calibration curve, the solution containing 18-crown-6 contained 7.0×10^{-5} M potassium ion.

The concentration of fluoride in the original 0.16 M crown solution can be calculated by multiplying 7.0×10^{-5} M by 50, since 1.0 ml of the original solution was diluted to 50.0 ml with distilled water. This gives 3.5×10^{-3} M potassium fluoride in 0.16 M crown ether in acetonitrile at room temperature. In the absence of crown ether, the solubility is 3×10^{-4} M.[114]

The concentration of potassium fluoride in 1.01 M 18-crown-6 in benzene at room temperature was also determined. However, due to the insolubility of benzene in water, a slightly modified procedure was used. In this determination, 0.5 ml of 1.01 M crown ether in benzene was evaporated to dryness on a rotary evaporator and diluted to 50.0 ml with distilled water to give the blank solution. The other standard solutions were prepared by evaporating 0.5 ml of the same stock solution of 1.01 M crown ether in benzene to dryness on the rotary evaporator, adding various volumes of a stock solution of aqueous potassium fluoride

of known concentration, and diluting this entire solution to the mark in a 50.0 ml volumetric flask with distilled water. As before, a calibration curve was prepared by adjusting the flame photometer to read zero scale divisions with the blank solution and 100 scale divisions with the standard solution of highest concentration (ca. 1×10^{-3} M KF).

The unknown solution was prepared by stirring excess anhydrous potassium fluoride with the 1.01 M crown ether in benzene stock solution at room temperature for 1.5 hr. After this time, the mixture was centrifuged, 1.0 ml of the clear supernatant was evaporated to dryness on the rotary evaporator, and the residue was diluted to exactly 100.0 ml with distilled water. When run on the flame photometer, this solution had a concentration of potassium ion of 5.2×10^{-4} M. Thus in the original solution of 1.01 M crown ether in benzene, the concentration of potassium ion, and hence fluoride ion, was 5.2×10^{-4} M times 100, or 5.2×10^{-3} M.

In the same manner, the concentration of potassium fluoride in 0.34 M 18-crown-6 in benzene was determined to be 1.4×10^{-2} M at room temperature.

Potassium Acetate

The approximate solubility of potassium acetate in solutions of 18-crown-6 was determined by nmr. Solutions

of the crown ether in benzene and acetonitrile-d (Diaprep) were prepared and stirred at room temperature over excess anhydrous potassium acetate for 1.5 hr. The nmr of the supernatant liquid was then taken and the concentration of acetate determined from the integration of the crown and acetate singlets. In the absence of 18-crown-6, no acetate peak at all could be found in the nmr of the supernatant liquid. The results are shown in Table 1.

Table 1. Solubility of Potassium Acetate in Acetonitrile and Benzene Solutions of 18-Crown-6.

Solvent	18-Crown-6 (M)	Potassium Acetate (M)
Benzene	0.55	0.4
Benzene	1.0	0.8
Acetonitrile-d_3	0.14	0.1

CHAPTER III

RESULTS AND DISCUSSION

Reactions of 18-Crown-6

To date, little work has been published concerning the use of crown ethers for synthetic purposes. Furthermore, the research which has been done has usually involved salts which show an inherent solubility in the reaction medium. Thus, the reactions reported in this work in which virtually insoluble potassium salts are dissolved in benzene and acetonitrile with the aid of 18-crown-6 are unique. Furthermore, the nucleophilic reactivity of the acetate anion in particular is remarkable. We believe that the methods described herein will lead to a wealth of new synthetic procedures based upon the properties of inorganic anions as both nucleophiles and bases when solubilized in organic solvents by 18-crown-6.

The preparation of simple fluorine-containing organic molecules has always been difficult. Factors such as strong reagents, high temperatures, poor yields, and lack of a few generally effective methods have hampered preparation of many of these simple molecules. The preparation of such

compounds, generally in good yield, using potassium fluoride and 18-crown-6 represents a major step toward a generally applicable, simple and effective process for fluorination.

Most of the reactions were carried out in acetonitrile. This solvent was selected based upon our experience with the potassium acetate reactions. A low-boiling solvent in which these displacement reactions occurred rapidly, yet which was inert to the anion present, was desired. Acetonitrile and benzene were tried after the discovery that methylene chloride reacted with acetate anion. Although the reactions proceded smoothly in both solvents, shorter reaction times were apparent with acetonitrile for potassium fluoride. Thus, acetonitrile was mainly used in this work.

The reactions which have been successfully run are tabulated in Table 2. Reactive substrates such as benzyl bromide, α-bromoacetophenone, 2,4-dinitrochlorobenzene and acetyl chloride produce the corresponding fluorides generally in good yield.

Using the conditions described in the Experimental section, benzyl fluoride showed no tendency toward violent decomposition on distillation as has been reported for other

Table 2. Products of the Reaction of Potassium Fluoride with Various Substrates in the Presence of 18-Crown-6.

Product	Solvent	Temp (°C)	Crown Conc.	Substrate Conc.	Time (hr)	% Yield Glpc	% Yield Isolated
Benzyl Fluoride	CH_3CN	83°	0.3 M	3.04M	20	88	69
α-Fluoroacetophenone	CH_3CN	25°	0.24	1.1	88	34	27
2,4-Dinitrofluorobenzene	CH_3CN	83°	0.053	1.71	21	95	91
Acetyl Fluoride	CH_3CN	25°	0.14	7.0	23	> 95	(nmr)
1-Fluorooctane	CH_3CN	83°	0.19	1.2	115*	50	--
	benzene	80°	0.68	2.9	128*	50	--
	Crown/ CH_3CN complex	97°	(0.05 mole)	(0.106 mole)	22	86	83
1-Fluorohexane	CH_3CN	83°	0.13	2.41	150*	30	--
	benzene	80°	0.13	2.40	300*	5	--
	Crown/ CH_3CN complex	ca.95°	(0.014 mole)	(0.036 mole)	20	87	--
2-Fluorooctane	Crown CH_3CN complex	ca.95°	(0.036 mole)	(0.143 mole)	70	17	7.5
2-Fluoro-2-Methylcyclohexanone	CH_3CN	83°	0.17	2.8	100	--	--

*The reaction was not complete at the time shown. The glpc yield given is the % of product formed at the time shown.

preparations.[115] A possible reason for this lies in the fact that some potassium fluoride and crown ether were present. This should function as pyridine does in reported procedures to remove any acids from the mixture prior to and during distillation. Furthermore, the isolated yield (69%) is superior to most preparations reported. Previously, the best methods have involved use of N-methylpyrrolidone and potassium fluoride at elevated temperatures (65-70% yield)[116] or tetraethylammonium fluoride in hexamethylphosphoramide (25°, 8 hr, 55%).[117] Olah[118] has recently reported a quantitative yield of benzyl fluoride by reaction of selenium tetrafluoride with benzyl alcohol. Although the yield is high, the selenium tetrafluoride is toxic, hydrolyzes easily to give HF, and must be prepared from selenium metal and highly reactive ClF_3. Thus, the simplicity and relatively low level of toxicity in our procedure are advantageous.

α-Fluoroacetophenone has also been prepared by the reaction of tetraethylammonium fluoride in HMPA with the corresponding bromide (25°, 8 hr, 30%).[117] Although low, the yield by the crown ether procedure (27%) is comparable to that obtained in HMPA, one of the best of the dipolar, aprotic solvents using one of the more soluble fluoride salts. In the crown ether reaction, much tar remained after vacuum

distillation of the product. The low yield may be due to the formation of base-catalyzed condensation products.

The reaction of 2,4-dinitrochlorobenzene with potassium fluoride and catalytic amounts of crown ether in acetonitrile at the reflux to give 91% of the fluoro compound is a considerably milder procedure than comparably high yield methods reported. Reactions of potassium fluoride with 2,4-dinitrochlorobenzene at 200° for 10 hr in the absence of a solvent produces 90% of the 2,4-dinitrofluorobenzene.[119]

Acetyl fluoride has been prepared from the corresponding chloride with anhydrous zinc fluoride (quantitative)[120] or sodium fluoride in tetramethylene sulfone (48%)[121] and from acetic acid with potassium fluoride and benzoyl chloride (3 hr, 100°, 77%)[122] or cyanuric fluoride (70%).[123] The mild conditions and use of inexpensive potassium fluoride shown in the reaction of acetyl chloride with catalytic amounts of crown ether thus compare favorably with these other methods.

The preparation of primary alkyl fluorides has always been a difficult task. Organic Syntheses[124] gives preparations for 1-fluorohexane (40-45%) and 1-fluorooctane (34%) using potassium fluoride and the corresponding alkyl

bromide in ethylene glycol (160°, 5 hr). Newer preparations have used more exotic reagents, such as the diphenyltrifluorophosphorane[125] reaction with n-octyl alcohol in acetonitrile to give n-octyl fluoride (170°, 10 hr, 76%). Olah[126] has reported fluorination of alcohols using 70% HF/30% pyridine (w/w) in good yield at room temperature with reaction times of about one hour. Some especially interesting examples for comparison with our methods are the reactions of potassium fluoride in the polar, aprotic solvents N-methylpyrrolidone and hexamethylphosphoramide (HMPA). In N-methylpyrrolidone, n-octyl chloride was converted to the fluoride in one to three hours at about 200° in 80% yield.[127] In HMPA, reaction of n-heptyl bromide at 100° for 10.5 hr yields only 1% of the primary fluoride and 2% olefin.[128] Use of tetraethylammonium fluoride, however, gives 56% fluoride and 19% olefin in six days at 25°.[117]

With respect to the methods presented previously, the reaction of alkyl bromides with potassium fluoride and 18-crown-6 compare favorably. The reagents are inexpensive or readily made, no extreme temperatures, extremely toxic or exotic reagents are necessary, the reactions are carried out in ordinary glass apparatus and yields are high. In contrast to the reactions run in HMPA, much less olefin is ob-

tained.

For synthetic purposes using these procedures, bromides react slightly faster than tosylates which react faster than chlorides. Furthermore, the reactions occur faster in acetonitrile than in benzene under comparable conditions. Table 3 summarizes the data.

Table 3. Preparation of 1-Fluorohexane from the Corresponding Bromide, Chloride and Tosylate in Acetonitrile and Benzene.

Substrate	Substrate Conc. (M)	Crown Conc. (M)	Solvent	Temp. (°C)	Time (hr)	%1-Fluorohexane
Bromide	2.41	0.13	CH_3CN	83°	150	30
	2.40	0.13	C_6H_6	80°	300	5
	0.0360 mole	0.014 mole	Crown/ CH_3CN complex	95°	20	87
Chloride	2.40	0.13	CH_3CN	83°	150	less than 5
	2.40	0.13	C_6H_6	80°	300	trace
	0.0359 mole	0.014 mole	Crown/ CH_3CN complex	95°	20	24
Tosylate	0.0361 mole	0.014 mole	Crown/ CH_3CN complex	95°	20	62

Unfortunately, reaction times are lengthy when only catalytic amounts of 18-crown-6 are used. However, this is easily rationalized by the solubility of potassium fluoride

in the solutions. The data collected from flame photometric determination of the potassium ion concentration at 25° are collected in Table 4. Obviously, little fluoride is being dissolved. However, in the presence of almost stoichiometric quantities of crown ether, such as in the crown ether acetonitrile complex reactions, enough potassium fluoride is dissolved to effect reaction in reasonable lengths of time.

Table 4. Solubility of Potassium Fluoride in Crown Ether Solutions at 25°.

Solvent	Conc. of 18-Crown-6 (moles/liter)	Conc. of KF with Crown (moles/liter)	Without Crown[114] (moles/liter)
Benzene	1.01	5.2×10^{-2}	--
	0.34	1.4×10^{-2}	--
Acetonitrile	0.16	3.5×10^{-3}	3×10^{-4}

A comparison of the two solvents is also interesting. At the same concentrations of crown ether and substrate, the benzene reactions are slower. Since crown ether is more readily soluble in benzene than in acetonitrile, a reaction was run using increased concentration of both crown ether and 1-bromooctane substrate to determine if this increase of the cyclic polyether would greatly decrease the reaction time. When the crown ether concentration was increased by

a factor of three and the substrate concentration by a factor of 2.5 over the values for the acetonitrile reaction, the benzene reaction was about equal in the rate of product production to the acetonitrile reaction at the lower concentrations. As yet, no experimental evidence is available to definitely explain this, though it can be rationalized by assuming that the ions are less associated and hence more reactive in the more polar acetonitrile.

Attempted displacement of bromide from 2-bromooctane with potassium fluoride in molten crown ether/acetonitrile complex produces predominantly (81%) olefinic products, although a small quantity of the 2-fluorooctane was isolated and characterized.

In an attempt to prepare 2-methylcyclohexenone using fluoride as a base, 2-chloro-2-methylcyclohexanone was reacted with a catalytic amount of crown ether and potassium fluoride in acetonitrile. Some of the olefin was isolated, along with 2-fluoro-2-methylcyclohexanone. Although this second product is the result of a formal displacement at a tertiary carbon, it is unknown at present whether an S_N2 displacement is actually occurring or if some other mechanism is responsible for this product.

In this study of potassium fluoride reactions, con-

trol runs were also made without crown ether. Thus, it was shown that the crown ether is responsible for the significantly reduced reaction times observed. Using the crown ether complex method, high yields of primary alkyl fluorides may be obtained with little olefin formation and reasonable reaction times. Furthermore, the reagents are relatively inexpensive and less difficult to handle than in many of the other recent preparations. With reactive substrates, even catalytic quantities of crown ether bring about reaction in convenient time periods, making this method quite good for such molecules.

Reactions of potassium acetate solubilized by 18-crown-6 provide an even more dramatic example of the utility of these methods. Due to the high lattice energy of potassium fluoride, it was anticipated that it would be a limiting case in solubility, and that other salts could be dissolved much more effectively. This is certainly the case with potassium acetate. The results have previously been tabulated in Table 1, p. 48. In the absence of crown ether, the inherent solubility of potassium acetate in acetonitrile is about 5×10^{-4} M.[129] Thus, the crown ether dramatically enhances solubility of this salt.

The reactivity of the crown ether solubilized ace-

tate is astonishing. Table 5 shows some of the reactions carried out. With a reactive substrate such as benzyl bromide, the reaction is rapid at room temperature with only catalytic quantities of crown ether present. This method compares favorably with the preparation of benzyl acetate via phase transfer catalysis by quarternary ammonium salts in which only 75% of the product was isolated after two hours at 147°.[130] Comparison can also be made with a recent report of esterification using sodium salts and iodides or bromides in HMPA. The general procedure involves reaction of the salt in HMPA with the bromide for 20-24 hr at room temperature.[131] Although yields are high and conditions mild, the cost of HMPA is a definite disadvantage.

In the reactions with 1- and 2-bromooctane, little olefin formation is observed in contrast to the behavior with fluoride ion. With potassium acetate and the primary substrate no alkene can be detected by glpc or nmr. In the case of the secondary substrate, about 10% of the olefinic products is present.

Various leaving groups were also investigated in these potassium acetate reactions to determine which would be best for synthetic purposes. With n-hexyl bromide, chloride and tosylate at room temperature, the rate of forma-

Table 5. Some Products of Reactions of Potassium Acetate with Catalytic 18-Crown-6 in Acetonitrile.

Product	Substrate Conc. (M)	Crown Conc.(M)	Temp (°C)	Time (hr)	Glpc Yield	Isolated Yield
Benzyl Acetate	3.39	0.11	25°	1	95	94
Methylene Diacetate	Substrate was solvent(16)	0.34	40°	94	--	79
n-Octyl Acetate	1.44	0.102	83°	3	--	96
Ethylene Acetate	1.3	0.10	83°	3.5	90	75
2-Bromoethyl Acetate	1.9	0.12	83°	2	ca.66	31
2-Octyl Acetate	1.41	0.11	83°	20	87	82

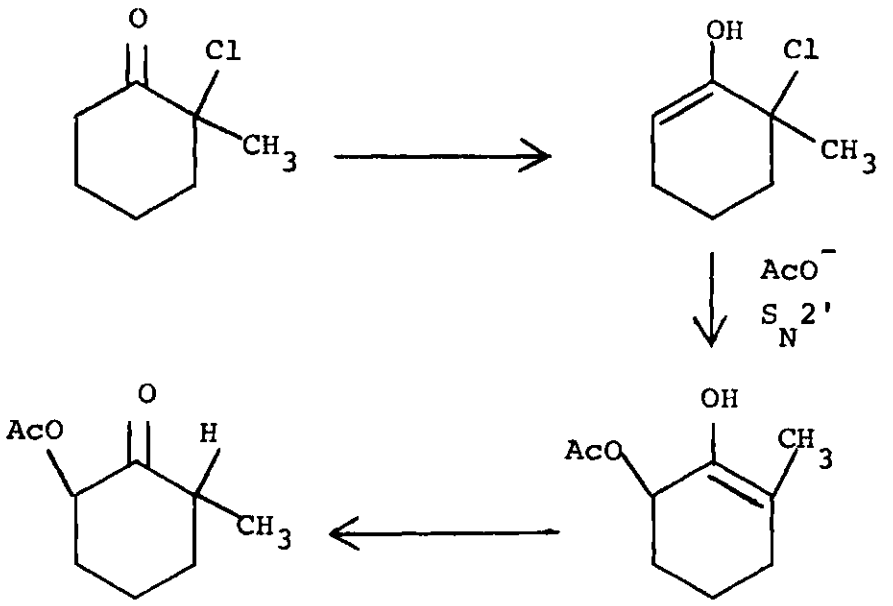
tion of the primary acetate followed the order bromide > tosylate > chloride, with the bromide disappearing about four times as fast as the chloride. The effect of the leaving group on these reactions in which excess solid potassium acetate is present must be examined as a combined effect upon two processes, the solubilizing process and the actual reaction process. Once sufficient substrate has been consumed, competition between the nucleophile and the leaving group for the cation in solution will begin. Thus, the relative solubility of the reactant and product salt may affect the rate of the reaction just as the rate of displacement of the leaving group will.

The two reactions with ethylene bromide illustrate that either the mono- or the diacetate may be prepared simply by using an excess of the appropriate reagent. In the case of methylene diacetate, however, none of the monoacetate could be isolated.

Reaction of potassium acetate with 2-chloro-2-methylcyclohexanone produced a good yield of three acetoxy ketones, cis- and trans-2-acetoxy-6-methylcyclohexanone and 2-acetoxy-2-methylcyclohexanone, with the more stable cis-2-acetoxy-6-methyl isomer as the major product. This reaction was much faster, cleaner, and produced higher yields

than the lead tetraacetate reaction used to prepare authentic samples of these compounds.[112]

The formation of cis- and trans-2-acetoxy-6-methylcyclohexanone may be rationalized by the following scheme:



Finally, the attempted preparation of cyclohexyl acetate from the bromide produced only cyclohexene, just as was the case in the reaction with potassium fluoride.

Both of the anions discussed were allowed to react with 2-chloro-2-methylcyclohexanone in the hope of producing 2-methylcyclohexenone. However, other products were also formed, resulting in low yields of the olefin. By using a catalytic amount of potassium chloride as the dehydrohalo-

genating agent, displacement of chloride would regenerate the basic chloride. Furthermore, displacement by chloride at the 2-position would only produce the reactant again. This reaction occurred quite facilely at reflux temperature, producing the desired olefin in a yield equivalent to that given in Organic Syntheses.[106] Unfortunately, the crown ether does not decrease the reaction time to the considerable extent observed for the displacement reactions.

Finally, reaction of potassium acrylate with excess 1,2-dibromoethane to give 2-bromoethyl acrylate was carried out. Although the isolated yield is low (43%), this was based upon the potassium t-butoxide used to form the salt with acrylic acid. Yields using commercially available potassium acrylate should be much higher. This further illustrates that the monoester may be prepared by use of an excess of one reactant.

These acetate reactions illustrate the feasibility of preparing acetate and other organic acid esters via the crown ether method. The conditions are mild, the reagents inexpensive, and even the preparation of secondary esters should be possible. In addition, the reactions can easily be carried out under anhydrous conditions not possible with quarternary ammonium or phosphonium phase transfer catalysts.

Also, expensive high-boiling, polar, aprotic solvents are not necessary.

CHAPTER IV

CONCLUSIONS

Reactions of 18-Crown-6

The work reported in this section shows that enhanced solubility of potassium fluoride and potassium acetate is observed in acetonitrile and benzene in the presence of 18-crown-6. Reactions carried out with potassium fluoride in acetonitrile indicate that fluorination of reactive molecules such as benzyl bromide, acetyl chloride and 2,4-dinitrochlorobenzene procedes readily in the presence of only catalytic quantities of crown ether. Less reactive substrates such as primary alkyl bromides are converted to the primary fluorides in good yield by reaction with potassium fluoride in molten crown ether/acetonitrile complex. With secondary alkyl bromides, elimination rather than displacement becomes the major reaction. In the absence of crown ether, these reactions occur at a negligible rate.

Potassium acetate was found to be about 200 times more soluble in 0.14 M crown ether in acetonitrile than in acetonitrile alone. Furthermore, this acetate in solution

proved to be very nucleophilic. Benzyl bromide produced benzyl acetate at room temperature in one hour in the presence of only catalytic amounts of crown ether. Primary alkyl bromides yield the corresponding acetates in only three hours at reflux temperature in acetonitrile with catalytic amounts of crown ether. Even 2-bromooctane gave 87% of the secondary acetate.

With both potassium salts studied, the rate of displacement of bromide, chloride and tosylate from primary alkyl substrates was studied. In both cases, the order of displacement was bromide > tosylate > chloride.

The reaction of potassium fluoride with primary alkyl substrates was also investigated in the solvent benzene. In these reactions, acetonitrile gave faster production of product than did benzene.

During this study, the observation was also made of two solid "complexes" formed between acetonitrile and 18-crown-6. These "complexes" had melting points 25° to 35° higher than the crown ether and showed nmr spectra indicating 2:3 and 1:2 crown ether: acetonitrile ratio. It was found that recrystallization of the 2:3 crown ether/acetonitrile complex from hot acetonitrile excluded impurities normally present in distilled 18-crown-6. Removal of the

acetonitrile from the complex with heat and vacuum gave pure 18-crown-6.

Finally, elimination reactions were studied on 2-chloro-2-methylcyclohexanone. With potassium acetate, the 2- and 6-acetoxyketones were the dominant products. With potassium fluoride, only the elimination product and 2-fluoro-2-methylcyclohexanone were isolated. Catalytic amounts of potassium chloride in acetonitrile produced the desired 2-methylcyclohexenone, but the yield was only 50%.

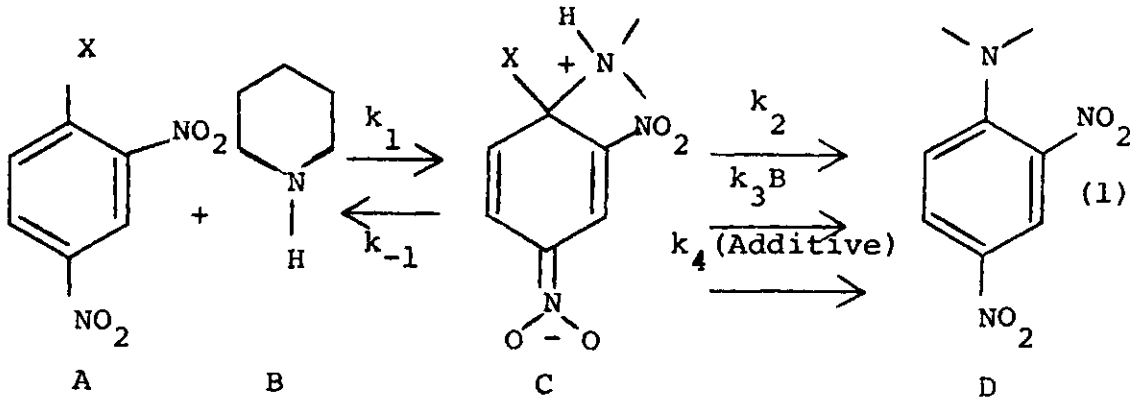
CHAPTER V

HISTORICAL BACKGROUND

Nucleophilic Aromatic Substitution

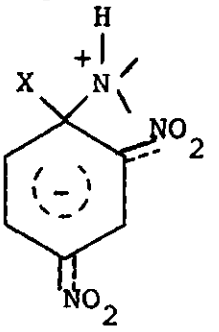
The general subject of nucleophilic aromatic substitution has been frequently reviewed.[132-134] In recent years, there has been a trend away from the use of polar, protic solvents toward the use of non-polar, aprotic solvents, in which catalytic effects may be more easily evaluated by eliminating polar effects and hydrogen bonding to solvent molecules. Work on reactions in such solvent systems is somewhat limited, particularly with respect to studies on the "element effect."[135] This chapter will deal mainly with studies of this type in which the effects of changing the leaving group in nucleophilic aromatic substitutions in non-polar, aprotic media are examined.

Studies by Bunnett and co-workers led to the postulation of a multi-step, addition-elimination mechanism for nucleophilic aromatic substitution such as the following:



(1)

Attack by the nucleophile (B) on the substrate (A) results in the formation of an intermediate σ-anionic complex (C), a Meisenheimer complex:



(2)

The decomposition of such intermediates may occur either through an uncatalyzed process involving a spontaneous loss of the ammonium proton and ejection of the leaving group X, or by a catalyzed route involving a second molecule of the nucleophile or another additive . The catalyzed pathway may be effected by additives such as acids, bases, salts, or bifunctional species. These effects, however, depend strongly on the nature of the nucleophile, substrate and solvent.

The kinetic treatment of this addition-elimination, or Bunnett, mechanism may be easily derived. (In the following treatment, A, B, C, and D represent concentrations of these species in equation 1).

$$\frac{-dA}{dt} = \frac{dD}{dt} = k_1AB - k_{-1}C \tag{3}$$

Using the steady-state approximation on the intermediate C,

$$\frac{dC}{dt} \approx 0 = k_1AB - k_{-1}C - k_2C - k_3BC \tag{4}$$

and solving for C,

$$C = \frac{k_1AB}{k_{-1} + k_2 + k_3B} \tag{5}$$

Substituting this value for C gives

$$\frac{-dA}{dt} = \frac{dD}{dt} = k_1AB - \frac{k_{-1}k_1AB}{k_{-1} + k_2 + k_3B} \tag{6}$$

Rearranging terms,

$$\frac{dD}{dt} = \frac{k_1AB(k_{-1} + k_2 + k_3B) - k_{-1}k_1AB}{k_{-1} + k_2 + k_3B} \qquad (7)$$

$$\frac{dD}{dt} = \frac{(k_1k_2 + k_1k_3B)AB}{k_{-1} + k_2 + k_3B} \qquad (8)$$

The observed rate is given by

$$\frac{dD}{dt} = k_{obs}AB \qquad (9)$$

Thus, the observed second-order rate coefficient is

$$k_{obs} = \frac{k_1k_2}{k_{-1} + k_2 + k_3B} + \frac{k_1k_3B}{k_{-1} + k_2 + k_3B} \qquad (10)$$

If it is assumed that $k_{-1} >> (k_2 + k_3B)$, then formation of the intermediate complex C is rapid and its decomposition is slow and the expression for k_{obs} will become

$$k_{obs} = \frac{k_1k_2}{k_{-1}} + \frac{k_1k_3B}{k_{-1}} \qquad (11)$$

This equation indicates that a plot of k_{obs} vs. the concen-

tration of nucleophile will be linear, with a slope equal to $\frac{k_1 k_3}{k_{-1}}$ and an intercept equal to $\frac{k_1 k_2}{k_{-1}}$. Thus the slope is related to the catalyzed (k_3) process and the intercept is related to the uncatalyzed (k_2) process.

At low concentration of B, the above linear relation is observed. At high concentration of B, however, it can be assumed that $k_{-1} << (k_2 + k_3 B)$. Therefore, the rate-determining step now becomes the initial formation of the intermediate complex C, rather than its decomposition as was previously the case. With this assumption, the expression for the observed second-order constant reduces to

$$k_{obs} = k_1 \tag{12}$$

At high concentration of B, the plot of k_{obs} vs. concentration of B is parallel to the X-axis. At intermediate concentration of B, curvature of the plot is observed.

If an additive also catalyzes the reaction, then k_{obs} may be written as:

$$k_{obs} = \frac{k_1 k_2 + k_1 k_3 B + k_1 k_4 (\text{Additive})}{k_{-1} + k_2 + k_3 B + k_4 (\text{Additive})} \tag{13}$$

If it is assumed that $k_{-1} >> [k_2 + k_3B + k_4(\text{Additive})]$, then

$$k_{obs} = \frac{k_1k_2}{k_{-1}} + \frac{k_1k_3B}{k_{-1}} + \frac{k_1k_4(\text{Additive})}{k_{-1}} \qquad (14)$$

Therefore, if the concentration of the nucleophile B is held constant, a plot of k_{obs} vs. the concentration of the additive will be linear with a slope equal to $\frac{k_1k_4}{k_{-1}}$ (termed the catalytic coefficient) and an intercept equal to $\frac{k_1k_2}{k_{-1}} + \frac{k_1k_3B}{k_{-1}}$.

Of the systems in which nucleophilic aromatic substitution has been studied in non-polar, aprotic media, the 2,4-dinitrohalobenzenes are the most thoroughly researched. Several groups have devoted considerable effort toward the elucidation of this mechanism by studying solvent effects, catalysis and fluorine vs. chlorine mobility. All of these studies postulate the Bunnett mechanism for their system.

The effects of additives on the dielectric of the solvent (medium effects) have been used to rationalize slight catalysis by certain molecules, notably pyridine. Suhr[136] has investigated the influence of various solvents

on the reaction of p-nitrofluoro- and -chlorobenzene with piperidine at 50°. The polarity of the solvent is generally the most important parameter governing the rate of reaction, with rates increasing with increasing dielectric constant. In all of the solvents studied, the fluoro compound reacted faster than the chloro compound.

Numerous additives have been studied as catalysts for the reaction of 2,4-dinitrochlorobenzene (2,4-DNCB) and 2,4-dinitrofluorobenzene (2,4-DNFB) with piperidine in benzene at 25°. For those additives which showed a linear increase in second-order rate constant with increasing additive concentration at constant piperidine concentration, catalytic coefficients may be calculated. These reactions can be described by equation 14, the slope of which $\left(\frac{k_1 k_4}{k_{-1}}\right)$ is the catalytic coefficient. These values, along with other additives used, are collected in Table 6.

Of the additives shown, the effects of pyridine[137,138] and dimethyl sulfoxide[139] (DMSO) on the 2,4-DNFB reaction have been attributed mainly to an increase in the dielectric of the medium, rather than to true catalysis. In the case of DMSO, kinetic evidence was cited. A plot of k_{obs} *vs.* concentration of piperidine at several constant added concentrations of DMSO was prepared. If base cataly-

Table 6. Catalysts Used in the Reactions of 2,4-DNFB and 2,4-DNCB with Piperidine in Benzene at 25°.

Additive	Catalytic Coefficient $\frac{k_1k_4}{k_{-1}}$ in 2,4-DNFB Reaction	Effect on Rate of 2,4-DNCB Reaction	Reference
α-Pyridone	3200 $M^{-2}sec^{-1}$	No effect	142
Piperidine	615	Increase	137,138
Phenol	220	No effect	141
DABCO	32.25		137,138
DMSO	22.2	Increase	139
Methanol	21.2		137,138,140
Pyridine	2.15		137,138
Tetra-n-butylammonium chloride	Large	No effect	141
Tetra-n-butylammonium perchlorate	No effect	No effect	141
Triethylamine	No effect		137,138,140
Dioxane	No effect		139
Anisole	No effect		141
N-methyl-α-pyridone	No effect	No effect	142

sis was the sole effect, the additive should contribute only a term $\frac{k_1k_4DMSO}{k_{-1}}$ to equation 15:

$$k_{obs} = \frac{k_1k_2}{k_{-1}} + \frac{k_1k_3B}{k_{-1}} + \frac{k_1k_4DMSO}{k_{-1}} \qquad (15)$$

Therefore, the slope of the lines in the plot should be the same; only their intercepts should vary. This is not the

case. In the absence of DMSO, the slope was 615, while at 0.1 and 0.13 M DMSO, it was 800 and 910 $M^{-2}sec^{-1}$, respectively.

The effect of 1,4-diaza[2.2.2.]bicyclooctane (DABCO)[137,138] and piperidine[137,138] has been ascribed to base catalysis. Although triethylamine is a tertiary amine like DABCO, no catalysis was observed.[137,138,140] This was attributed to steric factors.

Pietra and Fava[140] have also found that in the reaction of 2,4-DNFB with piperidine, the order of the reaction with respect to piperidine changed from one to two as the amine concentration increased. With 2,4-DNCB, the order remained at unity. Use of deuterated piperidine showed no measurable isotope effect. Since methanol was likewise shown to increase the rate, electrophilic catalysis by piperidine of the breaking of the carbon-fluorine bond in the rate-determining step was postulated. The absence of a deuterium isotope effect further required that breaking of the nitrogen-hydrogen bond was not involved in this step.

Other experiments with methanol have been reported using a constant concentration of the alcohol while varying the piperidine concentration.[137,138] The results are shown in Figure 1.

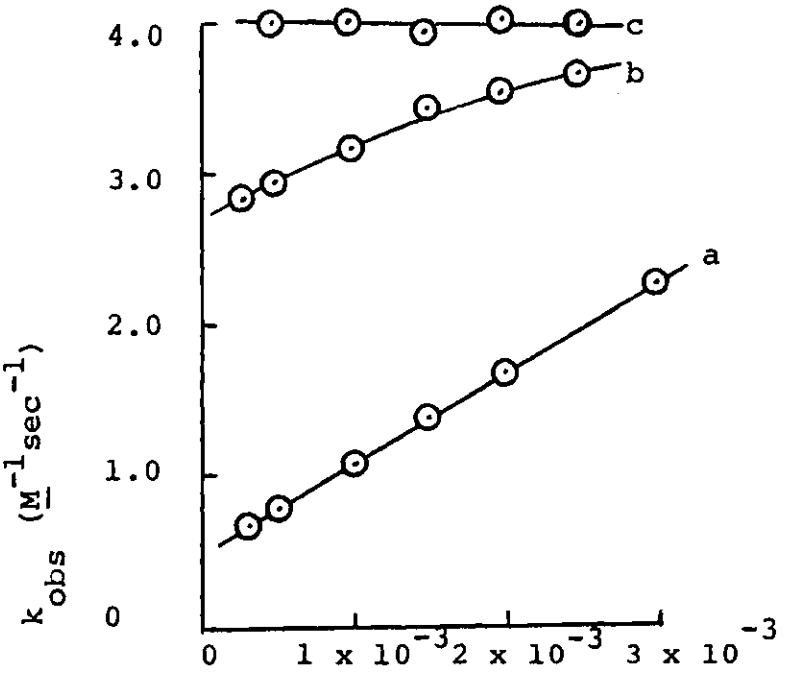


Figure 1. Rate Constants of the Reaction of Piperidine with 2,4-DNFB in the Presence of Added Methanol

a-without methanol

b-0.10 $\underline{M}$ methanol

c-0.15 $\underline{M}$ methanol

Since the catalytic coefficient for 0.05 M DABCO found by an analogous experiment was about three times that for methanol, it was anticipated that the same line would be produced by addition of 0.15 M methanol. However, this was not the case. From curve c of Figure 1, it can be seen that the rate constant is now independent of the concentration of piperidine, i.e., the rate is described by equation 12 in which k_{obs} is a constant and $k_{-1} << [k_2 + k_3B + k_4(\text{Additive})]$. The previous result with 0.05 M DABCO indicated that this behavior was not due to an overwhelmingly large concentration of methanol and thus the authors concluded that methanol catalyzes the reaction by increasing k_2 and k_3 and/or by lowering k_{-1}.

The behavior shown in Figure 1 has also been taken as substantial evidence for the Bunnett mechanism. By a one-step process analogous to an S_N2 displacement, such results are difficult to rationalize. However, as has been shown in the section concerning the mathematical treatment for the addition-elimination mechanism, such results are expected for the Bunnett mechanism due to a change in the rate-determining step.

As a parallel to the methanol study, 1,4-dioxane was also investigated.[139] Since the dielectric constant of

this cyclic ether is almost exactly that of the solvent benzene, no medium effects should be observed. However, no catalysis was observed either. Thus it was concluded that the acidic proton of methanol must be necessary for its activity.

The soluble salt tetra-n-butylammonium chloride shows a large catalytic effect[141] on the reaction of 2,4-DNFB with piperidine. The reaction with 2,4-DNCB showed no rate increase, however. Thus, it was postulated that the salt was involved in catalyzing the decomposition of the intermediate into products since the reaction with 2,4-DNCB showed no effect and is known to show rapid decomposition of the intermediate. Furthermore, non-basic anions such as perchlorate were not catalytic.

A search has likewise been made for evidence for acid catalysis in the reaction of piperidine with 2,4-DNFB.[141] Phenols were found to be catalysts; though within experimental error, no change in the catalytic effect was observed in changing the substituents, and hence the acidity, of the phenol. This was interpreted as bifunctional catalysis with a compensating effect between acid and base catalysis causing the lack of a change in rate with substituent. The acidic proton was involved, since anisole was

not effective as a catalyst.

Table 7. Rate Coefficients for the Reaction of 2,4-DNFB with Piperidine in Benzene at 25° in the Presence of Various p-X-substituted Phenols.[141]

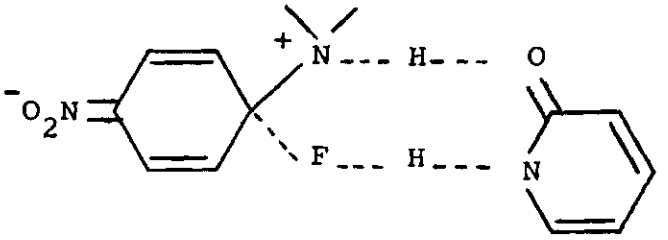
X =	OCH_3	H	Cl
$k(M^{-2}sec^{-1})$*	235 ± 16	201 ± 17	226 ± 13

* This is the catalytic coefficient value.

Bifunctional catalysis has also been postulated for the effect ofα-pyridone on the 2,4-DNFB reaction.[142] Addition of this compound dramatically increases the rate, while N-methyl-α-pyridone is not effective as a catalyst. Furthermore, neither additive affects the rate of reaction of piperidine with 2,4-DNCB. These results were rationalized with the Bunnett mechanism by assuming that the formation of the intermediate complex is rate-determining in the chloro case, while decomposition of the intermediate must be rate-limiting for the fluoro compound.

Since this very efficient catalyst α-pyridone is a much weaker base (in water) than pyridine and a much weaker acid (in water) than phenol, its activity was described as bifunctional. The catalyst was pictured as assisting in a

concerted separation of both the ammonium proton and the fluoride:



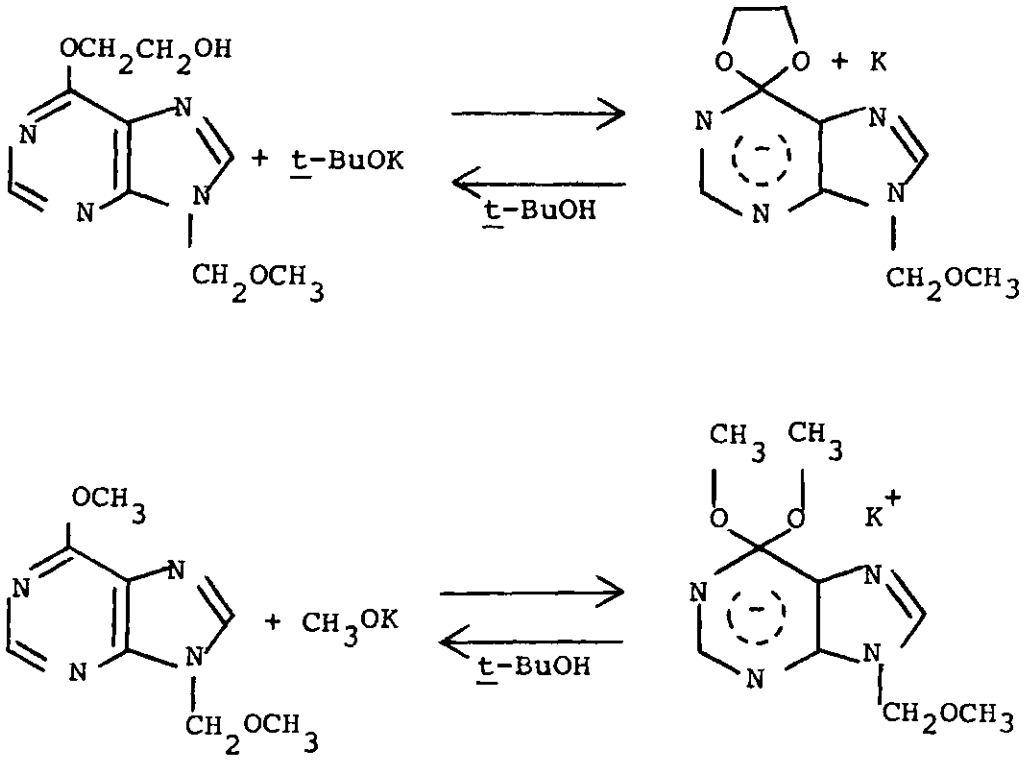
Nucleophilic heteroaromatic substitution has received less attention than substitution on benzene systems, particularly in non-polar, aprotic solvents. Fluorine vs. chlorine mobility in reactions with methanolic methoxide and with piperidine in a variety of solvents using 2-halogenopyridines, 2- and 4-halogenoquinolines, and 2-halogenoquinoxalines has been reported.[143] In all cases examined, the reactivity order $k_F > K_{Cl}$ was observed and the activation energy for fluorine displacement was lower than that for chlorine. Work has also been done on the reaction of 2- and 4-chloropyrimidines with piperidine in isooctane, benzene, methanol and dimethylformamide and the influence of substituents on chlorine mobility in the 2- and 4-positions.[144] A small positive isotope effect ($k_H/k_D = 1.25$) has been reported for the reaction of 4-fluoro-2-methoxyquinoline in neat piperidine or piperidine-N-d.[145] For the 2-fluoro-4-methoxyquinoline as well as for the 2- and 4-chlo-

roquinolines, no isotope effect was observed.

Some studies have been reported on purine systems, though these have been done in protic media. Barlin and Chapman[146] have examined the rates of reaction of 2-, 6-, and 8-chloro-9-methylpurine with piperidine in ethanol at 40°. The order of reactivity is 6 > 8 >> 2. A similar study used the same substrates with sodium ethoxide in ethanol at 20°. [147] Here, the 8-chloro isomer reacts faster than the 6-chloro isomer, while the 2-chloro is again the least reactive. Nucleophilic substitution by nitrogen, sulfur and oxygen compounds has been investigated in aqueous solution with 6-chloro-purine ribonucleoside.[148]

Two interesting σ-anionic (Meisenheimer) complexes have been observed in our group for the purine molecule.[149] Observation by nmr of the complexes formed from reaction of 6-(β-hydroxyethoxy)-9-methoxymethylpurine with potassium t-butoxide in t-butanol and of 6-methoxy-9-methoxymethyl-purine with potassium methoxide in t-butanol provide evidence for the formation of such intermediates in nucleophilic substitution reactions on this molecule.

Finally, work on nucleophilic aromatic substitution on 6-chloro-9-substituted purines has been the subject of two previous theses from our group.[150,151]



In spite of the variations in substrates, nucleophiles, solvents, catalysts and interpretation of catalytic effects, the Bunnett mechanism is still the most widely accepted mechanism for nucleophilic aromatic substitution.

CHAPTER VI

EXPERIMENTAL, NUCLEOPHILIC AROMATIC SUBSTITUTION

Instrumentation

All boiling points and melting points reported herein are uncorrected, and all temperatures are in degrees centigrade. Melting points were determined in Fisher capillary tubes on a Mel-Temp unit. Weights were determined on either a Mettler Type H 15 or Type B 6 balance. Solutions were prepared using a thick-walled Pyrex glass bath equipped with a Sargent thermonitor unit, model NSI-12, and an NBS calibrated 0°-100° thermometer. The slopes used in calculating rate constants were determined with the standard linear regression program of the Wang 700 A/B Electronic Calculator. Infrared spectra were obtained as thin liquid films (neat) or as potassium bromide pellets on a Perkin-Elmer Model 237B grating infrared spectrophotometer with the 1601.4 cm^{-1} absorption of polystyrene as a reference. All ultraviolet spectra and kinetic measurements were made on a Cary Model 14 Recording Spectrophotometer equipped with a variable speed chart drive and a Lauda Thermostated Constant Temperature Unit (range 0° to 100°). The reaction

temperatures were measured with an NBS calibrated 0°-100° thermometer inserted into the sample compartment. Standard 1.0 cm Beckman silica cells were used to contain samples and reaction mixtures. The nmr data were obtained on either a Varian A60D or a Varian T60 spectrometer. Mass spectra were determined with either a Varian M66 or a Hitachi Perkin-Elmer RMU-7L instrument. All exact mass determinations were run on the Hitachi. Elemental microanalyses were performed by Atlantic Micro-Laboratories, Atlanta, Georgia (C, H and N) and by Midwest Microlab, Ltd., Indianapolis, Indiana (F only).

Chemicals

A. C. S. Spectranalyzed isooctane (Fisher) was used without further purification. A. C. S. Spectranalyzed benzene (Fisher) was distilled from sodium (3 g per liter), bp 80.1° (740 mm) [lit[103] bp 80.1° (760 mm)]. Fisher certified t-butanol was also distilled from sodium (1 g per 500 ml), bp 82.0° (732 mm) [lit[103] 82.2°-82.3° (760 mm)]. Carbon tetrachloride (Fisher) was dried by distillation from phosphorus pentoxide, bp 76° (740 mm) [lit[103] bp 76.5 (760 mm)].

Piperidine (Fisher) was purified by distillation from sodium.[152] About 250 ml of piperidine was allowed to reflux over 6 g of sodium metal for six to 12 hr and dis-

tilled through a two-foot Vigreux column bp 105° (740 mm) [lit[103] bp 106° (760 mm)].

Dry acetone for use as an additive to the piperidine-fluoropurine reaction was prepared by distilling acetone (Fisher) from phosphorus pentoxide through a two-foot Vigreux column, bp 55.8° (743 mm) [lit[103] bp 56.2° (760 mm)].

Benzyl alcohol (Fisher) was distilled in Bantamware apparatus through a 15 cm Vigreux column, bp 202-203° (741 mm) [lit[103] bp 205° (760 mm)].

Both p-chlorobenzyl alcohol (Aldrich) and p-methylbenzyl alcohol (Aldrich) were recrystallized from isooctane. After drying overnight at room temperature in vacuuo, the p-chlorobenzyl alcohol had mp 73-74° [lit[153] mp 75°] and the p-methylbenzyl alcohol had mp 60-61° [lit[153] mp 61-62°].

Both 1-butanol (Fisher, Spectranalyzed) and methanol (Fisher) were purified by the method of Lund and Bjerrum.[154] The two alcohols were distilled through a two-foot Vigreux column, 1-butanol bp 117° (748 mm) [lit[103] bp 117° (760 mm)] and methanol bp 64.3° (737 mm) [lit[103] bp 65° (760 mm)].

2-Azacyclononanone (Aldrich) was sublimed at 0.2 mm with slight heating from a steam bath. The pure compound showed mp 77-78° (lit[155] mp 77-79°].

Tetrahydrofuran (Fisher) was distilled from sodium

metal, refluxed two hr over $LiAlH_4$, and distilled through a two-foot Vigreux column, bp 65.5-65.8° (741 mm) [lit[159] bp 65-66° (760 mm)].

Tetrahydropyran (Aldrich) was refluxed over $LiAlH_4$ for three hours and distilled through a two-foot Vigreux column, bp 87.4° (739 mm) [lit[103] bp 88° (760 mm)].

The compounds listed in Table 8 were all allowed to reflux over anhydrous barium oxide (Fisher) for two hr and distilled through a two-foot Vigreux column.

Table 8. Physical Data on the Purification of Additives

Compound	Boiling Point (Observed)	Boiling Point (Lit)[103]	Source
Pyridine	114.0°(740 mm)	115.5°(760 mm)	Fisher
Triethylamine	88.7°(738 mm)	89.3°(760 mm)	Eastman
2,6-Dimethyl-piperidine (a mixture of cis and trans isomers)	125.6°-126.0° (727 mm)	127.5°-128.3° (768 mm)	Aldrich
1-Aminobutane	76.8°(745 mm)	77.8°(760 mm)	Fisher
1,2-Ethanediamine	116.0°(748 mm)	116.5°(760 mm)	Fisher

The 6-chloro-9-methoxymethylpurine used to prepare the corresponding fluoropurine was obtained from Aldrich and was purified by recrystallization from a mixture of hexane isomers, mp 116-117°[lit[157] mp 117°].

6-Chloro-9-ethylpurine

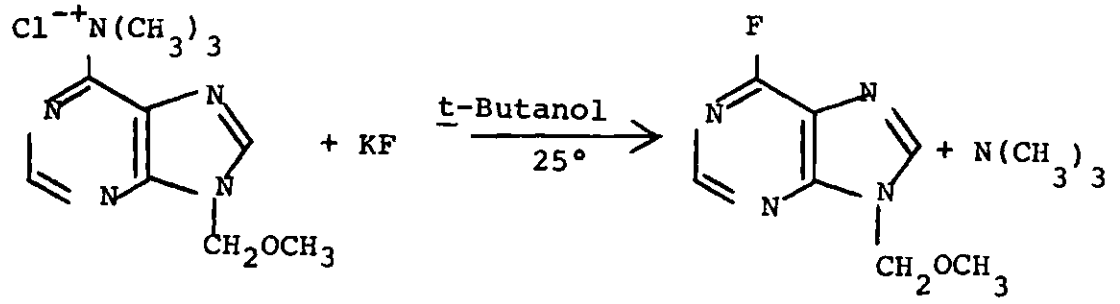
6-Chloro-9-ethylpurine was prepared by the method of Montgomery and Temple.[158] A 200-ml Erlenmeyer flask was charged with 2.0 g 6-chloropurine (Nutritional Biochemicals, 0.013 mole), 130 ml dry dimethylsulfoxide (Fisher), 1.88 g anhydrous potassium carbonate (Baker, 0.0136 mole), and 4.05 g ethyl iodide (Baker, 0.026 mole). The flask was tightly stoppered and stirred at room temperature for 16 hr. After this time, the reaction mixture was diluted with 130 g ice and extracted with two 100-ml portions of benzene and two 100-ml portions of ether. The organic extracts were each extracted with two 50-ml portions of water and dried ($MgSO_4$). These extracts were filtered under vacuum, combined, and concentrated on a rotary evaporator. The yellow solid was chromatographed on a silica gel (E. Merck Ag., Darmstadt, Germany, 70-325 mesh) column prepared with benzene in a 50-ml burette. Benzene was used to elute the yellow color, then 50/50 (V/V) benzene/ether was used to remove the 6-chloro-9-ethylpurine. Recrystallization from isooctane gave 200 mg (10%) of the white product: mp 79.5-80.0° [lit[158] mp 81-84°]; ultraviolet λ max 266 nm (ε 9600) [lit[158] λ max 266 (ε 9340)].

Trimethyl-9-methoxymethylpurin -6-ylammonium chloride

This compound was prepared by a slight modification of the procedures of Kiburis and Lister.[159,160] A one-liter, three-necked, round-bottomed flask equipped with a reflux condenser and calcium chloride drying tube, two stoppers, and a magnetic stirrer was charged with 400 ml of dry benzene and 1.34 g recrystallized 6-chloro-9-methoxymethylpurine (Aldrich, 0.00677 moles). To the stirred solution was added in one portion about 12 ml of anhydrous trimethylamine (Eastman, ca. 0.13 mole). The solution was stirred at room temperature for 11 hr after which time a precipitate had formed. This was quickly collected by filtration under vacuum and dried at room temperature in vacuo. The off-white solid (1.50 g, 86%), which was stable for weeks at room temperature when stored in a desiccator, had the following properties: mp ca. 110°-112°, probably with decomposition; infrared absorption (KBr pellet) at 2940 cm^{-1} (broad, amine salt); and nmr peaks (D_2O, external TMS) at δ 9.00 (1 H singlet, purine ring H), at 8.86 (1 H singlet, purine ring H), at 5.78 (2 H singlet, CH_2), at 3.84 (9 H singlet, $N(CH_3)_3$) and at 3.32 (3 H singlet, OCH_3).

6-Fluoro-9-methoxymethylpurine

A one-liter, single-necked, round-bottomed flask equipped with a magnetic stirrer and a $CaCl_2$ drying tube



was charged with 500 ml of dry t-butanol, 1.56 g of anhydrous potassium fluoride (Allied Chemical Company, 0.0269 mole), and 1.50 g of trimethyl-9-methoxymethylpurin-6-ylammonium chloride. The reaction was stirred at room temperature for 15 hr. After this time, the reaction mixture was filtered under vacuum and the t-butanol was removed on a rotary evaporator at ca. 40°. The solid residue was recrystallized from a mixture of hexane isomers and dried 15 hr at room temperature in vacuo.

The stable, white solid (0.760 g, 71%, 62% overall) showed the following properties: mp 62.5-63.0°; infrared absorptions (KBr pellet) at 1620 and 1575 cm^{-1} (pyrimidine) and at 1090 cm^{-1} (ether CO); nmr peaks (CCl_4, external TMS) at δ 8.78 and 8.46 (1 H each, each a singlet, purine ring H), at 5.90 (2 H singlet, CH_2) and at 3.66 (3 H singlet, $-OCH_3$); ultraviolet λ max isooctane 246 (ε 5500) and 239 nm (ε 5700); and mass spectrum m/e 182.0606 (calculated

182.0604) and abundant fragments at 152, 151, 45 and 28.

Analysis:

Calc'd for $C_7H_7N_4OF$: C, 46.14; H, 3.88; F, 10.44; N, 30.77.

Found C, 46.11; H, 3.91; F, 10.28; N, 30.61.

6-Piperidino-9-methoxymethylpurine

The product of the reaction being studied was prepared in sufficient quantity for definite identification. To a 50.0-ml volumetric flask was added 0.272 g of 6-fluoro-9-methoxymethylpurine (0.00149 mole, 0.0298 M in solution) and about 20 ml of isooctane (Fisher, Spectranalyzed). To this suspension was added 20 ml of piperidine (Fisher, 0.20 mole, 4.0 M in solution) and enough isooctane to bring the total volume of solution up to the mark. A magnetic stirring bar was added and the reaction was stirred for 12 days at room temperature. After this time, the reaction mixture was filtered under vacuum and the solvent and excess piperidine were removed on a rotary evaporator. The resulting oil was crystallized twice from hexane and dried overnight in vacuo. The white material (0.273 g, 74%) had the following properties: mp 74.5-75.5°; infrared absorptions (KBr pellet) at 2925 and 2860 cm^{-1} (aliphatic CH), at 1575 cm^{-1} (pyrimidine) and at 1100 cm^{-1} (ether CO); nmr peaks (CCl_4, internal TMS) at δ 8.15 and 7.75 (1 H each, each a singlet, purine

ring H), at 2.45 (2 H singlet, CH_2), at 4.25 (4 H multiplet, piperidine CH_2), at 3.30 (3 H singlet, OCH_3), and at 1.70 (6 H multiplet, piperidine CH_2); ultraviolet $\lambda_{max}^{isooctane}$ 295.6 (ε 10.300), 284.0 (ε 18,300), and 275.3 nm (ε 18,800); mass spectrum m/e 247.14355 (calc'd 247.14331) and abundant fragments at 202, 174, 84, 45, 32 and 28. The λ max and ε values for this pure compound agree well with those found in representative reaction mixtures used for kinetic data.

Piperidine-N-d

Piperidine-N-d was prepared by the method of Hawthorne.[161] A dry 250-ml round-bottomed flask equipped with a distilling head with a calcium chloride drying tube was charged with 102 g of piperidine (Fisher, 1.2 moles), 30 ml of deuterium oxide (99.8%, 1.5 moles), and 5.0 ml of deuterated phosphoric acid (prepared by reacting phosphorus pentoxide with deuterium oxide). The solution was allowed to reflux for 12 hr. After this time, about 50 ml of the mixture was distilled off and 30 ml of deuterium oxide and 3 ml of deuterated phosphoric acid was added. The reaction was refluxed for an additional 44 hr. The crude piperidine-N-d was distilled from this flask, bp 100-103° (740 mm) and was then distilled twice from sodium metal. The fraction used for kinetic runs boiled at 105° (745 mm) [lit[161]

106.3 (760 mm)]. The nmr spectrum of the product showed no N-h peak.

Kinetic Procedure

General

Solutions of piperidine used in this work were prepared by dilution from a stock solution of piperidine in isooctane or benzene. Piperidine was added to a weighed 100-ml volumetric flask and the flask and contents were then reweighed. About 80 ml of solvent was added and the solution was allowed to equilibrate to 25.0° in a water bath for 15 minutes. After this time, more solvent at 25.0° was added to bring the total volume to within a few drops of the mark on the flask, the solution was shaken to thoroughly mix the components, and was allowed again to equilibrate for 15 minutes. The final addition of solvent brought the total volume up to the mark. Kinetic solutions were prepared by diluting pipetted samples of this stock at 25.0° to the mark at 25.0° in 50.0-ml volumetric flasks. To ensure reproducibility of the kinetic data, two or three different initial stock solutions were used for each set of points at a given temperature.

To prepare the stock solution of purine, a stoppered, 10-ml flask was weighed on the micro balance, then the

purine was added and the flask and contents were reweighed. About 8 ml of solvent was added to the flask to dissolve the purine and was transferred to a 100.0 ml volumetric flask. This washing procedure was repeated five to ten times to ensure quantitative transfer of the purine. Once the purine had been added, enough solvent was added to the volumetric flask to give a total volume of about 80 ml, the flask was equilibrated to 25.0° in the water bath and was diluted to the mark in the manner previously described. The solutions used for kinetics were dilutions of this stock calculated to produce a concentration of purine of about 1×10^{-4} M at 25.0°.

The solutions of piperidine and catalysts (except for 2-azacyclononanone) were prepared by weighing the catalyst in a weighed 10.0-ml volumetric flask, adding a solution of piperidine in isooctane at 25.0° with a pipette, and diluting the mixture of piperidine and catalyst to the mark at 25.0° with isooctane as previously described.

The solutions using 2-azacyclononanone as a catalyst were prepared by pipetting various volumes from a stock solution at 25.0° into a 10.0-ml volumetric flask. The appropriate amount of stock piperidine solution at 25.0° was then pipetted into the same flask and the mixture was

diluted to the mark with isooctane as before.

All of the reaction rates reported in this thesis were determined using u.v. spectrophotometry. The Cary 14 u.v. spectrophotometer was set at a fixed wavelength corresponding to one of the maxima of the product 6-piperidino-9-methoxymethylpurine. The two wavelengths used throughout this thesis were 284.0 and 295.6 nm. It has been previously shown[150] that the observed rate of reaction does not vary with a change in the wavelength monitored. The compartment of the instrument was maintained at a constant temperature with a Lauda Thermostated Constant Temperature Unit. One cell of a matched pair was designated as the reference cell and an equal volume of piperidine solution and of pure solvent was mixed in it. In the reactions involving an added catalyst, equal volumes of piperidine and catalyst solution and of solvent were mixed. The two cells, the flasks containing the piperidine and purine solutions, and a Hamilton gas-tight syringe were placed into the thermostated compartment of the Cary 14 and allowed to equilibrate for 20 minutes. The syringe, which had been adjusted previously with its Chaney adapter to deliver 1.5 ml, was filled with the nucleophile solution and left to equilibrate in the compartment for 15 minutes. The volume of solution was then adjusted

with the Chaney adapter to precisely 1.5 ml and the solution injected into the cuvette. The syringe was thoroughly washed with about ten portions of acetone and dried with an air gun and a dry nitrogen jet. After cleaning, the syringe was filled with purine solution and left inside the compartment to equilibrate. When equilibrium was reached, the Cary was turned on and allowed to warm up for about 10 minutes. The syringe was then withdrawn, the volume of solution adjusted to 1.5 ml, and the solution forcefully injected into the cuvette. The force of the injection proved sufficient to mix the components thoroughly. The lid on the compartment was quickly replaced and the master switch on the instrument was turned on. The instrument then produced a plot of absorbance of the product piperidinopurine vs. time.

Reactions run at 10.0° were done in a different manner. A short pipette was fabricated to hold about 1.5 ml. This was placed into the thermostated compartment with the purine and the piperidine solutions to equilibrate. When equilibrium was reached, the pipette was withdrawn, a portion of the piperidine solution was drawn up to the mark and then drained into the cuvette. The pipette was then thoroughly cleaned with acetone, replaced into the compart-

ment to equilibrate, and used in a similar fashion to deliver a volume of purine solution equal to that of piperidine solution. The cuvette was tightly capped, shaken, placed into the instrument, and the reaction was followed as before.

All of the reactions reported herein were run under pseudo-first-order conditions with the nucleophile at least 100 times the concentration of the purine. To check the assumption that true, pseudo-first-order kinetics were indeed being followed, reactions were run in which the concentration of piperidine was held constant while the concentration of purine varied. A run using 6.65×10^{-5} M purine with 0.0224 M piperidine was made in isooctane at 25.0° by the previously described procedure. The calculated rate constant was 0.159 $sec^{-1}M^{-1}$.

The initial purine solution was then diluted tenfold and another run was made using the same piperidine solution and identical experimental conditions. Due to the low absorbance value of the resulting piperidinopurine, 10.0 cm Beckman silica cells were used to bring the observed absorbance value to about that of the former run. The kinetic procedure here was slightly different. Solutions of the purine (6.65×10^{-6} M) and the piperidine were contained in 10.0-ml volumetric flasks filled to the mark. These and

the u.v. cells were equilibrated in the instrument compartment for 20 minutes. The reference cell contained 10.0 ml of piperidine solution and 10.0 ml of isooctane. After equilibration, the two flasks were carefully emptied into the cell. The cell was capped, shaken, replaced into the compartment, and the reaction was monitored at 295.6 nm. The calculated rate constant for this run was 0.151 $sec^{-1}\underline{M}^{-1}$ which agrees well with the previous rate constant. This result shows that a ten-fold dilution of the purine does not affect the rate of the reaction at constant piperidine concentration, and thus true pseudo-first-order kinetics are indeed being observed.

The data obtained from the Cary 14 were treated using the Guggenheim method[162,163] which allows determination of the rate constant without having to know the absorbance at infinite time. From the absorbance vs. time data taken from the Cary 14, absorbance values were taken at times t_1, t_2, t_3, . . ., and at times $t_1 + \Delta$, $t_2 + \Delta$, $t_3 + \Delta$, . . ., where Δ is a constant time increment equal to two to three half-lives of the run. The Guggenheim equation may be written as $\ln(A_{t+\Delta} - A_t) = -kt + \text{constant}$, where $A_{t+\Delta}$ is the absorbance value at time $(t + \Delta)$ and A_t is the absorbance value at time t. A plot of log $(A_{t+\Delta} -$

A_t) *vs.* time produces a straight line with a slope of -k/2.303. Since the reaction was run under pseudo-first-order conditions, this k is the pseudo-first-order rate constant, k_{pseudo}. The second-order rate constant is found by dividing k_{pseudo} by the concentration of the piperidine used.

Density Correction Factor[150]

A 50.0-ml volumetric flask whose neck was marked at exact intervals was filled to the mark with benzene at 25.0°. To this was added with a pipette 2.0 ml of benzene at 25.0°. By recording the graduation to which the volume rose, the volume increment per graduation was determined. The flask was then refilled to the 50.0-ml mark at 25.0°, stoppered tightly, and allowed to equilibrate to either 40.0° or 10.0° in the Cary 14 u.v. compartment. After equilibration, the flask was removed, the volume of benzene determined from the graduations, and the ratio of the volumes at 25.0° and at the reaction temperature was determined (V_{25}/V_{rxn}). This ratio, the density correction factor, was then used to determine the corrected $k_{observed}$ values by dividing all of the second-order rate constants by this factor.

The density correction factors used for isooctane were taken from a graph of temperature *vs.* the density

Table 9. Density Correction Data for Benzene.

Reaction Temperature (°C)	Volume at Reaction Temperature (V_{rxn})	Volume at 25.0°C (V_{25})	Correction Factor (V_{25}/V_{rxn})
10	48.76	49.60	1.017
25	50.00	50.00	1.000
40	50.92	50.00	0.982

Table 10. Density Correction Data for Isooctane.

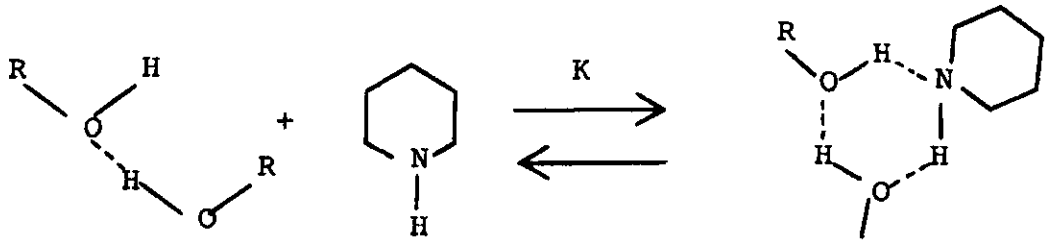
Reaction Temperature (°C)	Correction Factor (V_{25}/V_{rxn})
10	1.020
25	1.000
40	0.984

correction factors found by Don Weser.[150] The values used in the kinetics in this thesis are tabulated in Table 10.

Calculation of the Effects of Association of the Catalytic Alcohols with Piperidine[150]

Calculations were done to correct the observed rate constants for association of the catalytic alcohols with the nucleophile piperidine. The equilibrium in question is between the alcohol, which is assumed to be dimeric in the concentration range investigated, and an associated

piperidine-dimer species which is assumed to be neither nucleophilic nor catalytic:



9 10 11

The calculation involves assuming an equilibrium constant K varying from K = 1 to K = 6 and substituting into the expression

$$K = \frac{x}{[\text{alcohol dimer-x}]\ [\text{piperidine-x}]}$$

in which

x = unknown concentration of the associated piperidine-dimer species (11),

[alcohol dimer-x] = the "free" alcohol dimer, i.e., the formal concentration of the dimer minus that quantity associated with piperidine,

[piperidine-x] = the "free" concentration of piperidine, i.e., the formal concentration minus that associated with the alcohol dimer.

By finding the "free" values for piperidine, k'_{obs} may be calculated by dividing k_{pseudo} (the pseudo-first-order rate constant) by the concentration of "free" piperidine. Subtracting the value of the second-order rate constant corresponding to the "free" piperidine concentration

(from Figure 3) gives the k_{obs} value for the concentration of "free" dimeric alcohol. These k_{obs} values were then plotted against the concentration of dimeric alcohol.

However, plots of the concentration of dimeric alcohol *vs.* k_{obs} became linear above very low concentrations of alcohol, and linearity was not improved by assuming increasing values of K. Further, the slope of the graph (the catalytic coefficient) varied by a maximum of 40% for the three alcohols in going from k = 1 to k = 6. Thus, the assumption was made that the alcohol is predominantly dimeric and unassociated with the piperidine. These assumptions will give reasonable minimum values for the catalytic coefficients.

CHAPTER VII

RESULTS AND DISCUSSION

Nucleophilic Substitution on 6-Fluoro-9-Methoxymethylpurine

The purpose of this kinetic study was to elucidate the mechanism of nucleophilic aromatic substitution by piperidine on 6-fluoro-9-methoxymethylpurine in isooctane for comparison with a study already made on 6-chloro-9-ethylpurine with similar conditions and catalysts.[150] It has been found that the Bunnett mechanism readily accounts for the experimental observations. Appendixes 1 and 2 give a tabulation of the second-order rate constants for the reaction of the fluoro compound in isooctane at 10.0°, 25.0°, and 40.0°. All temperatures are ± 0.1° and rate constants have a maximum error of about ± 3 per cent. Plots of k_{obs} *vs.* concentration of piperidine-N-*h* and -N-*d* for these three temperatures (Figures 2, 3, and 4) show that the second-order rate constant (k_{obs}) increases linearly with the concentration of piperidine. As discussed in Chapter 1, this is to be expected for the Bunnett mechanism:

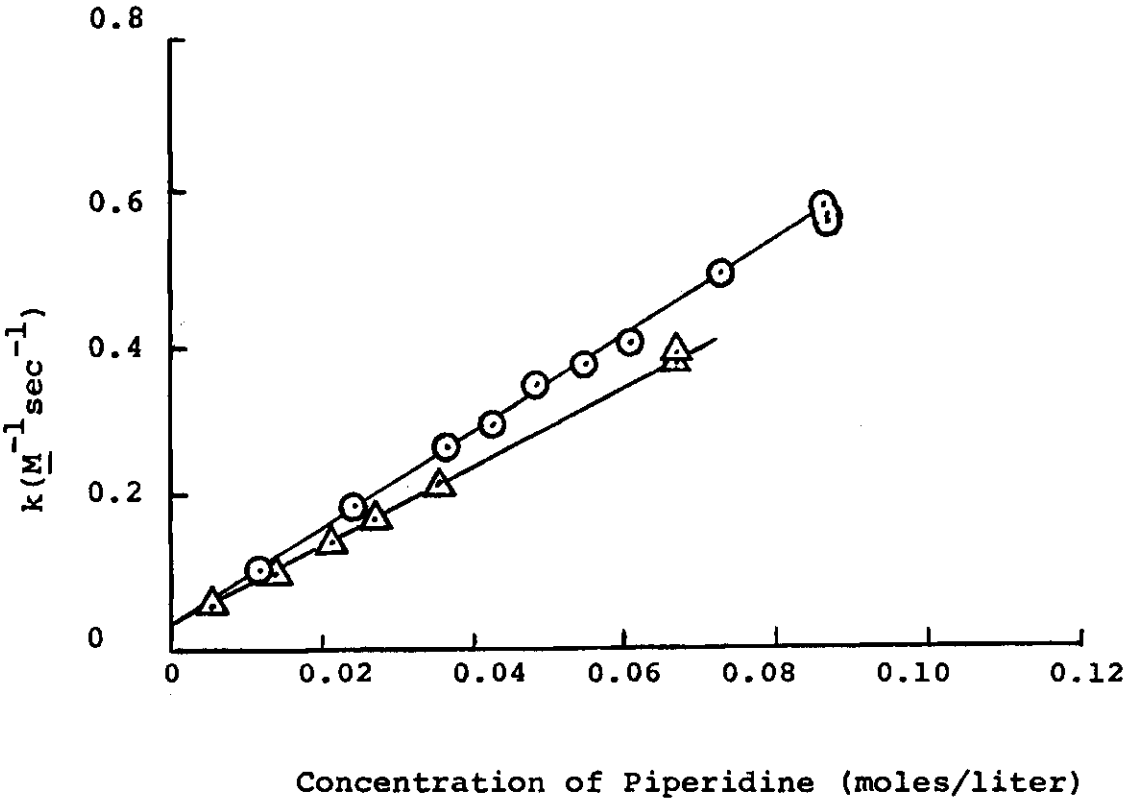


Figure 2. Piperidine-Purine Reactions at 10.0°.

⊙ -Pip-N-h

△ -Pip-N-d

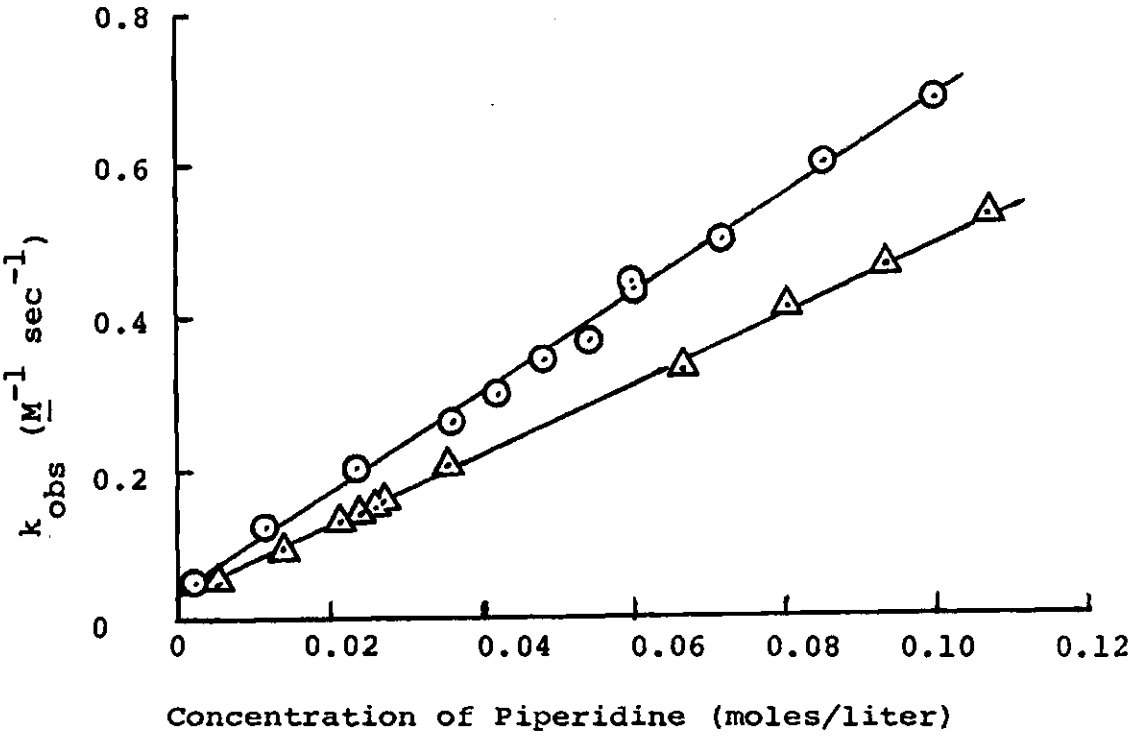


Figure 3. Piperidine-Purine Reactions at 25.0°

⊙ -Pip-N-h

△ -Pip-N-d

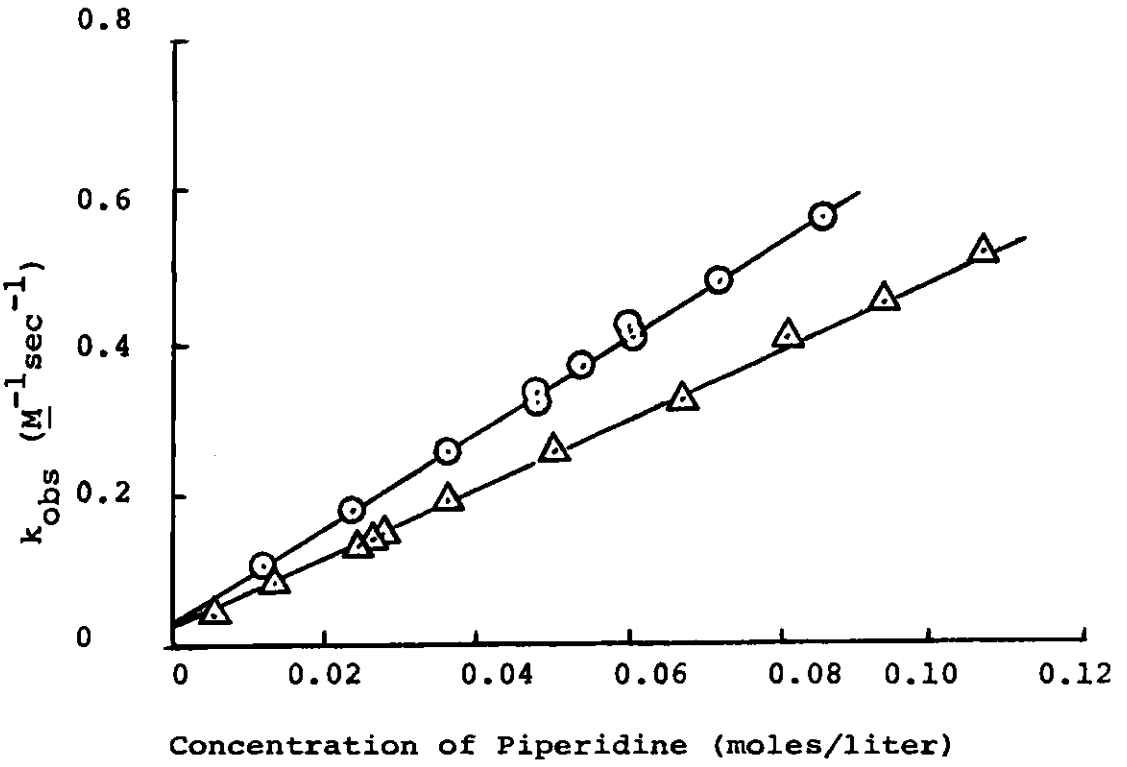
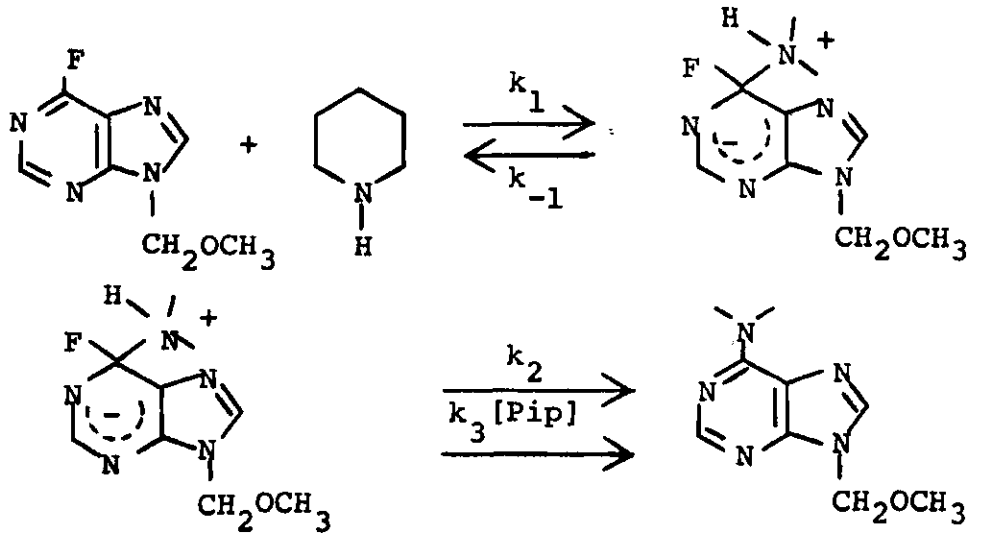


Figure 4. Piperidine-Purine Reactions at 40.°

⊙ -Pip-N-h

△ -Pip-N-d



Using the steady-state approximation as outlined earlier,

$$k_{obs} = \frac{k_1 k_2 + k_1 k_3 B}{k_{-1} + k_2 + k_3 B}$$

If $k_{-1} >> (k_2 + k_3 B)$, this equation reduces to:

$$k_{obs} = \frac{k_1 k_2}{k_{-1}} + \frac{k_1 k_3 B}{k_{-1}}$$

At low concentration of amine, a plot of k_{obs} vs. concentration of piperidine should be linear as is observed.

At higher concentrations of amine, curvature of these plots should occur until a point is reached at which $k_{-1} << (k_2 + k_3 B)$ and the plot becomes a horizontal line

with $k_{obs} = k_1$. In the case of the 6-chloro-9-ethylpurine,[150] curvature is indeed apparent. This behavior is further evidence for the Bunnett mechanism.

The extent of association of piperidine in isooctane was also investigated in the previous work.[150] Using vapor pressure studies, it was concluded that at relatively low concentrations the piperidine is primarily monomeric. This conclusion was considered valid up to a concentration of about 0.8 M piperidine. Since the fluoropurine study has concentrations of less than 0.1 M, it is assumed that the reactant piperidine is essentially monomeric over the concentration range used. Further evidence comes from other workers who have used nmr techniques to determine that diethylamine in cyclohexane[164] or carbon tetrachloride[165] is essentially monomeric below 0.1 M.

From the plots shown in Figures 2, 3 and 4, rate coefficients may be determined for the catalyzed ($\frac{k_1 k_3}{k_{-1}}$, slope) and uncatalyzed ($\frac{k_1 k_2}{k_{-1}}$, intercept) steps using the Bunnett mechanism. For comparison, the data are also tabulated for the chloropurine system.[150]

An anomaly in the chloropurine work was apparent in the reaction with piperidine-N-h at 49.5°. In the k_{obs} vs. concentration of piperidine plot, the curve for piperidine-

Table 11. Rate Data for the Reaction of Piperidine-N-h and -N-d with 6-Fluoro-9-Methoxymethylpurine in Isooctane.

Temperature (°C)	Catalyzed (Slope, $M^{-2}sec^{-1}$)	Uncatalyzed (Intercept, $M^{-1}sec^{-1}$)	Slope/ Intercept Ratio
	Piperidine-N-h		
10.0°	6.2 ± 0.6	0.03 ± 0.01	197
25.0°	6.4 ± 0.2	0.032± 0.004	204
40.0°	6.2 ± 0.3	0.030± 0.007	202
	Piperidine-N-d		
10.0°	5.2 ± 0.2	0.028 ± 0.005	183
25.0°	4.66 ± 0.08	0.024 ± 0.002	191
40.0°	4.6 ± 0.2	0.021 ± 0.007	214

Table 12. Rate Data for the Reaction of Piperidine-N-h and -N-d with 6-Chloro-9-Ethylpurine in Isooctane.

Temperature (°C)	Catalyzed (Slope, $M^{-2}sec^{-1}$)	Uncatalyzed (Intercept, $M^{-1}sec^{-1}$)	Slope/ Intercept Ratio
	Piperidine-N-h		
4.75°	5.50×10^{-3}	1.72×10^{-4}	32.0
29.75°	1.29×10^{-2}	4.45×10^{-4}	29.0
49.5°	2.07×10^{-2}	1.06×10^{-3}	19.5
	Piperidine-N-d		
4.75°	-----	-----	-----
29.75°	1.43×10^{-2}	4.61×10^{-4}	31
49.5°	2.69×10^{-2}	9.32×10^{-4}	29

N-h crossed that for piperidine-N-d. This was resolved by repeating the work. The data included in Table 12 are the corrected values. The k_{obs} and concentration of piperidine values are collected in Appendix 3.

Several points may be taken from the tabulated data. Most apparent is the fact that the usual order of halogen mobility, F > Cl, is observed. The most startling finding is that the fluoropurine reaction shows virtually no temperature dependence. This is displayed graphically in Figure 5. Although difficult to interpret, these results may be rationalized by assuming that the first step of the mechanism is a reversible equilibrium between the reactants and the σ-anionic (Meisenheimer) complex which is shifted toward reactants with increasing temperature. An effect similar to this has been used to explain the decrease in rate with increasing temperature in the reaction of nitric oxide with oxygen.[166]

A second point may be taken from the slope/intercept ratios for the fluoropurine versus those for the chloropurine. The ratios are considerably larger for the fluoro case. These ratios give a measure of the effect of catalysis on the reaction, since the value is actually k_3/k_2, a ratio of the catalyzed to the uncatalyzed pathways. Thus, the change in halogen from chlorine to fluorine results in

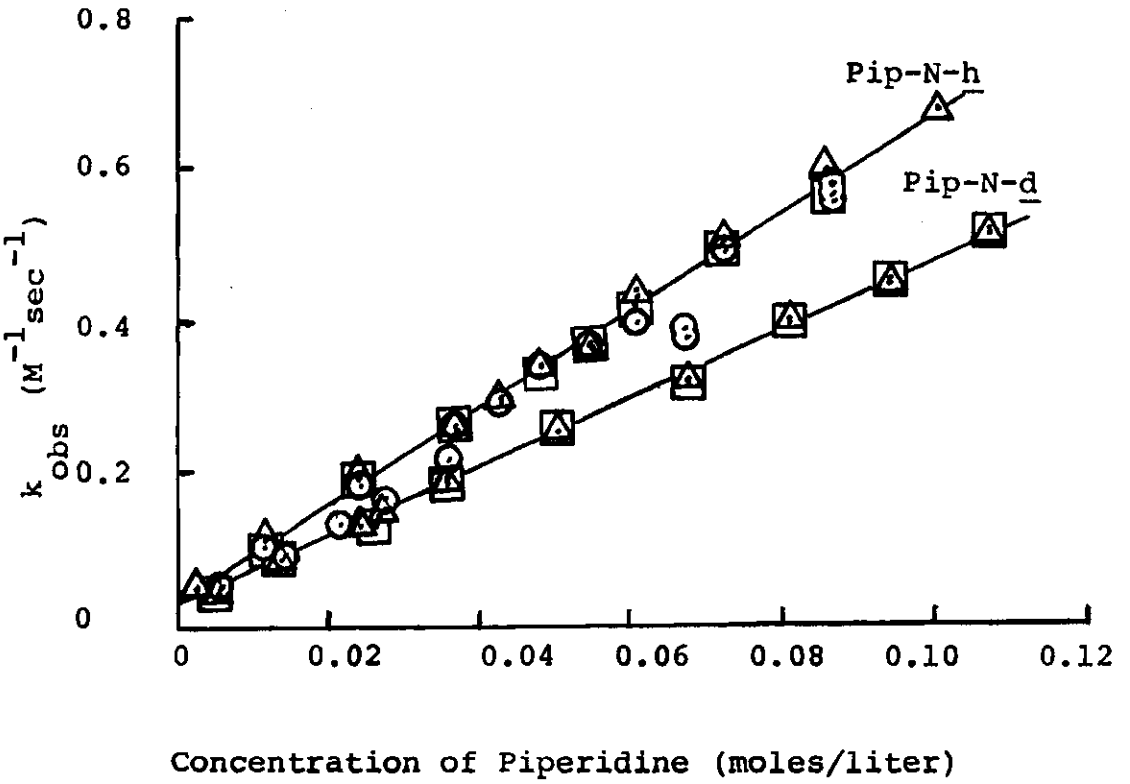


Figure 5. Reaction of Piperidine-N-h and -N-d with 6-Fluoro-9-Methoxymethylpurine in Isooctane at Various Temperatures

10.0° ⊙

25.0° △

40.0° ⊡

a much stronger catalysis of the decomposition of the intermediate complex.

Deuterium isotope effects have long been used as a mechanistic tool. With the data collected for piperidine-N-h and -N-d, isotope effects may be calculated by determining the slope ratios from the k_{obs} vs. concentration of piperidine plots. These values give k_{3H}/k_{3D}, indicating that the isotope effect is in the k_3 step. No isotope effect is found in k_2 since the intercepts are identical for both piperidines. The isotope effects are summarized in Table 13.

Table 13. Slope Ratios (k_H/k_D) for the Reaction of 6-Fluoro-9-Methoxymethylpurine with Piperidine in Isooctane.

Temperature (°C)	Slope Ratio (k_H/k_D)
10.0°	1.2 ±0.1
25.0°	1.38 ±0.05
40.0°	1.35 ±0.09

Invariably, kinetic deuterium isotope effects for nucleophilic aromatic substitution reactions are smaller than might be expected.[133] These observed effects, though

small, may be attributed to a primary isotope effect due to the breaking of the nitrogen-hydrogen bond in the rate-determining step. This is consistent with the proposed Bunnett mechanism in which decomposition of the intermediate complex is rate-determining. Since this decomposition is catalyzed by a second molecule of piperidine in the k_3 step, such an isotope effect would be expected in k_3. In contrast, the chloropurine reaction has k_H/k_D values of about 0.9 at both 29.75° and 49.5°.[150]

Further information may be extracted from the data gathered. If the reciprocal of equation 10 is taken,

$$k_{obs} = \frac{k_1k_2 + k_1k_3B}{k_{-1} + k_2 + k_3B} \qquad (10)$$

the following relation arises:

$$1/k_{obs} = \frac{k_{-1} + k_2 + k_3B}{k_1k_2 + k_1k_3B}$$

$$= \frac{k_{-1}}{k_1k_2 + k_1k_3B} + \frac{k_2 + k_3B}{k_1k_2 + k_1k_3B}$$

$$= \frac{k_{-1}}{k_1k_2 + k_1k_3B} + \frac{1}{k_1}$$

If $k_1k_3B >> k_1k_2$ (at high concentration of piperidine), then

$$1/k_{obs} = \frac{k_{-1}}{k_1k_3}\left[\frac{1}{B}\right] + \frac{1}{k_1}$$

Therefore, a plot of $1/k_{obs}$ *vs.* 1/piperidine will give a line of slope equal to k_{-1}/k_1k_3 and intercept equal to $1/k_1$. From this intercept, values of k_1 may be found. These are collected in Table 14.

Table 14. Values for k_1 for the Reaction of 6-Fluoro-9-Methoxymethylpurine with Piperidine in Isooctane.

Temperature (°C)	Pip-N-*h* k_1 ($M^{-1}sec^{-1}$)	Pip-N-*d* k_1 ($M^{-1}sec^{-1}$)
10.0°	2.7 ± 0.6	2.08 ± 0.09
25.0°	2.0 ± 0.4	2.4 ± 0.5
40.0°	5.6 ± 0.3	4.4 ± 1.5

For comparison, the values of k_1 for the 6-chloro-9-ethylpurine reaction[150] were 0.0277 ± 0.0138 $M^{-1}sec^{-1}$ (29.75°) and 0.0263 ± 0.0130 (49.5°) with piperidine-N-*h* and 0.0231 ±

0.0115 (29.75°) and 0.0345 ± 0.0172 (49.5°) for piperidine-N-d. An increase in k_1 with temperature is generally apparent for both purines. Furthermore, the values for the fluoro compound are about 100 times greater than those of the chloro compound.

In order to understand the catalysis step of the mechanism better, various additives were tested for their effect on the reaction rate. By the mathematical treatment of the mechanism given in Chapter V:

$$k_{obs} = \frac{k_1 k_2}{k_{-1}} + \frac{k_1 k_3 B}{k_{-1}} + \frac{k_1 k_4 (\text{Additive})}{k_{-1}} \qquad (14)$$

Thus, at a constant concentration of the nucleophile B, a plot of k_{obs} vs. concentration of additive will be linear with a slope equal to $\frac{k_1 k_4}{k_{-1}}$ (the catalytic coefficient). Each catalyst was tested to be sure it did not react appreciably with the fluoropurine during the time span of the reaction.

Several additives produced no effect. These are listed in Table 15. The complete set of rate constants are given in Appendix 4.

If proton removal from the intermediate complex was the sole factor involved in catalysis, these compounds

Table 15. Additives Which Had No Effect on the Reaction of Piperidine with 6-Fluoro-9-Methoxymethylpurine.

Additive	Additive Concentration (moles/liter)
Triethylamine	0.0 - 0.109
2,6-Dimethylpiperidine	0.0 - 0.147
Tetrahydrofuran	0.0 - 0.125
Tetrahydropyran	0.0 - 0.100
Acetone	0.0 - 0.152
Pyridine	0.0 - 0.155

would show a catalytic effect since all are Lewis bases. Triethylamine may have a steric factor associated with it to preclude any effect, but pyridine, acetone or the ethers should not be subject to such restrictions. Although piperidine itself is catalytic, 2,6-dimethylpiperidine (a mixture of cis and trans isomers) was not. This can be easily rationalized by its added steric encumbrance.

From the additives used thus far, it appears that simple base catalysis is not effective. The same result was also found with 6-chloro-9-ethyl purine.[150]

Other additives such as amines, alcohols and a cyclic lactam were tried. In these cases, catalysis was evident. By far the most powerful catalyst was the lactam 2-azacyclononanone. From these observations, it appears

that a proton bound to an electronegative atom is essential for catalysis. The additives and their catalytic coefficients are shown in Table 16. The complete set of data is in Appendix 5.

Table 16. Catalytic Constants for Additives in the Reaction of Piperidine with 6-Fluoro-9-Methoxymethylpurine and 6-Chloro-9-Ethylpurine in Isooctane (Assuming No Association)

Catalyst	Catalytic Coefficient $\left(\frac{k_1 k_4}{k_{-1}} \ \underline{M}^{-2}\text{sec}^{-2}\right)$	
	6-Chloro(at 29.75°)	6-Fluoro(at 25.0°)
Pyridine	9.16×10^{-4}	No effect
n-Butyl Amine	1.16×10^{-2}	4.34
Ethylenediamine	1.17×10^{-2}*	4.12*
Piperidine	1.29×10^{-2}	6.4
2-Azacyclononanone	27.6×10^{-2}	347
t-Butanol	5.18×10^{-2}	8.8
Methanol	8.54×10^{-2}	29.2
1-Butanol	9.44×10^{-2}	21.6

*Statistically corrected for the presence of two amine groups.

As might be expected, the catalytic coefficients for the fluoro molecule are about two orders of magnitude larger than those for the chloro molecule. This is consistent with the earlier observation that the k_3/k_2 ratio was much larger for the fluoropurine.

Varying the constant concentration of the piperidine

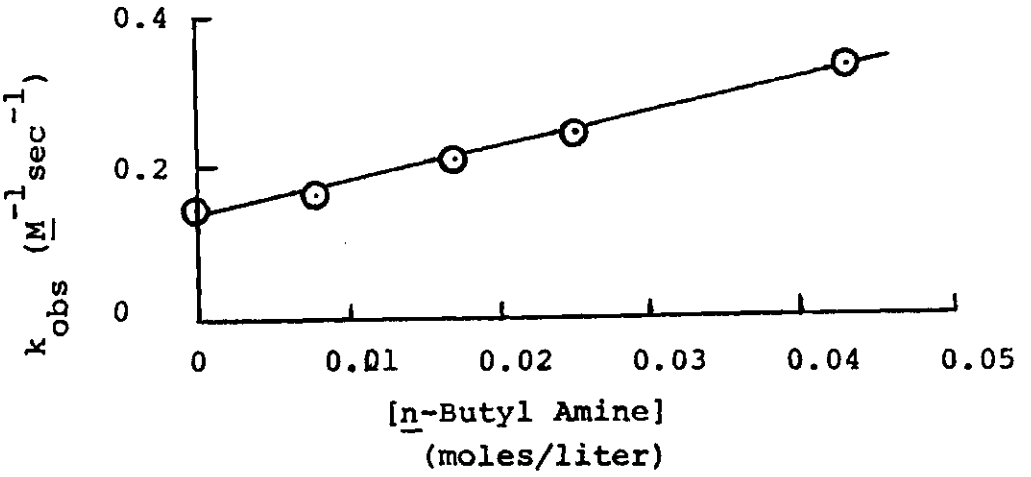


Figure 6. Addition of n-Butyl Amine to the Piperidine-Purine Reaction

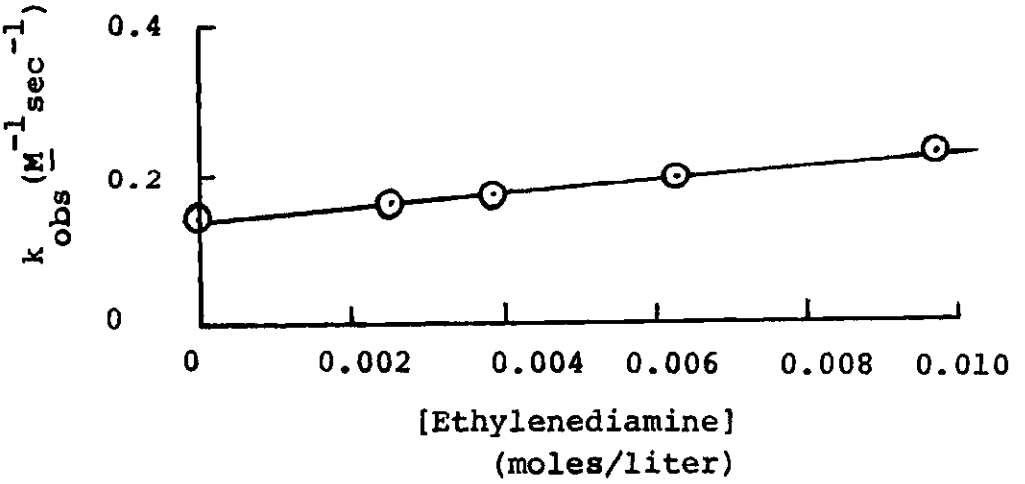


Figure 7. Addition of Ethylenediamine to the Piperidine-Purine Reaction

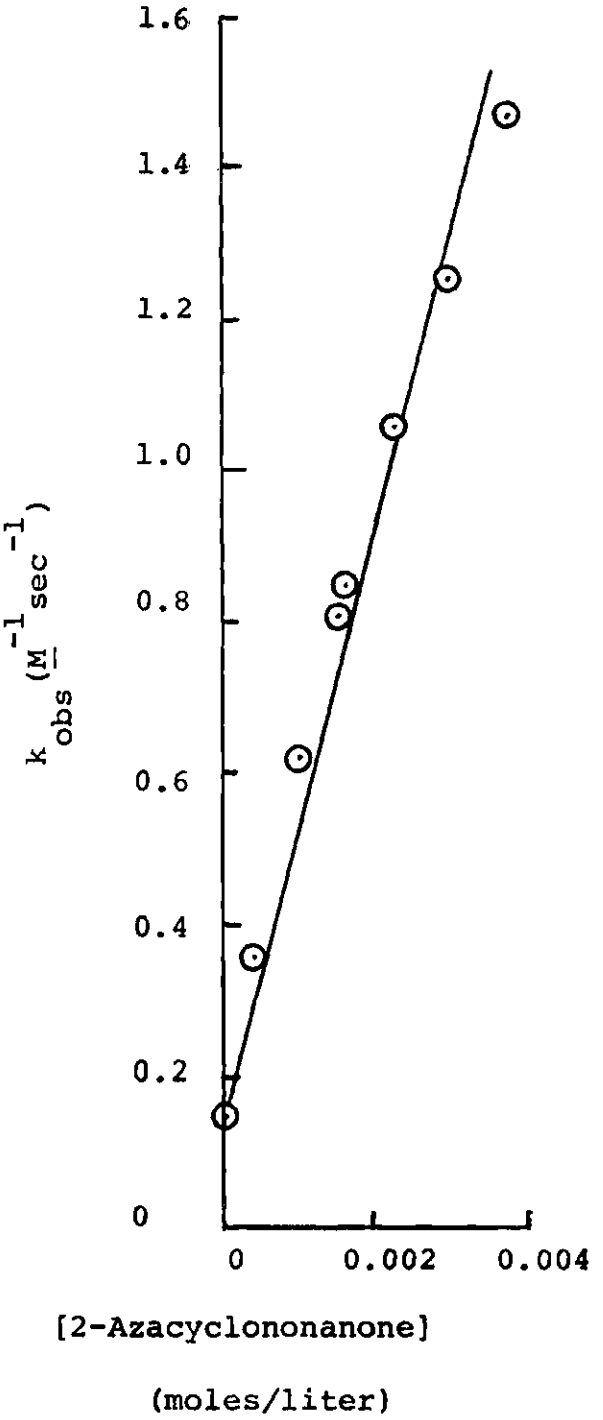
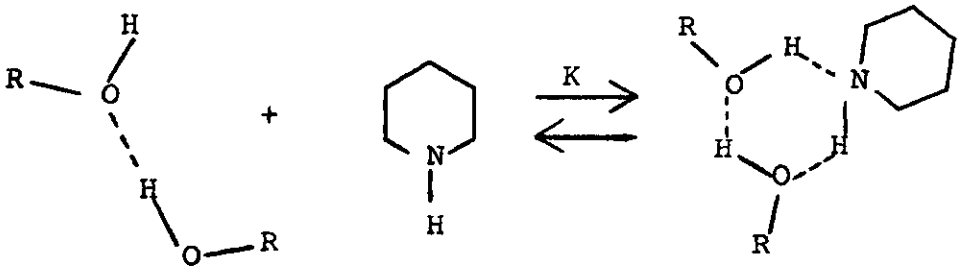


Figure 8. Addition of 2-Azacyclononanone to the Piperidine-Purine Reaction

used with the alcohols produced little change in the rate coefficients. Plots of k_{obs} *versus* concentration of alcohol were about the same when k_{obs} for the concentration of piperidine used in the absence of alcohol was subtracted from that k_{obs} found in the presence of the alcohol. This is in contrast to the behavior of the 6-chloro-9-ethylpurine in which the rate coefficient due to the catalysis did change noticeably with a variation in the piperidine concentration. This was explained as a medium effect, possibly association between piperidine and the alcohol.[150]

Calculations were done to correct the observed rate constants for association of the alcohol with the nucleophile piperidine as outlined in the Experimental chapter. In deference to the consensus, it was assumed that the alcohol was predominantly dimeric and would associate with the piperidine according to the equilibrium:



9 10 11

The species 11 was assumed to be neither catalytic nor nucleophilic. Values of K were varied from one to six and concentrations of "free" piperidine and "free" dimeric alcohol were determined and used to calculate rate constants. However, as K increased, linearity did not improve. The catalytic coefficient ($\frac{k_1 k_4}{k_{-1}}$, the slope of the k_{obs} *vs.* concentration of alcohol plot) increased, but only to a maximum of about 40% over that found assuming dimeric alcohol and no association between piperidine and alcohol. Thus, the catalytic coefficients for the alcohols have been tabulated based upon the simplistic view that the alcohol is present as a dimer which is not associated with the piperidine. It is understood that the values should be taken as a reasonable minimum.

Although numerous studies have been reported concerning the association of alcohols in organic solvents, controversy still exists. Infrared studies on ethanol in carbon tetrachloride have indicated monomer fractions up to 0.85 at a concentration of 0.102 *M* ethanol. In more dilute solutions, the monomer fraction increases to about 0.98 at 0.0102 *M* alcohol.[167] In cyclohexane, average degrees of association have been found to be about two for 1-butanol and about 1.7 for *t*-butanol in the concentration range of 0.05

to 0.1 M.[168] Nmr studies in carbon tetrachloride for methanol, ethanol and t-butanol are also interpreted as dimeric association below 0.1 M.[169,170] Other work with ultraviolet spectrophotometry has shown methanol to be about 28% associated at 0.0247 M in hexane.[171]

From these literature studies, the assumption that the alcohols exist as dimers in the concentration range studied (less than 0.08 M) is a reasonable approximation. Plots of k_{obs} vs. concentration of dimeric alcohol are shown in Figures 9, 10, and 11. The data for these figures are tabulated in Appendix 6. From the slope of the linear portions of these plots, catalytic coefficients ($\frac{k_1 k_4}{k_{-1}}$) may be determined as before. These are shown in Table 17.

Table 17. Catalytic Constants for Added Alcohols in the Reaction of Piperidine with 6-Fluoro-9-Methoxymethylpurine at 25.0° in Isooctane (Assuming Dimeric Alcohol)

Catalyst	Catalytic Coefficient ($\frac{k_1 k_4}{k_{-1}}$, $M^{-2}sec^{-1}$)*
t-Butanol	17.9
1-Butanol	43.4
Methanol	62.7

*Values of the catalytic coefficients are averages determined from the slope of the k_{obs} vs. concentration of dimer plots using all of the points on the linear portion.

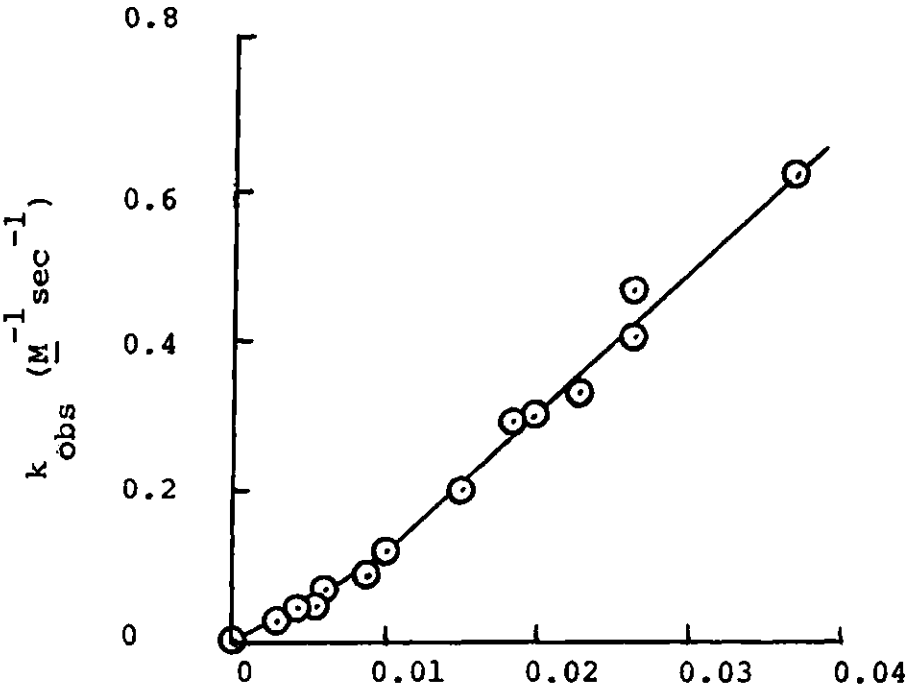


Figure 9. Addition of t-Butanol to the Piperidine-Purine Reaction (Assuming Dimeric Alcohol)

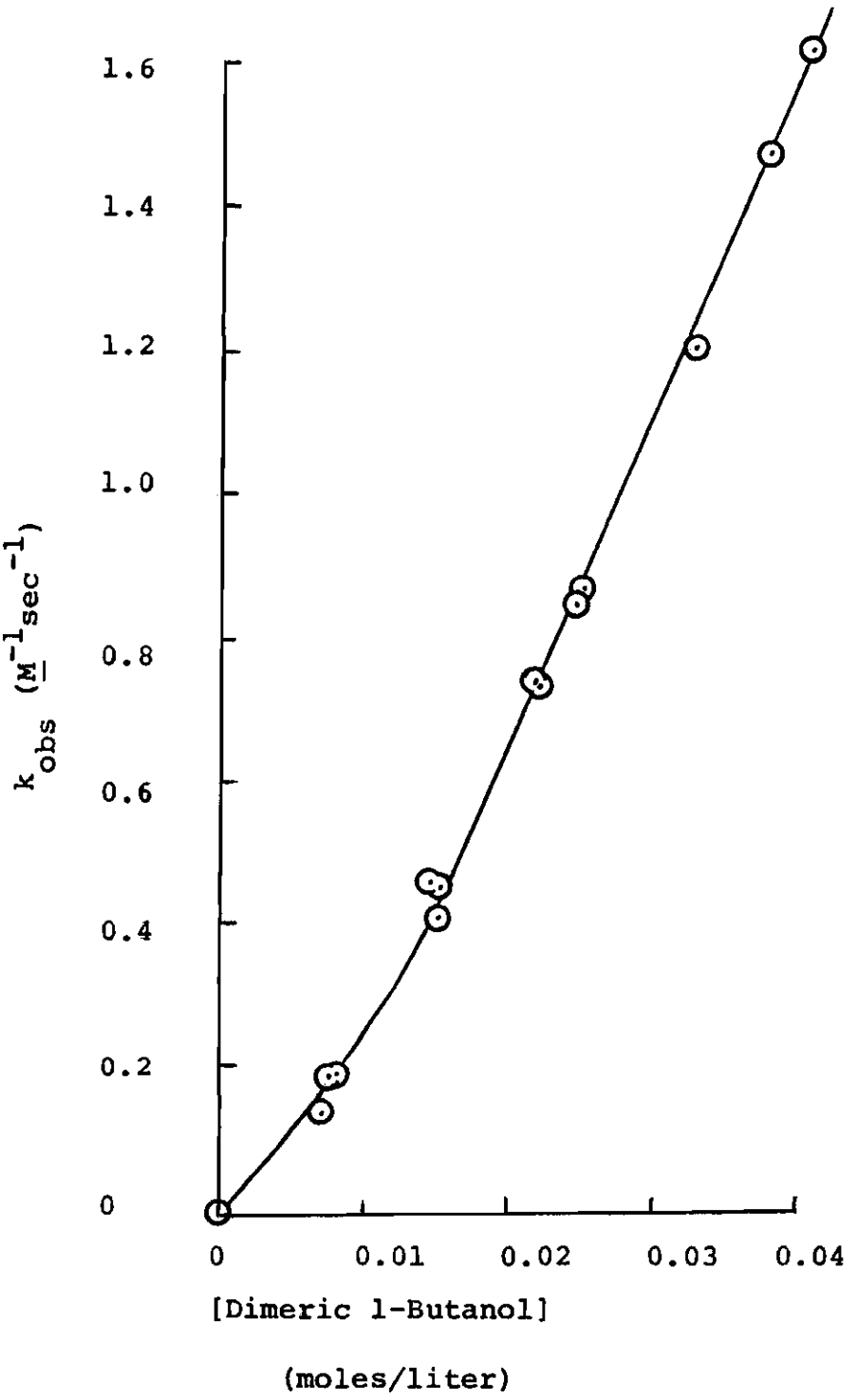


Figure 10. Addition of 1-Butanol to the Piperidine-Purine Reaction (Assuming Dimeric Alcohol)

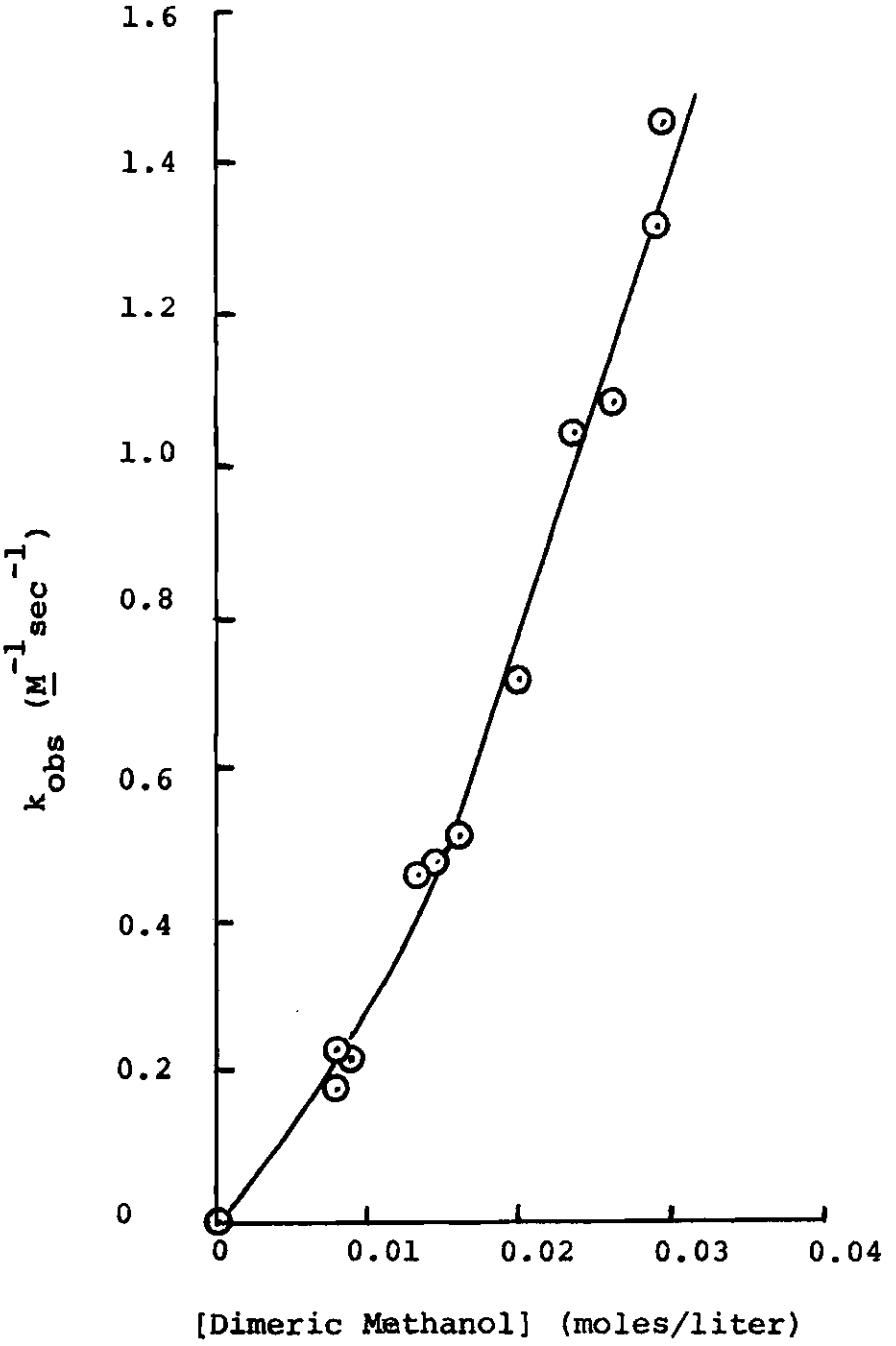
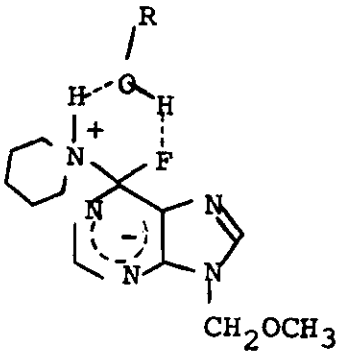
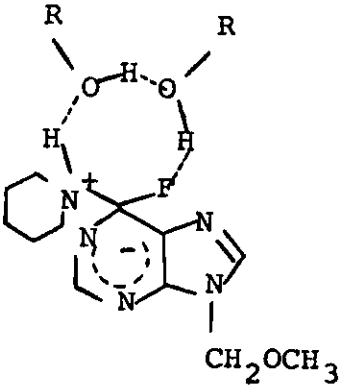


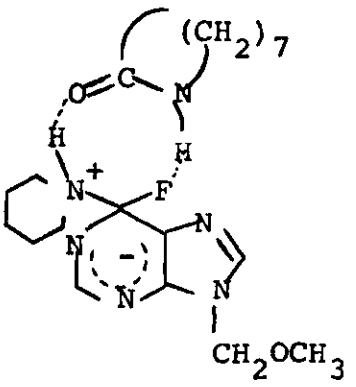
Figure 11. Addition of Methanol to the Piperidine-Purine Reaction (Assuming Dimeric Alcohol)

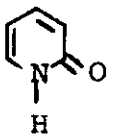
Based upon the experimental observations, the catalysis by alcohols and amines may be viewed as either a simple acid catalysis or as a bifunctional type of catalytic effect as shown below for both monomeric and dimeric alcohol.





The interpretation of bifunctional catalysis is strengthened by the exceptionally strong effect obtained with the lactam 2-azacyclononanone. As shown, this type of molecule has a geometry well suited for assisting the removal of both the ammonium proton and the fluoride ion. Although in more concentrated solutions lactams self-



associate to form dimers, ir studies in CCl_4 indicate that the molecules are completely dissociated up to 0.002 M.[172] Our studies use a maximum concentration of only 0.00373 M. Thus, it is assumed that the catalyst is predominantly monomeric. The value of the catalytic coefficient shown in Table 15 should be regarded as a reasonable minimum, however. Such effects have been previously postulated for the catalysis of the reaction of 2,4-dinitrofluorobenzene with piperidine in benzene by α-pyridone ().[142]

Further evidence for the bifunctional nature of the catalysis step has been found in a Hammett plot constructed with benzyl alcohols used as catalysts. Since these alcohols have similar steric requirements, only the electronic factors should influence the rate. The second-order rate constants and concentrations of alcohols are listed in Appendix 7. A plot of $k_{observed}$ vs. concentration of the substituted benzyl alcohol is given in Figure 12. From this graph, the catalytic coefficient, termed $k_{substituent}$ ($\frac{k_1 k_4}{k_{-1}}$, the slope value) for each of the benzyl alcohols may be determined and a Hammett plot constructed from the data gathered in Table 18. The plot is shown in Figure 13.

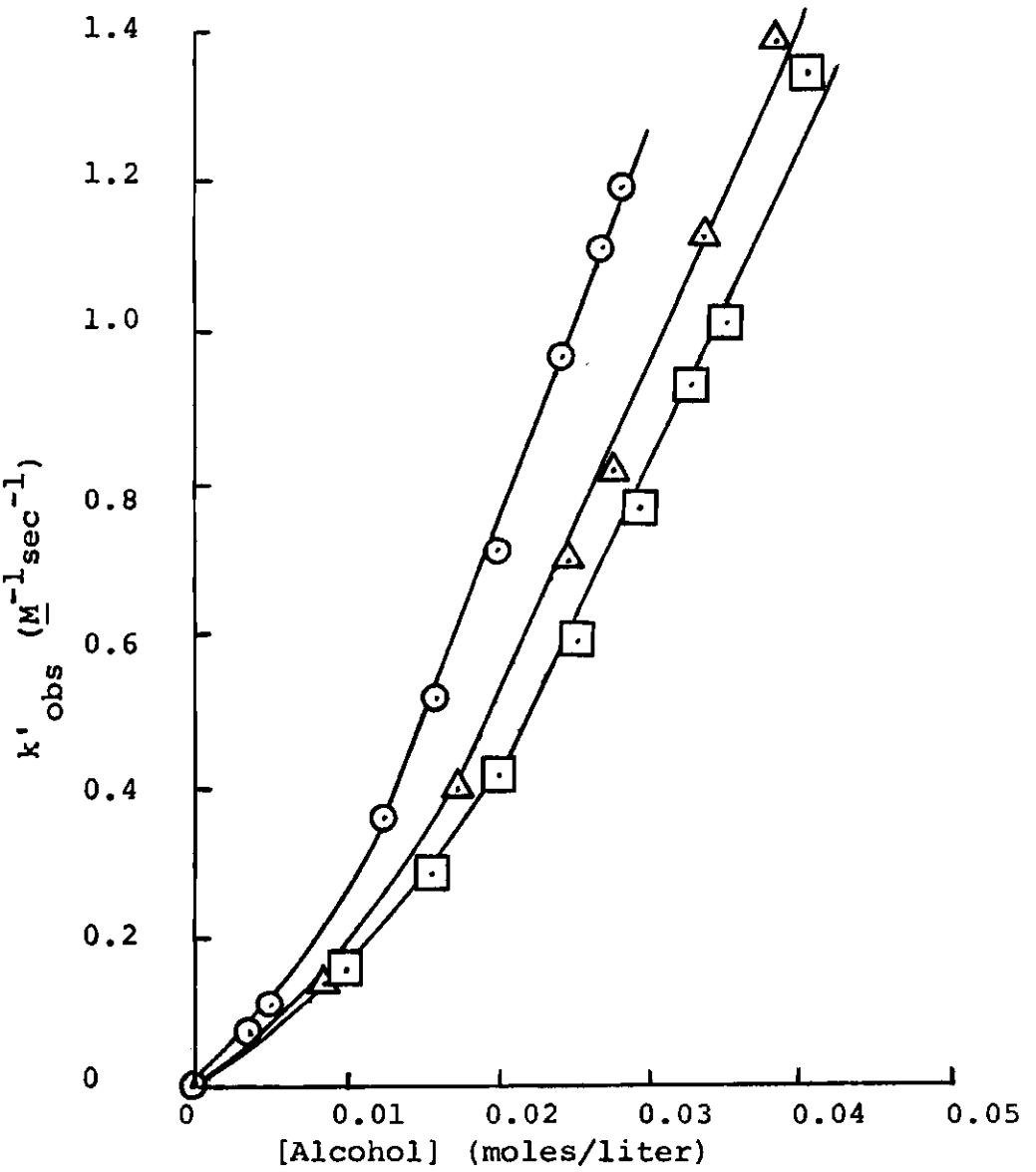


Figure 12. Addition of Substituted Benzyl Alcoholsto the Piperidine-Purine Reaction
(Assuming No Association)
⊙ - p-Chlorobenzyl Alcohol
△ - Benzyl Alcohol
⊡ - p-Methyl Benzyl Alcohol

Table 18. Hammett Plot Calculations for the Piperidine-Fluoropurine Reaction Assuming No Association of the Benzyl Alcohols.

Substituent	$k_{substituent}$ (slope) $(M^{-2}sec^{-2})$	$\log \frac{k_{substituent}}{k_H}$	σ^{173}
p-CH_3	48.2 ± 4	-0.0150	-0.17
H	49.9 ± 8	0.00	0.00
p-Cl	53.6 ± 6	+0.0311	+0.227

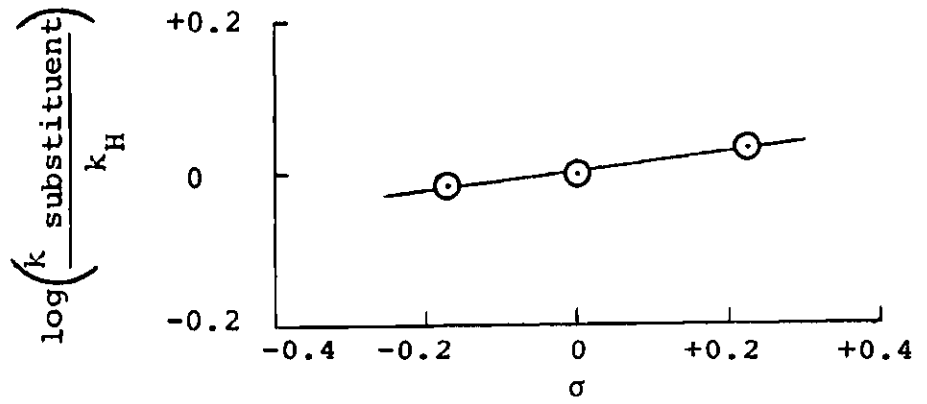


Figure 13. Hammett Plot for the Addition of Benzyl Alcohols to the Piperidine-Purine Reaction in Isooctane at 25.0° (Assuming No Association)

If it is again assumed that the alcohols are present as dimers which are not associated with the piperidine, the only effect observed on the data in Table 18 will be to

double the $k_{substituent}$ values. However, since the plot contains the log $(\frac{k_{substituent}}{k_H})$ term, the slope of the Hammett plot (ρ value) will remain the same.

From the slope of the Hammett plot, the ρ value is found to be +0.17. This small positive value indicates that electron-withdrawing groups attached to the catalyst increase its effectiveness by increasing the acidity of the proton bound to the oxygen of the alcohol. Thus, slight acid catalysis is implied. However, the relatively small magnitude of ρ further implies that acid and base catalysis play almost equal roles in assisting the decomposition of the intermediate. This behavior adds greater strength to the idea of bifunctional catalysis previously postulated.

In the case of the 6-chloro-9-ethylpurine, similar results were found.[150] For this purine, ρ varied from +0.22 to +0.26, depending upon the state of association assumed for the alcohol.

A study was begun to determine the effects of a variation of the solvent on the reaction of piperidine with 6-fluoro-9-methoxymethylpurine for comparison with the work done by Alvaro Abidaud on 6-chloro-9-methoxymethylpurine.[151] As before, the error in the rate constants is ± 3%. The second-order rate constants and concentrations of piperidine

used are tabulated in Appendix 8. Figure 14 graphically portrays these data.

From the Bunnett mechanism, a plot of $k_{observed}$ *vs.* concentration of piperidine should produce a straight line of slope $\frac{k_1 k_3}{k_{-1}}$ (the catalyzed process) and intercept $\frac{k_1 k_2}{k_{-1}}$ (the uncatalyzed process). The data extracted from these plots are summarized in Table 19. For comparison, the same data are tabulated for 6-chloro-9-methoxymethyl-purine[151] in Table 20.

Table 19. Rate Data for the Reaction of Piperidine-N-*h* with 6-Fluoro-9-Methoxymethylpurine in Benzene.

Temperature (°C)	Catalyzed Step (Slope, $M^{-2}sec^{-1}$)	Uncatalyzed Step (Intercept, $M^{-1}sec^{-1}$)	Slope/Intercept Ratio
10.0°	2.34 ± 0.3	0.069 ± 0.021	33.9
25.0°	3.09 ± 0.09	0.0588 ± 0.0073	52.6
40.0°	3.54 ± 0.17	0.0908 ± 0.021	39.0

Table 20. Rate Data for the Reaction of Piperidine-N-h with 6-Chloro-9-Methoxymethylpurine in Benzene.[151]

Temperature (°C)	Catalyzed Step (Slope, $M^{-2}sec^{-1}$)	Uncatalyzed Step (Intercept, $M^{-1}sec^{-1}$)	Slope/Intercept Ratio
23.0°	0.0071	0.0025	2.8
32.0°	0.0099	0.0041	2.4
44.5°	0.0141	0.0084	1.7

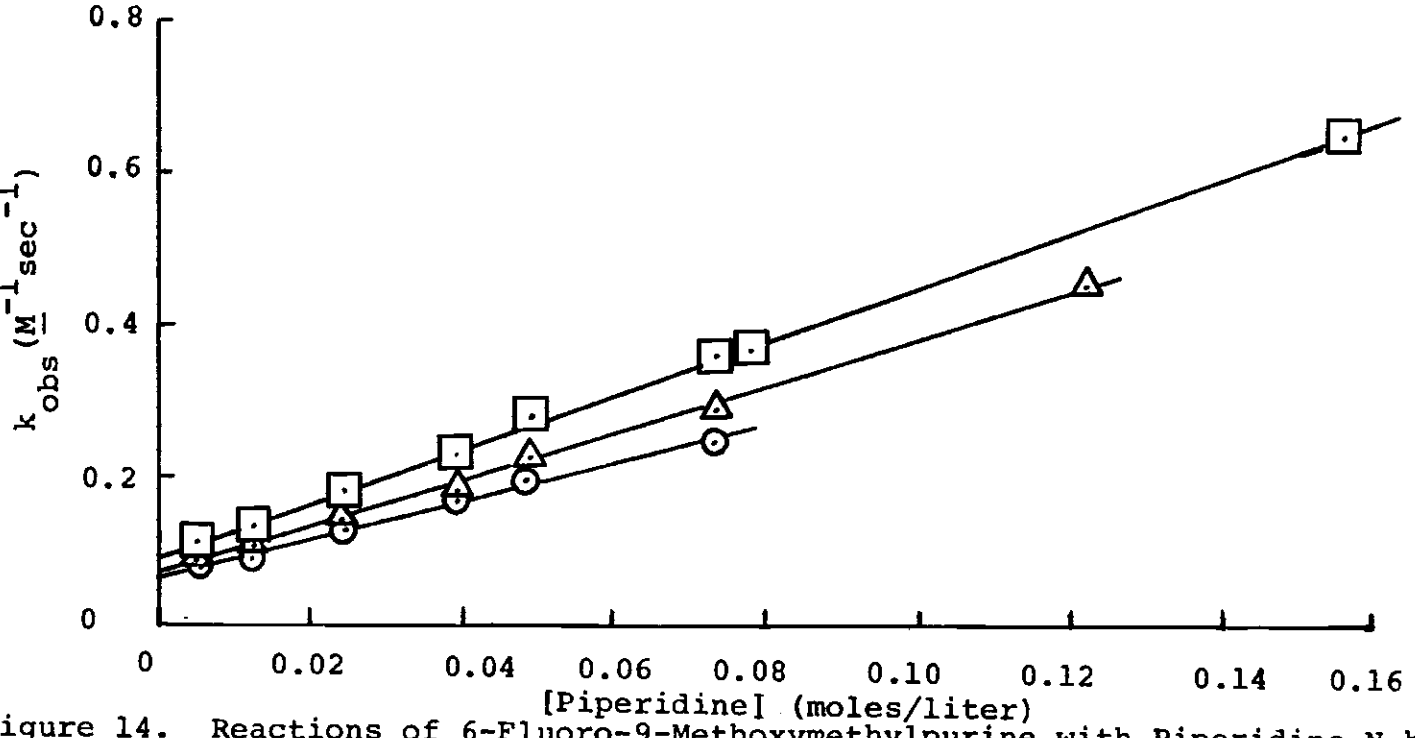


Figure 14. Reactions of 6-Fluoro-9-Methoxymethylpurine with Piperidine-N-h at Various Temperatures in Benzene

⊡ - 40.0° ± 0.1°

△ - 25.0° ± 0.1°

⊙ - 10.0° ± 0.1°

In benzene, as in isooctane, the fluoropurine reacts faster than the chloropurine. However, the magnitude of the slope to intercept ratio has decreased considerably with the change of solvent for both purines. In both cases, the uncatalyzed step has increased in magnitude indicating that the decomposition of the intermediate complex has become faster in benzene.

By plotting $1/k_{obs}$ *vs.* 1/[piperidine] for high concentrations of piperidine, a line is obtained whose slope is $1/k_1$. The values for the two purines are shown in Tables 21 and 22. As is expected, the values increase with temperature and the k_1 values for the fluoropurine are larger than those for the chloropurine.

Table 21. Values for k_1 for the Reaction of 6-Fluoro-9-Methoxymethylpurine with Piperidine-N-*h* in Benzene

Temperature (°C)	k_1 ($M^{-1}sec^{-1}$)
10.0°	0.669
25.0°	0.714
40.0°	0.847

Table 22. Values for k_1 for the Reaction of 6-Chloro-9-Methoxymethylpurine with Piperidine-N-*h* in Benzene.[151]

Temperature (°C)	k_1 ($M^{-1}sec^{-1}$)
23.0°	0.0183 ± 0.0073
32.0°	0.0195 ± 0.0078
44.5°	0.0317 ± 0.0126

Since a "normal" temperature effect is observed for the reaction of the fluoropurine with piperidine in benzene, ΔE_{act} and $\Delta S^{\ddagger}_{act}$ values may be calculated. These are shown in Table 23 with the corresponding values for the chloropurine in Table 24.[151]

Table 23. Activation Data for the Reaction of Piperidine-N-h with 6-Fluoro-9-Methoxymethylpurine in Benzene.

Reaction Step Considered	ΔE_{act} (kcal/mole)	$\Delta S^{\ddagger}_{act}$(25°C) (cal/deg/mole)
k_1	1.42	-56.4
Catalyzed*	1.69	-52.6
Uncatalyzed*	5.43	-47.9

*Calculated from the coefficients for these steps at 25.0° and 40.0°.

Table 24. Activation Data for the Reaction of Piperidine-N-h with 6-Chloro-9-Methoxymethylpurine in Benzene.

Reaction Step Considered	ΔE_{act} (kcal/mole)	$\Delta S^{\ddagger}_{act}$ (23°C) (cal/deg/mole)
k_1	4.87 ± 1.95	-51.98 ± 20.79
Catalyzed	5.49 ± 0.16	-51.8 ± 1.5
Uncatalyzed	10.29 ± 4.11	-37.6 ± 15.0

From the values of ΔE_{act}, the k_1, k_2 and k_3 proces-

ses are all of lower energy for the fluoropurine than for the chloropurine.

From the data presented, the uncatalyzed step of the mechanism has increased in benzene. Such effects have previously been observed for the reactions of 2- and 4-chloropyrimidines with piperidine. The observation may be rationalized by postulating a base catalysis due to the greater polarizability of the benzene molecule.[144] When benzene is added to the reaction in isooctane, no effect is observed up to a concentration of 2.79 M benzene. The data are given in Appendix 9.

CHAPTER VIII

CONCLUSIONS

Nucleophilic Substitution on 6-Fluoro-9-Methoxymethylpurine

The results of this study on nucleophilic substitution with piperidine-N-h and -N-d on 6-fluoro-9-methoxymethylpurine in the non-polar, aprotic solvent isooctane indicate that the Bunnett mechanism adequately describes the observed facts. The reaction goes through an intermediate complex whose breakdown to products may either be catalyzed or uncatalyzed. Additives such as ketones, ethers, and tertiary amines have no influence upon the reaction rate. However, molecules having an acidic proton attached to the electronegative atom such as primary and secondary amines and alcohols do catalyze the reaction. The large effect of the lactam 2-azacyclononanone appears to indicate a bifunctional catalysis. This conclusion is further strengthened by the small positive ρ value of +0.17 found in a Hammett study of the catalysis step using substituted benzyl alcohols. This value shows a bifunctional catalysis with a slight emphasis on acid character.

The observation of a deuterium isotope effect in the catalysis step of the reaction indicates that the bond between the proton and the piperidine nitrogen is broken in the rate-determining step.

Although the reaction in isooctane shows no temperature dependence, the reaction in benzene shows a slight temperature dependence. The uncatalyzed step of the reaction is also faster with respect to the catalyzed step.

In a comparison with analogous chloropurines in these two solvents, it is found that the rate of displacement of fluorine is always faster than the rate of displacement of chlorine.

CHAPTER IX

RECOMMENDATIONS

In the area of reactions using 18-crown-6, much work still must be done. Relative nucleophilicities of anions already investigated and other commonly used nucleophiles should be determined in organic solvents. In addition to nucleophilicities, the basic properties of these anions (especially fluoride) may also prove interesting in the field of weak-base-promoted eliminations.

Solvent effects will provide another area of research. As yet, little work has been done toward determining the optimum solvent for displacement and elimination reactions involving 18-crown-6. Such an investigation is especially needed in the case of the potassium fluoride reactions. A combination of 18-crown-6 with some of the dipolar, aprotic solvents such as N-methylpyrrolidone or DMSO may dissolve enough salt to decrease reaction times greatly.

The study on nucleophilic substitution on 6-fluoro-9-methoxymethylpurine should be continued to include the effects of changes in solvent as a parallel to the thesis work of Alvaro Abidaud.[151]

Appendix 1. Second-Order Rate Constants for the Reactions of Piperidine-N-h with 6-Fluoro-9-Methoxymethylpurine in Isooctane (Concentration of Fluoropurine is ca. 5×10^{-5} M).

Concentration of Piperidine-N-h (moles/liter)	$k_{observed}$ ($M^{-1}sec^{-1}$)
10.0° ± 0.1°C	
0.0120	0.101
0.0241	0.184
0.0364	0.260
0.0424	0.293
0.0481	0.343
0.0546	0.370
0.0606	0.399
0.0722	0.489
0.0866	0.563
0.0866	0.565
0.0866	0.579
25.0° ± 0.1°C	
0.00241	0.0483
0.0120	0.116
0.0241	0.198
0.0364	0.253
0.0424	0.297
0.0485	0.340
0.0481	0.340
0.0546	0.366
0.0606	0.435
0.0722	0.493
0.0866	0.599
0.101	0.681

Appendix 1. Continued

Concentration of Piperidine-N-h (moles/liter)	$k_{observed}$ ($M^{-1}sec^{-1}$)
40.0° ± 0.1°C	
0.0120	0.102
0.0240	0.175
0.0364	0.253
0.0481	0.321
0.0485	0.332
0.0546	0.365
0.0606	0.406
0.0606	0.411
0.0606	0.416
0.0606	0.417
0.0722	0.476
0.0866	0.563
0.101	0.645

Appendix 2. Second-Order Rate Constants for the Reactions of Piperidine-N-d with 6-Fluoro-9-Methoxymethylpurine in Isooctane (Concentration of Fluoropurine is ca. 5×10^{-5} M)

Concentration of Piperidine-N-d (moles/liter)	$k_{observed}$ ($M^{-1}sec^{-1}$)
10.0° ± 0.1°C	
0.00541	0.0562
0.0135	0.0998
0.0216	0.139
0.0270	0.168
0.0358	0.218
0.0670	0.372
0.0670	0.373
0.0670	0.381
0.0670	0.375
0.0670	0.384
25.0° ± 0.1°C	
0.00541	0.0472
0.0135	0.0898
0.0216	0.123
0.0243	0.139
0.0268	0.148
0.0270	0.150
0.0358	0.197
0.0670	0.329
0.0804	0.404
0.0938	0.457
0.107	0.526

Appendix 2. Continued.

Concentration of Piperidine-N-d (moles/liter)	$k_{observed}$ ($M^{-1}sec^{-1}$)
40.0° ± 0.1°C	
0.00541	0.0425
0.0135	0.0877
0.0243	0.130
0.0268	0.140
0.0270	0.145
0.0358	0.188
0.0501	0.254
0.0670	0.319
0.0804	0.400
0.0938	0.444
0.107	0.509

Appendix 3. Second-Order Rate Constants for the Reaction of Piperidine-N-h with 6-Chloro-9-Ethylpurine in Isooctane at 49.5°C.

Concentration of Piperidine-N-h (moles/liter)	$k_{observed}$ ($M^{-1}sec^{-1}$)
0.0253	0.00147
0.0507	0.00214
0.0900	0.00292
0.1014	0.00326
0.196	0.00519
0.299	0.00722
0.299	0.00723
0.399	0.00853
0.399	0.00911
0.490	0.00988
0.490	0.00996
0.490	0.0102
0.785	0.0147
0.868	0.0160
0.868	0.0161
0.868	0.0162
0.991	0.0180

Appendix 4. Second-Order Rate Constants for the Reaction of 6-Fluoro-9-Methoxymethylpurine with 0.0499M Piperidine in Isooctane at 25.0°C in the Presence of Additives.

Additive	Additive Concentration (moles/liter)	k_{obs} ($M^{-1}sec^{-1}$)
None	0.000	0.340
	0.000	0.337
	0.000	0.335
Triethylamine	0.0178	0.331
	0.0635	0.328
	0.0728	0.332
	0.109	0.322
2,6-Dimethylpiperidine	0.0387	0.345
	0.0799	0.346
	0.0906	0.351
	0.147	0.371
Tetrahydrofuran	0.0412	0.339
	0.0659	0.331
	0.0850	0.330
	0.125	0.331
Tetrahydropyran	0.0296	0.328
	0.0499	0.326
	0.0750	0.321
	0.100	0.316
Acetone	0.0376	0.338
	0.0751	0.321
	0.114	0.324
	0.152	0.321
Pyridine	0.0441	0.344
	0.0441	0.331
	0.0962	0.341
	0.155	0.331

Appendix 5. Second-Order Rate Constants for the Reaction of 6-Fluoro-9-Methoxymethylpurine with Piperidine in Isooctane at 25.0°C in the Presence of Catalytically Active Additives.

Additive	Additive Concentration (moles/liter)	Piperidine Concentration (moles/liter)	k_{obs} ($M^{-1}sec^{-1}$)
None	0.000	0.0200	0.143
	0.000	0.0200	0.144
n-Butyl Amine	0.00807	0.0200	0.168
	0.0173	0.0200	0.211
	0.0252	0.0200	0.242
	0.0431	0.0200	0.329
Ethylene Diamine	0.00252	0.0200	0.154
	0.00390	0.0200	0.170
	0.00630	0.0200	0.189
	0.00975	0.0200	0.222
2-Azacyclononanone	0.000394	0.0201	0.357
	0.000985	0.0201	0.613
	0.00149	0.0201	0.807
	0.00158	0.0201	0.846
	0.00224	0.0201	1.05
	0.00298	0.0201	1.25
	0.00373	0.0201	1.46
t-Butanol	0.00560	0.0200	0.164
	0.0110	0.0200	0.187
	0.0178	0.0200	0.231
	0.0302	0.0200	0.344
	0.0457	0.0200	0.477
None	0.0528	0.0200	0.544
	0.000	0.0300	0.206
	0.000	0.0300	0.205
	0.000	0.0300	0.201
t-Butanol	0.00884	0.0300	0.248
	0.0201	0.0300	0.325
	0.397	0.0300	0.493

Appendix 5. Continued.

Additive	Additive Concentration (moles/liter)	Piperidine Concentration (moles/liter)	k_{obs} ($M^{-1}sec^{-1}$)
None	0.000	0.0401	0.276
	0.000	0.0401	0.275
	0.000	0.0401	0.272
t-Butanol	0.0118	0.0401	0.345
	0.0371	0.0401	0.570
	0.0533	0.0401	0.739
	0.0741	0.0401	0.890
Methanol	0.0173	0.0201	0.359
	0.0292	0.0201	0.622
	0.0479	0.0201	1.18
	0.0595	0.0201	1.59
	0.0758	0.0201	2.10
	0.0156	0.0301	0.382
	0.0326	0.0301	0.712
	0.0526	0.0301	1.38
	0.0776	0.0301	2.15
	0.0159	0.0401	0.502
	0.0273	0.0401	0.734
	0.0401	0.0401	0.987
	0.0587	0.0401	1.58
1-Butanol	0.0142	0.0200	0.283
	0.0306	0.0200	0.554
	0.0507	0.0200	0.01
	0.0822	0.0200	1.75
	0.0167	0.0301	0.394
	0.0314	0.0301	0.655
	0.0496	0.0301	1.05
	0.0764	0.0301	1.67
	0.0154	0.0401	0.459
	0.0300	0.0401	0.727
	0.0445	0.0401	1.01
	0.0662	0.0401	1.47

Appendix 6. Second-Order Rate Constants for the Reaction of 6-Fluoro-9-Methoxymethylpurine with Piperidine in Isooctane at 25.0° in the Presence of Alcohols (Assuming Dimeric Association of Alcohol).

Additive	Dimer Concentration (moles/liter)	Piperidine Concentration (moles/liter)	k'_{obs} ($M^{-1}sec^{-1}$)
t-Butanol	0.0028	0.0200	0.0200
	0.0055	0.0200	0.0430
	0.0089	0.0200	0.0870
	0.0151	0.0200	0.200
	0.0228	0.0200	0.333
	0.0264	0.0200	0.400
	0.0442	0.0300	0.0440
	0.0101	0.0300	0.121
	0.0198	0.0300	0.298
	0.0059	0.0401	0.0710
	0.0186	0.0401	0.296
	0.0266	0.0401	0.465
	0.0370	0.0401	0.616
Methanol	0.00865	0.0201	0.215
	0.0146	0.0201	0.478
	0.0240	0.0201	1.04
	0.0298	0.0201	1.45
	0.0379	0.0201	1.96
	0.0078	0.0301	0.178
	0.0163	0.0301	0.508
	0.0263	0.0301	1.18
	0.0388	0.0301	1.95
	0.00795	0.0401	0.228
	0.0136	0.0401	0.460
	0.0201	0.0401	0.713
	0.0294	0.0401	1.31
1-Butanol	0.0071	0.0200	0.139
	0.0153	0.0200	0.410
	0.0254	0.0200	0.866
	0.0411	0.0200	1.61

Appendix 6. Continued.

Additive	Dimer Concentration (moles/liter)	Piperidine Concentration (moles/liter)	k'_{obs} ($M^{-1}sec^{-1}$)
1-Butanol	0.00835	0.0301	0.190
	0.0157	0.0301	0.451
	0.0248	0.0301	0.846
	0.0382	0.0301	1.47
	0.0077	0.0401	0.185
	0.0150	0.0401	0.453
	0.0222	0.0401	0.736
	0.0331	0.0401	1.20

*$k'_{obs} = k_{obs}$ for the reaction in the presence of alcohol minus k_{obs} for the reaction in the absence of alcohol.

Appendix 7. Second-Order Rate Constants for the Reaction of 0.0200 M Piperidine with 6-Fluoro-9-Methoxymethylpurine in Isooctane at 25.0° in the Presence of Substituted Benzyl Alcohols.

Concentration of Alcohol (moles/liter)	k_{obs} Alcohol ($M^{-1}sec^{-1}$)	k_{obs} Piperidine ($M^{-1}sec^{-1}$)	Concentration of Dimeric Alcohol (moles/liter)	k'_{obs}* ($M^{-1}sec^{-1}$)
		p-Chlorobenzyl Alcohol		
0.00351	0.221	0.144	0.00176	0.077
0.00498	0.253	0.144	0.00249	0.109
0.0126	0.498	0.144	0.0063	0.354
0.0160	0.659	0.144	0.0080	0.515
0.0201	0.853	0.144	0.0101	0.709
0.0244	1.11	0.144	0.0122	0.966
0.0269	1.25	0.144	0.0134	1.106
0.0282	1.33	0.144	0.0141	1.186
		Benzyl Alcohol		
0.00842	0.286	0.144	0.00421	0.142
0.0173	0.538	0.144	0.00865	0.394
0.0247	0.832	0.144	0.0124	0.688
0.0278	0.954	0.144	0.0139	0.810
0.0338	1.26	0.144	0.0169	1.116
0.0387	1.51	0.144	0.0194	1.37
0.0448	1.92	0.144	0.0224	1.776
		p-Methylbenzyl Alcohol		
0.00994	0.298	0.144	0.00497	0.154
0.0156	0.427	0.144	0.0078	0.283
0.0201	0.558	0.144	0.0101	0.414
0.0249	0.732	0.144	0.0124	0.588
0.0294	0.911	0.144	0.0147	0.767
0.0327	1.07	0.144	0.0164	0.926
0.0352	1.21	0.144	0.0176	1.066
0.0406	1.48	0.144	0.0203	1.336

*$k'_{obs} = k_{obs}$ for the reaction in the presence of alcohol minus k_{obs} for the reaction in the absence of alcohol.

Appendix 8. Second-Order Rate Constants for the Reactions of Piperidine-N-h with 6-Fluoro-9-Methoxymethylpurine in Benzene (Concentration of the Fluoropurine is ca.5 x 10^{-5}M).

Concentration of Piperidine-N-h (moles/liter)	k_{obs} ($M^{-1}sec^{-1}$)
10.0°C 0.1°C	
0.00489	0.0760
0.0122	0.0888
0.0244	0.140
0.0390	0.168
0.0489	0.186
0.0735	0.236
0.0735	0.237
0.0735	0.239
25.0°C 0.1°C	
0.00489	0.0722
0.0122	0.0999
0.0244	0.135
0.0390	0.172
0.0489	0.219
0.0780	0.279
0.122	0.447
40.0°C 0.1°C	
0.00489	0.105
0.0122	0.130
0.0245	0.179
0.0390	0.227
0.0489	0.276
0.0735	0.357
0.0780	0.360
0.156	0.642

Appendix 9. Second-Order Rate Constants for the Reaction of 0.0248M Piperidine-N-h with 5.7×10^{-5}M 6-Fluoro-9-Methoxymethylpurine in Isooctane at 25.0° with Added Benzene.

Concentration of Benzene (moles/liter)	k_{obs} ($M^{-1}sec^{-1}$)
0.00	0.173
0.554	0.179
1.66	0.180
2.74	0.180
2.74	0.174

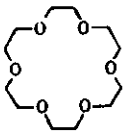
Appendix 10.

[Reprinted from the Journal of the American Chemical Society, 96, 2250 (1974).]

The Chemistry of "Naked" Anions. I. Reactions of the 18-Crown-6 Complex of Potassium Fluoride with Organic Substrates in Aprotic Organic Solvents[1]

Sir:

Fluoride ion, unencumbered by strong solvation forces, should prove to be both a potent nucleophile and base.[2] Solubility problems, however, have hampered studies of fluoride ion in weakly solvating media. The recent reports regarding the ability of crown ethers to complex metal salts and dissolve them in polar and nonpolar, aprotic solvents[3,4] has prompted us to investigate the chemistry of metal fluoride crown complexes. We wish to report the solubilization of potassium fluoride in acetonitrile and benzene containing 1,4,7,10,13,16-hexaoxacyclooctadecane (18-Crown-6) (1)[3,6] and the reactions of this solubilized fluoride, which



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we have termed "naked" fluoride, with a variety of organic substrates. The following reaction types are demonstrated: (1) displacement reactions at sp^3

(1) Presented in part at the First Fall Organic Conference, Cape Cod, Mass., Oct 1, 1973.

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Appendix 10. Continued

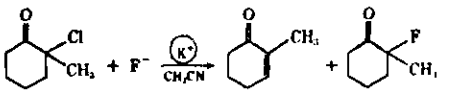
Table I. Reactions of "Naked" Fluoride with Organic Substrates

Substrate	Solvent	Products[a]	Concentrations (*M*) Crown	Substrate	Temp, °C	$t_{1/2}$, hr[b]
Benzyl bromide	CH_3CN	Benzyl fluoride	0.19	2.0	83	11.5
1-Bromooctane	CH_3CN	1-Fluorooctane (92%) 1-Octene (8%)	0.19	1.16	83	115
	C_6H_6	1-Fluorooctane (92%) 1-Octene (8%)	0.68	2.9	90	128
2-Bromooctane	C_6H_6	2-Fluorooctane (32%) 1- and 2-octenes (68%)	0.50	2.8	90	240
Bromocyclohexane	CH_3CN	Cyclohexene	0.15	3.61	83	104
2-Chloro-2-methylcyclohexanone	CH_3CN	2-Fluoro-2-methylcyclohexanone (31%) 2-Methyl-2-cyclohexenone (69%)	0.15	3.3	83	20
2,4-Dinitrochlorobenzene	CH_3CN	2,4-Dinitrofluorobenzene			25	5
					83	0.12
Acetyl chloride	CH_3CN	Acetyl fluoride	0.14	7.0	25	5.5

[a] In all cases conversion to products was quantitative. All spectral data (nmr, ir, and mass spectral) of the isolated products were consistent with the assigned structures. [b] The time for one-half conversion of starting materials to products is tabulated as an approximate indication of the relative rates of reaction.

hybridized carbon with leaving groups located at primary, secondary, tertiary, and benzylic positions, (2) competing elimination processes, and (3) displacement reactions at sp^2 hybridized carbon. The data are summarized in Table I. The reaction conditions are relatively mild and the conversions essentially quantitative. Less than 5% reaction takes place in the absence of crown ether under identical conditions covering the same periods of time.

The products of reaction are either fluorides, alkenes, or mixtures of these indicating that "naked" fluoride may act as both a nucleophile or a base. Benzyl bromide reacts rapidly to produce benzyl fluoride.[7] Primary halides give predominantly primary fluorides with only small amounts of alkene whereas secondary halides give exclusively or predominantly alkene products.[8] An interesting reaction illustrating the competition between displacement and elimination processes is the reaction of "naked" fluoride with 2-chloro-2-methylcyclohexanone (2) to produce 2-fluoro-2-methylcyclohexanone (3) and 2-methyl-2-cyclohexenone (4).[9] It has been found that alkyl chlorides react



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slowly with "naked" fluoride while the corresponding tosylates have reactivity comparable to that of bromides. This observation regarding leaving group abilities is in line with the tabulation reported by Streitwieser for homogeneous reactions.[10] In addition, reaction appears to be faster in acetonitrile than in benzene. Displacement at sp^2 hybridized carbon, as illustrated by the reactions of 2,4-dinitrochlorobenzene and acetyl chloride, occur smoothly at room temperature and rapidly at reflux to give 100% conversion to the corresponding fluorides.[11,12]

The reagent is prepared by dissolving 18-Crown-6 in dry acetonitrile[13] or dry benzene and then adding dry potassium fluoride.[14] After the heterogeneous system is stirred for 30 min, the organic substrate is added and the resulting mixture stirred until reaction is complete. It should be emphasized that efficient stirring is important for complete reaction to be attained. This, like the solubilization of $KMnO_4$ in benzene reported by Sam and Simmons,[4] is an example of solution of an insoluble salt directly in a solvent such as acetonitrile or benzene simply by adding crown ether. Usually a solvent exchange procedure is employed to solubilize the salt.[3] In all cases reported in Table I, the crown is present in catalytic concentrations.

The concentration of naked fluoride in solution at 25° has been determined from analysis of the potassium ion concentration by flame photometry. The results are shown in Table II. It is interesting to note that a plot of the solubility of potassium–crown–fluoride *vs.* the concentration of crown in solution produces a reasonable straight line passing near the origin. It appears, therefore, that the concentration of solubilized KF is independent of the dielectric constant of the medium.

(7) Benzyl fluoride has been prepared from benzyl bromide by a variety of methods with yields ranging from 30 to 70%: A. E. Pavlath and A. J. Leffler, "Aromatic Fluorine Compounds," American Chemical Society Monograph No. 155, Reinhold, New York, N. Y., 1962; J. Bernstein, J. S. Roth, and W. T. Miller, Jr., *J. Amer. Chem. Soc.*, 70, 2310 (1948); J. J. Delpuech and C. Beguin, *Bull. Soc. Chim. Fr.*, 791 (1967); J. F. Normant and J. Bernardin, *C. R. Acad. Sci., Ser. C*, 268, 2352 (1969); E. D. Bergmann and A. M. Cohen, *Isr. J. Chem.*, 8, 925 (1970).

(8) Alkyl fluorides have been prepared in yields ranging from 20 to 50% from alkyl halides and alkyl *p*-toluenesulfonates using KF in a variety of solvents: F. L. M. Pattison, "Toxic Aliphatic Fluorine Compounds," Elsevier, Amsterdam and New York, 1959; F. L. M. Pattison, R. L. Buchanan, and F. H. Dean, *Can. J. Chem.*, 43, 1700 (1965); F. L. M. Pattison and J. J. Norman, *J. Amer. Chem. Soc.*, 79, 2311 (1957), and references cited therein; F. W. Hoffman, *ibid.*, 70, 2596 (1948); W. F. Edgell and L. Parts, *ibid.*, 77, 4899 (1955).

(9) A 40% conversion of 2 to 4 has been reported using collidine at 145–200° or LiCl in dimethylformamide at 110°: "Organic Syntheses," Collect. Vol. IV, Wiley, New York, N. Y., 1963; pp 162–166.

(10) A. Streitwieser, Jr., "Solvolytic Displacement Reactions," McGraw-Hill, New York, N. Y., 1962, pp 29–31.

(11) 2,4-Dinitrofluorobenzene has been prepared in 92% yield by heating the corresponding chloride with KF in the absence of solvent at 190–200° for 7 hr. The same conversion was reported in 51–98% yield using KF, CsF, or RbF at 195° for 2 hr in a variety of solvents: N. N. Vorozhtsov, Jr., and G. G. Yakobson, *Zh. Obshch. Khim.*, 27, 1672 (1957); *Chem. Abstr.*, 52, 2777g (1958); *J. Gen. Chem. USSR*, 27, 1741 (1957); *J. Gen. Chem. USSR*, 31, 3459 (1961).

(12) Acetyl fluoride has been prepared by the action of ZnF_2 on acetyl chloride at 50° and by the action of hydrogen fluoride and sodium fluoride on acetic anhydride at 0°: A. L. Henne, *Org. React.* 2, 61 (1944), and references cited therein.

(13) It has been found that the upper concentration limit of 18-Crown-6 in acetonitrile is approximately 0.2 *M* at room temperature while concentrations as high as 1.5 *M* have been easily achieved in benzene.

(14) Commercial anhydrous KF was dried in an oven at 120° at atmospheric pressure for 12 hr. A mole ratio of potassium fluoride to organic substrate of 2:1 was used in all cases.

Appendix 10. Continued.

Table II. Solubility of Potassium Fluoride in Crown Ether Solution at 25°

Solvent	[18-Crown-6], *M*	[KF], *M*
Benzene	1.01	5.2×10^{-3}
	0.34	1.4×10^{-3}
Acetonitrile	0.16	3.5×10^{-4}

In conclusion, it has been shown (1) that the 18-Crown-6 is an effective agent for the solubilization of KF in polar and nonpolar, aprotic organic solvents, (2) that this solubilized fluoride ("naked" fluoride) is both a potent nucleophile and base, and (3) that the "naked" fluoride reagent provides a facile and efficient means of obtaining organic fluorine compounds in high yield.

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