

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

Solvent	[18-Crown-6], <i>M</i>	[KF], <i>M</i>
Benzene	1.01	5.2×10^{-2}
	0.34	1.4×10^{-2}
Acetonitrile	0.16	3.5×10^{-3}

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.

Charles L. Liotta,* Henry P. Harris

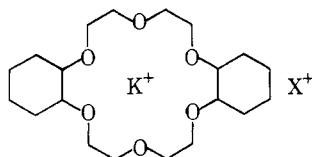
School of Chemistry, Georgia Institute of Technology
Atlanta, Georgia 30332

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Crown Ether Chemistry. Substitution Reactions of Potassium Halide and Potassium Hydroxide Complexes of Dicyclohexyl-18-crown-6¹

Sir:

The crown ethers form complexes with alkali and other metal salts which sometimes provide increased salt solubility and increased anion reactivity in aprotic organic solvents.²⁻⁵ We have now observed (1) enhanced reactivity of the KBr and KI complexes **1** and **2** in acetone in nucleophilic substitution and elimination reactions and (2) a surprisingly facile, nucleophilic aromatic substitution reaction of the previously reported² KOH complex **3** in aromatic hydrocarbons.



- 1, X⁻ = Br⁻
- 2, X⁻ = I⁻
- 3, X⁻ = OH⁻; OCH₃⁻

Potassium bromide is essentially insoluble in refluxing anhydrous acetone, even when an equimolar amount of dicyclohexyl-18-crown-6 is present. Pure crystalline **1** was prepared by Pedersen's method² using methanol to solubilize the KBr and crown ether. Dissolution of **1** in acetone then gives 0.06–0.07 *M* solutions. Complex **2** (0.16 *M* in acetone) and **3** (0.3 *M* in toluene) were prepared similarly.⁶

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

(2) (a) C. J. Pedersen, *J. Amer. Chem. Soc.*, **92**, 391 (1970); *Fed. Proc., Fed. Amer. Soc. Exp. Biol.*, **27**, 1305 (1968); (b) C. J. Pedersen and H. K. Frensdorff, *Angew. Chem.*, **84**, 16 (1972).

(3) D. J. Sam and H. E. Simmons, *J. Amer. Chem. Soc.*, **94**, 4024 (1972).

(4) (a) M. Svoboda, J. Hapala, and J. Zavada, *Tetrahedron Lett.*, 265 (1972); (b) R. A. Bartsch and K. E. Wiegers, *ibid.*, 3819 (1972).

(5) C. L. Liotta, Abstracts of First Fall Organic Conference, Cape Cod, Mass., Oct 1973, Abstract No. 5.

(6) The KCl complex was formed in methanol; however, attempts to prepare crystalline KCl and KF complexes or acetone solutions of these complexes were unsuccessful.

Reaction of the pure crystalline complexes **1** and **2** with *n*-butyl brosylate in acetone at 25.0° gave clean second-order nucleophilic substitution kinetics.⁸ Because of the insolubility of KBr in acetone, little or no reaction occurs in the absence of crown complexation. It was of interest to determine the type of reactive halide (ion or ion pair) in these S_N2 reactions and to compare their reactivity with other halide salts. From a comparison of the observed rate constants, *k*₂ (Table I), the

Table I. Kinetic Data for Reaction of 0.04 *M* Salts with *n*-Butyl Brosylate in Acetone at 25.0°

MX ^d	$10^3 k_2$, l. mol ⁻¹ sec ⁻¹ ^a	α	$10^3 k_2'$, l. mol ⁻¹ sec ⁻¹ ^b
CE-KCl (isomer A)			
CE-KBr (isomer A)	9.72	0.75–0.80 ^c	
CE-KI (isomer A)	2.08	0.58–1.0 ^c	
CE-KI (isomer B)	2.32		
Bu ₄ NCl	33.5	0.58	58
Bu ₄ NBr	9.09	0.70	13
Bu ₄ NI	1.68	0.84	2.0
LiCl	0.493	0.0097	51
LiBr	2.81	0.23	12
LiI	2.97	0.83	3.6

^a Duplicate runs in good agreement were obtained. We observed the same rate constants for Bu₄NX and LiX as Winstein.⁸

^b Rate constants corrected for ion dissociation; $k_2' = k_2/\alpha$. ^c Calculated degree of dissociation using k_2' of Bu₄NX and LiX; $\alpha_{CE} = k_{2CE}/k_2'$. α for Bu₄NX and LiX were determined by conductance.⁸

^d CE = dicyclohexyl-18-crown-6.

crown complex halides show a greater nucleophilic reactivity than the predominantly dissociated *n*-Bu₄N⁺ halides and the mostly undissociated LiBr.⁸ This increased reactivity is noteworthy since the *n*-Bu₄N⁺ halides are regarded as reactive halides in organic solvents. We believe this reactivity can be attributed to significant ion dissociation. Winstein⁸ and Weaver⁹ have provided good evidence that the numerical values and trends in ordering of observed rate constants are best ascribed to reactive dissociated halide ions rather than ion pairs.¹⁰ Also, Frensdorff^{2b,11} has shown that complexation of KCl with dicyclohexyl-18-crown-6 in CH₃OH–CHCl₃ increases dissociation of ion pairs as determined by increased conductance. We conclude that crown complexation of potassium ions leads not only to increased halide reactivity but also to greater ion dissociation than *n*-Bu₄N⁺. From the data in Table I, the degree of dissociation (α) at 4×10^{-2} *M*

(7) Two cis-ring juncture isomers of dicyclohexyl-18-crown-6 are obtained from hydrogenation of dibenzo-18-crown-6. Isomer A (mp 61–62°) is the syn isomer and isomer B is the anti isomer.^{7b} Satisfactory analyses were obtained for all complexes: isomer A–KBr mp 114–115°, –KI mp 184–185°; isomer B–KBr mp 100–102°, –KI mp 120–121°.

(8) D. E. Fenton, M. Mercer, and M. R. Truter, *Biochem. Biophys. Res. Commun.*, **48**, 10 (1972).

(9) S. Winstein, L. G. Savedoff, S. Smith, I. D. R. Stevens, and J. S. Gall, *Tetrahedron Lett.*, **9**, 24 (1960). Halide ions were assayed by potentiometric titration and the Volhard method. Infinity titer analyses showed only *n*-butyl halide products.

(10) W. M. Weaver and J. D. Hutchinson, *J. Amer. Chem. Soc.*, **86**, 261 (1964).

(11) The contribution of ion-pair reactivity is now known. To accommodate the data in Table I in terms of reactive ion pairs, it is difficult to rationalize that both the crown complexed and tetraalkylammonium halide ion pairs must be much more reactive than dissociated halide ions, whereas under identical kinetic conditions lithium halide ion pairs must be much less reactive than dissociated halide ions.

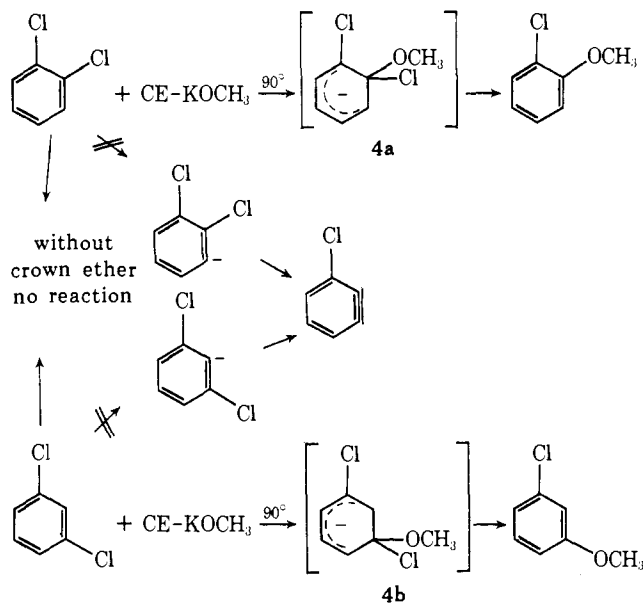
(11) H. K. Frensdorff, *J. Amer. Chem. Soc.*, **93**, 4684 (1971).

concentration calculated for isomer A-KBr complex and isomer A-KI complex, respectively, are 0.75-0.80 and 0.6-1.0.

Complex 2 can also be used as a base in aprotic solvents. This was demonstrated by reaction of 2 (0.5 M) with 2-bromooctane (0.5 M) in DMF at 100° for 6 hr. The single 2-octene product was obtained in 75-80% yield, which is nearly quantitative based on bromooctane.¹² Under identical conditions, *n*-Bu₄Br reacted similarly but slower and thus accounts for a lower yield of 2-octene (60-65%). In refluxing acetone 2 gave a lower yield of 2-octene, and the major product was mesityl oxide from acetone condensation.

We have found a surprising nucleophilic aromatic substitution reaction with the KOH complex 3.² It has been determined, however, that only 11% of the anions in toluene solution are actually OH⁻. The predominant anion is OCH₃⁻ (89%), which arises from reaction of KOH with CH₃OH during complex formation.^{13,14} This reagent has been used as a strong base in organic solvents and as an anionic polymerization catalyst. Increased chemical reactivity has been reported² for the hydroxide ion in the reagent, *e.g.*, in the saponification of hindered esters. We now report enhanced reactivity of the methoxide ion. On heating a 1.0 M solution of 3 in *o*-dichlorobenzene at 90° for 16 hr, nucleophilic aromatic substitution occurred and a 40-50% yield of *o*-chloroanisole was obtained as the sole product (Scheme I). No phenols or diphenyl ethers (hydroxide

Scheme I



ion products) or *m*-chloroanisole (benzyne product) were detected. Furthermore, the reaction with *m*-dichlorobenzene gave clean but low conversion to *m*-

(12) Liotta⁸ found that the KF-18-crown-6 complex in C₆H₆ or CH₃CN exists as a tight ion pair. Consistent with our views on the relative reactivity of ion *vs.* ion pair, the reaction of the KF complex with 2-bromooctane in C₆H₆ at 90° gave 1- and 2-octene and 2-fluorooctane and was very much slower (*t*_{1/2} = 240 hr).

(13) Attempts to prepare a KOH complex without Pedersen's solvent exchange method were unsuccessful. The use of *tert*-butyl alcohol as solvent instead of CH₃OH during complex formation gave 24% OH⁻ in the product due to a reduced equilibrium alkoxide concentration.

(14) Our assay was based on nmr, potentiometric total base titrations (OCH₃⁻ + OH⁻), Karl Fischer titrations (OH⁻, H₂O), and chemical evidence. We thank C. J. Pedersen for preparing a solution of 3 in toluene for our analyses. The titrametric results with this solution were the same as ours.

chloroanisole, perhaps because of reduced stabilization of intermediate 4b relative to 4a. No *o*-chloroanisole was detected, which clearly rules out a benzyne mechanism. Several control reactions were run, and, in the absence of crown ether, no reaction occurred. We have found no previous reference to nucleophilic aromatic substitution reactions of OCH₃⁻ with unactivated aromatic halides.

Donnie J. Sam,* Howard E. Simmons

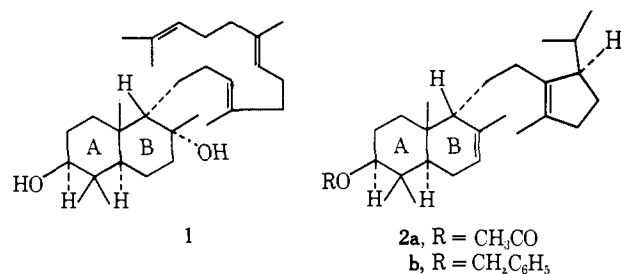
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E. I. du Pont de Nemours and Company
Wilmington, Delaware 19898

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Synthesis of Polyenes with Preformed A-B Ring Systems for Cyclization Studies in the Tetracyclic Terpenoid Series

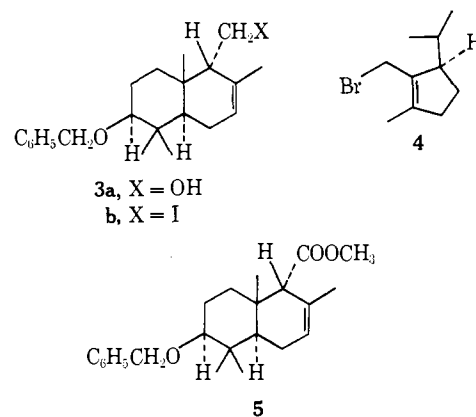
Sir:

As part of a program concerned with the bioorganic chemistry of polycyclic terpenoids, certain polyenes possessing preformed A and B rings came under consideration as potential substrates for enzymic or non-enzymic conversion to tetracyclic systems of the protosterol, lanosterol, or other type. Herein we describe stereoselective syntheses of polycycles 1 (*dl*) and 2a, sub-



jects of cyclization experiments described in the accompanying communication.

In preparation for a coupling reaction designed to produce system 2, components 3b (*dl*)¹ and 4 (*R*)² were



assembled along lines previously followed. Lithium aluminum hydride reduction of the *O*-benzyl *dl*-bicyclic ester 5 produced the expected alcohol 3a, which was

(1) (a) E. E. van Tamelen, M. Schwartz, E. J. Hessler, and A. Storni, *Chem. Commun.*, 409 (1966); (b) E. E. van Tamelen and J. P. McCormick, *J. Amer. Chem. Soc.*, **91**, 1847 (1969).

(2) E. E. van Tamelen, G. M. Milne, M. I. Suffness, M. C. Rudler-Chauvin, R. J. Anderson, and R. Achini, *J. Amer. Chem. Soc.*, **92**, 7202 (1970).