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Modified Crown Ether Catalysts. 3. Structural Parameters Affecting Phase Transfer Catalysis by Crown Ethers and a Comparison of the Effectiveness of Crown Ethers to That of Other Phase Transfer Catalysts

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Abstract: Simple crown ethers and several series of substituted dibenzo and dicyclohexano crown ethers were used to catalyze two-phase nucleophilic substitution reactions. The rates of the reaction obeyed pseudo-first-order kinetics. Within the series of substituted dibenzo crown ethers, variations in reaction rates correlated only to the electron-donating or -withdrawing effects of the substituents. Some secondary effects can be attributed to the size of the substituents. No rate correlation to the lipophilicity of the ligand was observed. On the other hand, both the binding ability and ligand lipophilicity of the simple crown ethers had major effects on catalyst performance. A comparison of the crown ethers with other phase-transfer catalysts indicated that, on a cost-effective basis, "onium" salts and poly(ethylene glycol)s were the catalysts of choice.

Introduction

One of the most important reactions in synthetic organic chemistry is the nucleophilic displacement reaction. A major problem associated with this reaction is the fact that salts containing the appropriate anion are often insoluble in the desired organic solvent. Brandström and co-workers[2a] observed that analytical chemists had for a long time been using quaternary ammonium salts to extract inorganic anions into organic solvents.[2b] They demonstrated that this technique could be used on a preparative scale for organic synthesis.[3] Starks[4] and Makosza[5] also have introduced this method into synthetic organic chemistry.

Starks has demonstrated that these "phase-transfer" reactions obey pseudo-first-order kinetics and that the observed rates of reaction were proportional to the amount of phase-transfer catalysts (PTC) used.[4,6] The reactions were found to take place in the organic layer, not in the aqueous layer or at the interface. The reaction of the nucleophile with the substrate was found to be rate limiting. Landini and co-workers[7] have shown that it is not necessary for the quaternary salt to be transported back and forth across the interface. They propose that only the anions make the crossing. They also demonstrated that for different catalysts nearly all differences in effectiveness results from differences in the partition of the catalysts between the two phases. The greater the proportion of the catalyst in the organic phase, the higher the rate of reaction.[8]

When Pedersen published his discovery of crown ethers in 1967, he demonstrated that the anions of the crown ether–salt complexes were very reactive.[9] His procedure employed no aqueous phase since the salt dissolved directly into the organic solvent. Others quickly developed the new solid–liquid phase transfer process. Phase-transfer reactions in organic chemistry have been recently reviewed.[10-13]

The neutrality of the ligand is an advantage for the use of crown ethers as phase-transfer agents. No extraneous anions are introduced into the reaction as sometimes occurs with quaternary salts. This neutrality, however, introduces several uncertainties into an understanding of the phase-transfer reaction. The active catalyst is not the neutral ligand that is added to the reaction mixture but it is the ligand–cation complex which forms in situ. The concentration of the ligand–cation complex in the organic phase, however, is a function of at least two factors: the partition of the ligand and ligand–cation complex between the organic and aqeous or dry salt phases and the stability of the ligand–cation complex in each of the phases present. It is not surprising, therefore, that little is known about what factors actually affect the performance of these catalysts. In particular it is not clear whether the stability of or the organophilicity of the crown–cation complexes exerts the predominant influence.[14,15] Knochel and co-workers have compared several ligands in solid–liquid PTC reactions, but the structure of their ligands did not vary in any systematic way.[16] Others have asserted that the more lipophilic ligands were superior catalysts in liquid–liquid PTC reactions, but their reaction conditions were not uniform and no rate data were actually given.[15,17]

To date, no study of PTC reactions has compared the catalytic ability of a series of crown ether compounds whose structures were varied systematically. Although some limited comparisons of the performance of crown esters and "onium" salts have appeared,[18,19] the PTC performance of the crown esters has not been compared to that of ammonium salts, phosphonium salts, cryptands, glymes, or poly(ethylene glycol)s under uniform reaction conditions. We now report the results of such a study.

Experimental Section

Materials and Equipment. All commercial materials were used as received, unless otherwise indicated. Chloroform (Fisher), potassium fluoride (J. T. Baker), and potassium thiocyanate (J. T. Baker) were ACS reagent grade. All other commercial materials were obtained as follows: benzodioxolane and *p*-nitrobenzyl bromide, Aldrich; hexadecyltributylphosphonium bromide, Tri-

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(1) (a) Brigham Young University. (b) Parish Chemical Co.

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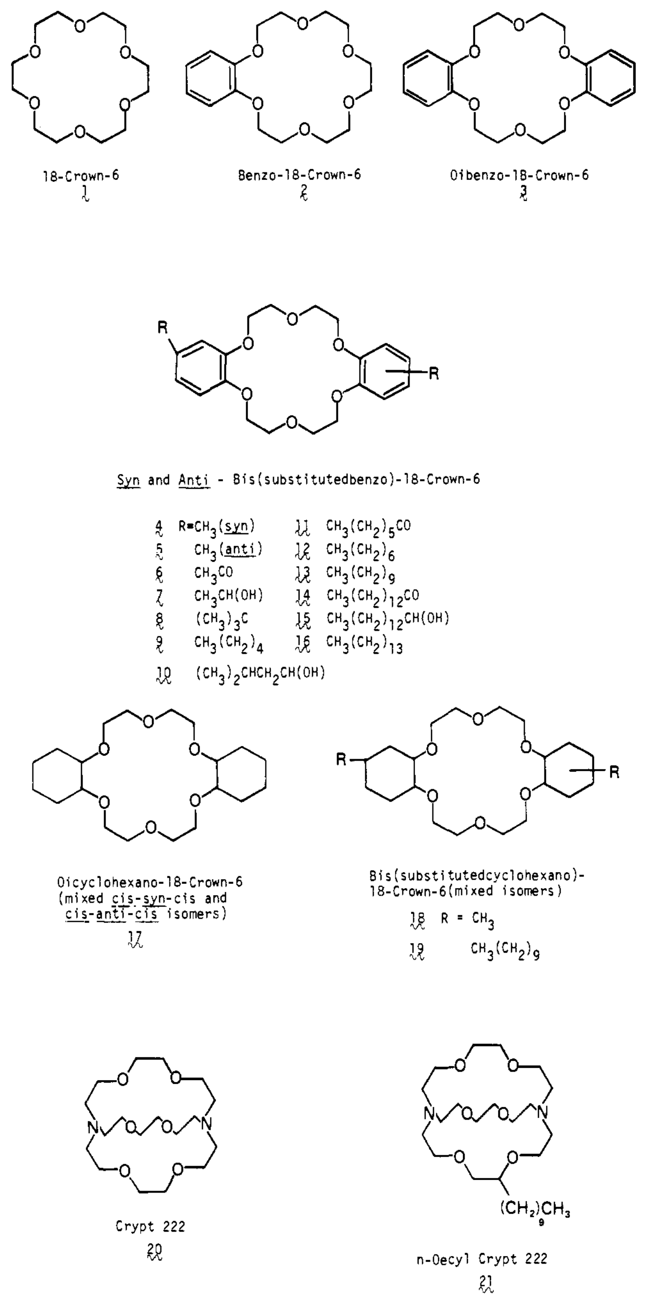

Figure 1. Crown compounds used in this study.

dom; tetrabutylammonium perchlorate, Eastman; Carbowax 20M, Varian; 18-crown-6, dibenzo-18-crown-6, dicyclohexano-18-crown-6, decaglyme, crypt 222, and *n*-decyl crypt 222, Parish Chemical Co. All other ligands (Figure 1) were prepared by us.[20,21]

All NMR spectra were obtained with a Varian EM 390 spectrometer. Infrared spectra were obtained with a Beckman Acculab 2 spectrophotometer. GLC separations were performed with a Hewlett-Packard 5700 gas chromatograph with a 6-ft Carbowax/Varaport 30 column. Regression analyses were performed with the internal program of a Hewlett-Packard 33E calculator. Elemental analyses were performed by M-H-W Laboratories, Phoenix, Ariz.

Liquid-Liquid Phase Transfer Reactions. All reactions were carried out in chloroform solution that was 0.25 M in *p*-nitrobenzyl bromide (PNBB) (substrate) and 0.15 M in benzodioxolane (BD) (internal standard). Prior to use, the chloroform was washed repeatedly with water and dried over anhydrous calcium chloride to remove ethanol, which is present in commercial reagent grade chloroform. To 15 mL of the stock solution of substrate and standard were added 0.0001 mol (accurate 0.1 mg) of the ligand to be evaluated and an approximately equimolar amount of powdered, dry salt, either potassium fluoride or potassium thiocyanate. This mixture was stirred for 5 min at 1000–1500 rpm to allow the ligand and the salt to equilibrate. A 10-mL volume of a 2.5 M solution of the corresponding salt in water was then added, and the two-phase system was stirred at 1000–1500 rpm. Samples, about 0.75 mL, of the chloroform layer were periodically removed and dried over anhydrous sodium sulfate and the ratio of substrate (PNBB) to standard (BD) was determined by NMR. The negative natural logarithms of the concentrations thus obtained were plotted as a function of time, and the slope was determined by regression analysis. The reactions were found to follow pseudo-first-order kinetics. The reaction rates are given in Tables I–III.

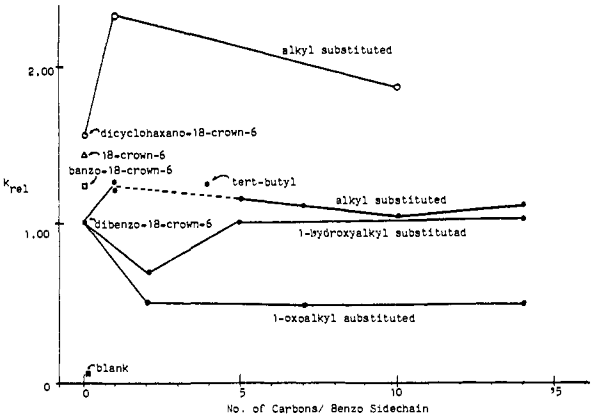

Figure 2. Liquid–liquid phase transfer catalysis of the reaction between potassium thiocyanate and *p*-nitrobenzyl bromide with substituted dibenzo-18-crown-6 compounds as catalysts unless otherwise specified.

Solid–Liquid Phase Transfer Reactions. A tenfold excess of powdered potassium iodide was added to a solution of the ligand to be tested, allyl bromide (substrate), and diisopropyl ether (internal standard) in chlorobenzene. The mixture was treated as previously described for the liquid–liquid PTC reactions.

Samples were analyzed by GLC to determine the ratio of substrate (allyl bromide) to internal standard (diisopropyl ether). A variety of ligand and substrate concentrations were used.

During the course of these experiments, when dibdenzo-18-crown-6 was the ligand, dark red-brown, cubic crystals precipitated from the reaction mixtures after several hours. The material was found to be the potassium triiodide complex of the ligand.

Anal. Calcd for $C_{20}H_{24}O_6KI_3$: C, 30.78; H, 3.10. Found: C, 31.00, H. 2.98.

Results and Discussion

The rates at which the experimental compounds catalyzed the reaction of aqueous potassium thiocyanate with *p*-nitrobenzyl bromide in chloroform solution were determined. The results were compared with each other and with the results of identical experiments carried out using common crown ethers as the catalysts. The results of these experiments (Table I) were reproducible, as is evidenced by the small differences between duplicate runs. A graphical presentation of the data (Figure 2) shows that the reaction rates are definitely related to the structures of the ligands. These correlations can be explained in terms of the ligand–metal binding constants and partition coefficients of the ligands and their complexes.

Landini[8] showed that for PTC with quaternary ammonium salts the observed rate, k_{obsd}, was proportional to the amount of catalyst in the organic phase. This may also be assumed for PTC reactions of the crown ethers. The important concentration in the latter case is that of the crown–metal complex in the organic phase. Equation 1 shows this relationship. The partitioning of crown–metal complexes has been investigated and experessions for the

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Table I. Liquid-Liquid Phase Transfer Catalysis of the Reaction between Aqueous Potassium Thiocyanate and *p*-Nitrobenzyl Bromide[a]

run no.	catalyst	k_{obsd}, 10^4 s^{-1}	r[b]	av k_{obsd}, 10^4 s^{-1}	k_{rel}
1	none	0.098	0.92		
2		0.122	0.87	0.11	0.05
3	18-crown-6 (1)	2.97	0.999		
4		3.03	0.995	3.00	1.44
5	benzo-18-crown-6 (2)	2.68	0.991		
6		2.42	0.989	2.55	1.23
7	dibenzo-18-crown-6 (3)	2.095	0.999		
8		2.072	0.994	2.08	1.00
9	*syn*-bis(methylbenzo)-18-crown-6 (4)	2.73	0.998		
10		2.56	0.999	2.64	1.27
11	*anti*-bis(methylbenzo)-18-crown-6 (5)	2.60	0.997		
12		2.48	0.997	2.54	1.22
13	bis(acetylbenzo)-18-crown-6 (6)	1.15	0.992		
14		0.99	0.994	1.07	0.51
15	bis[(1-hydroxyethyl)benzo]-18-crown-6 (7)	1.47	0.995		
16		1.46	0.995	1.465	0.70
17	bis(*tert*-butylbenzo)-18-crown-6 (8)	2.63	0.997		
18		2.60	0.995	2.62	1.26
19	bis(*n*-pentylbenzo)-18-crown-6 (9)	2.50	0.994		
20		2.31	0.994	2.40	1.15
21	bis[(1-hydroxyisopentyl)benzo]-18-crown-6 (10)	2.06	0.996		
22		2.09	0.999	2.075	1.00
23	bis(heptanoylbenzo)-18-crown-6 (11)	0.99	0.975		
24		1.06	0.996	1.01	0.49
25	bis(*n*-heptylbenzo)-18-crown-6 (12)	2.23	0.998		
26		2.32	0.998		
27		2.35	0.999		
28		2.32	0.999	2.30	1.11
29	bis(*n*-decylbenzo)-18-crown-6 (13)	2.18	0.996		
30		2.18	0.992	2.18	1.04
31	bis(tetradecanoylbenzo)-18-crown-6 (14)	0.93	0.998		
32		1.14	0.994	1.03	0.50
33	bis(1-hydroxytetradecyl)benzo]-18-crown-6 (15)	2.09	0.999		
34		2.18	0.998	2.135	1.03
35	bis(*n*-tetradecylbenzo)-18-crown-6 (16)	2.31	0.990		
36		2.30	0.986	2.305	1.11
37	dicyclohexano-18-crown-6 (17)	3.62	0.996		
38		3.29	0.993		
39		3.40	0.998	3.44	1.56
40	bis(methylcyclohexano)-18-crown-6 (18)	4.69	0.997		
41		5.05	0.991	4.87	2.34
42	bis(*n*-decylcyclohexano)-18-crown-6 (19)	3.86	0.999	3.86	1.86

[a] Each run consisted of four to six points. [b] Correlation coefficient.

various equilibria are available.[22] The association constant for the association of the anion with the crown-metal complex is assumed to be constant for our experiments. Since the total crown and metal concentrations were held constant, eq 1 can be reduced to the proportionality (2) without additional simplifying assumptions.

$$k_{obsd} = k[\mathrm{CRMA}]_{org} \tag{1}$$

CR = crown; M = metal cation; A = anion

$$k_{obsd} \propto K_s D_{\mathrm{CRMA}}/(1 + D_{\mathrm{CR}}) \tag{2}$$

$$K_s = [\mathrm{CRM}]_{org}/[\mathrm{M}]_{aq}[\mathrm{CR}]_{aq}$$

$$D_{\mathrm{CR}} = [\mathrm{CR}]_{org}/[\mathrm{CR}]_{aq} \text{ (crown partition)}$$

$$D_{\mathrm{CRMA}} = [\mathrm{CRMA}]_{org}/[\mathrm{CRMA}]_{aq} \text{ (complex partition)}$$

Based on the above expression, it would appear that changes in catalyst efficiency could be explained in terms of the ligand-metal complex stability constants and ligand lipophilicity. The latter factor, however, is difficult to predict since changes in the structure of the ligand will probably affect both partitions in the same direction, but to different degrees, and since changes in the two partitions have opposing effects on the reactions rates.

Figure 2 shows that catalysis by any of the alkylated dibenzo-18-crown-6 compounds gives rates that are 5–15% higher than those for the parent crown. All of the alkanoyl derivatives give rates only half that of the parent ligand. With the exception of the ethyl analogue, all the hydroxyalkyl derivatives gave the same rate as dibenzo-18-crown-6.

The direction of these rate changes is as would be expected on the basis of stability constants. The K_s would be lower for the electron-withdrawing carbonyl function as are the observed rates of reaction for those catalysts. The reverse is true of the alkylated ligands. Although the specific stability constants of these disubstituted dibenzo-18-crown-6 ligands are not known, their

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Table II. Comparison of Crown Ethers with Other Phase-Transfer Catalysts[a]

run no.	catalyst	k_{obsd}, 10^4 s^{-1}	r^b	av k_{obsd}, 10^4 s^{-1}	k_{rel}
3	18-crown-6 (1)	2.97	0.999		
4		3.03	0.995	3.00	1.44
5	benzo-18-crown-6 (2)	2.68	0.991		
6		2.42	0.989	2.55	1.23
7	dibenzo-18-crown-6 (3)	2.095	0.999		
8		2.072	0.994	2.08	1.00
37	dicyclohexano-18-crown-6 (17)	3.62	0.996		
38		3.29	0.993		
39		3.49	0.998	3.44	1.65
43	crypt 222 (20)	10.9		10.9	5.10
44	*n*-decyl crypt 222 (21)	12.8		12.8	6.15
45	decaglyme	2.93	0.997	2.93	1.41
46	tetrabutylammonium perchlorate	2.71	0.992		
47		2.64	0.994	2.68	1.29
48	hexadecyltetrabutylphosphonium bromide	2.09	0.996	2.09	1.00
49	carbowax 20M	1.70	0.997		
50		1.74	0.999	1.72	0.83

[a] Each run consisted of five to six points except runs 43 and 44, which were too fast to record more than two points. [b] Correlation coefficient.

Table III. Liquid-Liquid Phase Transfer of Fluoride Ion[a]

run no.	catalyst	k_{obsd}, 10^4 s^{-1}	r^b	av k_{obsd}, 10^4 s^{-1}
51	dicyclohexano-18-crown-6 (17)	2.57	0.965	
52		4.88	0.999	3.7
53	dicyclohexano-18-crown-6-KBr complex	13.96	0.993	
54		5.44	0.964	9.7
55	crypt 222 (20)	3.70	0.936	
56		7.42	0.995	5.5
57	*n*-decyl crypt 222 (21)	9.06	0.980	9.06
58	bis(*n*-tetradecylbenzo)-18-crown-6 (16)	2.27	0.954	2.27
59	bis(methylcyclohexano)-18-crown-6 (18)	7.59	0.920	7.59
60	18-crown-6 (1)	4.48	0.993	4.48
61	dibenzo-18-crown-6 (3)	no rxn		no rxn
62	tetrabutylammonium perchlorate	no rxn		no rxn
63	none	no rxn		no rxn

[a] Each run consisted of three to five points. [b] Correlation coefficient.

relative rate constants are similar to the relative stability constants observed by Smid and co-workers[23] for the binding of sodium ions by a similar series of 4-substituted benzo-15-crown-5 ligands. Thus, not only are the directions of the differences in k_{obsd} correlated to the stability constants of the complexes, but so are the general magnitudes of those differences.

In our series of substituted dibenzo-18-crown-6 compounds, the lipophilicity of the ligands is expected to increase as the size of the hydrocarbon substituent is increased. The rates of reactions catalyzed by these ligands, however, did not increase as the size of the substituent was increased. It can be assumed then that the concentration of crown-metal complex in the organic phase did not increase. In terms of the simplified expression (2), the lipophilicity of dibenzo-18-crown-6 is already so high that the ratio $D_{CRMA}/(1 + D_{CR})$ is approaching unity, and the reaction rate is solely dependent on the complex stability constant. In fact, dibenzo-18-crown-6 is reported to be almost completely in the benzene layer when partitioned between benzene and water.[22] Thus, it is not unreasonable that increasing the lipophilicity of the ligands did not produce more efficient catalysts.

Changes in ligand lipophilicity, however, can have an impact on catalyst performance. This is clearly manifest in the reaction rate data obtained for the simple crown ethers. Table I shows that the observed reaction rates with these crown ethers (runs 3–8, 37–39) do not correlate with the reported stability constants of the potassium complexes of these ligands.[24] The large increase in K_s between 18-crown-6 and dibenzo-18-crown-6 is not accompanied by an equally large increase in k_{obsd}. Furthermore, dicyclohexano-18-crown-6 catalyzed the reaction more efficiently than 18-crown-6 even though it has a lower K_s. The combined effect of both stability and partition constants does provide an explanation of the observed rates, however. The partition of dibenzo-18-crown-6 between benzene and water strongly favors the benzene, while that of 18-crown-6 strongly favors the water.[22] Thus, although 18-crown-6 binds potassium 2.3 times better than dibenzo-18-crown-6, it is less efficient at extracting the bound potassium into the organic phase and it can only accelerate the reaction 1.4 times faster than dibenzo-18-crown-6. Reported solubilities for the common crown ethers[25] indicate that the partitioning of dicyclohexano-18-crown-6 is probably intermediate to that of 18-crown-6 and dibenzo-18-crown-6. The effect of this

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is also apparent in the observed reaction rates. Even though its K_s with potassium is 10% lower than that of 18-crown-6, dicyclohexano-18-crown-6 accelerates the reaction 30% faster. Similarly, even though its K_s with potassium is 110% higher than that of dibenzo-18-crown-6, dicyclohexano-18-crown-6 is only able to accelerate the reaction 80% faster than dibenzo-18-crown-6.

The lower rates observed for reactions catalyzed by bis[(1-hydroxyethyl)benzo]-18-crown-6 (runs 15 and 16) can be explained in a similar manner. The addition of two hydroxyl groups without the addition of substantial hydrophobic bulk to the parent dibenzo crown ether results in higher water solubility for the ligand. This results in a lower concentration of the crown–metal complex in the organic phase and a correspondingly lower reaction rate. Substitution by alcohols of at least five carbons has no such deleterious effect on the reaction rates.

As the length of the alkyl group increases from one to ten carbon atoms, the bis(*n*-alkylbenzo)-18-crown-6 compounds are progressively poorer catalysts. All of these compounds are virtually water insoluble and are expected to have the same stability constants with potassium. Factors identified in expression 2, then, are probably not responsible for the observed effect and its cause is not totally clear. It is possible that longer substituents are more capable of interfering with the approach of the substrate molecule to the thiocyanate ion that is loosely associated with the crown–metal complex. The observed decline in activity is linear and has a value of 6×10^{-6} s^{-1} per carbon atom in each side chain. The same effect is noticed for reactions catalyzed by alkyl-substituted cyclohexano-18-crown-6 compounds, the methyl analogue being somewhat more effective than the *n*-decyl compound. The activity of the *tert*-butyl analogue of dibenzo-18-crown-6 is higher than would be predicted. This observation lends some support to the proposed explanation. Being spatially compact, the *tert*-butyl group is less able to interfere with the approach of a substrate molecule to the face of the complex than its linear analogue.

Glymes, poly(ethylene glycol), and crypt compounds are all known to be phase-transfer catalysts. These have never been directly compared to each other or to the more common "onium" salt and crown ether catalysts. Table II shows the results of the comparison of all these types of catalysts. The reactions used were the same as those already described for the crown ethers.

Several interesting observations can be made from these results. First, the crypt compounds are more effective catalysts than the crown ethers; however, they are very expensive ($30–150/g). Second, the alkylated (more lipophilic) cryptand was more effective than the parent compound. Third, decaglyme is just as effective as 18-crown-6. Fourth, tetrabutylammonium perchlorate was nearly as effective as 18-crown-6. In this case it should be noted that according to Landini's earlier work this salt would not be the best salt for use as a phase-transfer catalyst.[8] Fifth, Carbowax 20M [poly(ethylene glycol)] was nearly as effective as dibenzo-18-crown-6. The last observation is particularly interesting since the amount of Carbowax used was calculated on the basis of having an equimolar number of ethylene oxide moieties. Steric constraints undoubtedly prevent the polymer from simultaneously using all its oxygens for binding, while the crown ethers have no such restriction. In general, these results indicate that in liquid–liquid phase transfer reactions with soft anions crown ethers are not particularly attractive catalysts on a cost-effective basis.[26] Poly(ethylene glycol) and onium salts, therefore, appear to be the catalysts of choice.

Liquid–liquid phase transfer reactions were also carried out using aqueous potassium fluoride. Potassium fluoride was used as the reactant in order to determine whether the same factors affected the transfer of both hard and soft anions, and to the same degree. Table III shows the results of these experiments.

The reactions using potassium fluoride were so slow that they were barely detectable by the methods used. The results were not readily reproducible and the correlation coefficients (*r*) were not high. The resistance of fluoride ion to extraction from water into chloroform can be attributed to its very high enthalpy of hydration. This value is 10% higher for fluoride than for hydroxide,[27] which is noted for its resistance to phase transfer.[28] Fluoride ion has also been found to be one of the most difficult ions to transport through bulk chloroform membranes.[29]

Despite the difficulties in the potassium fluoride reactions, some tentative observations can be made. First, only the catalysts that gave the highest reaction rates with thiocyanate were able to generate any reaction with fluoride. Tetrabutylammonium perchlorate was an exception in that it was an excellent catalyst with thiocyanate but showed no reaction with fluoride. Second, within the experimental error, the ligands gave the same general order of reactivity as they did in the thiocyanate experiments. Third, with fluoride ion the increased reaction rates with the cryptands were less significant than those with thiocyanate ion.

The unexpectedly low relative efficiency of the cryptand compounds in catalyzing fluoride ion reactions may be due to a larger separation between the anion and the complexed cation with these ligands. This larger ion separation of the cryptate complexes is usually taken to be beneficial in phase-transfer catalysis, since it increases the reactivity of the anion.[30] However, association between the complexed cation and the anion does help provide the energy needed to desolvate the hydrated anion during the extractive process. This is shown by the positive correlation between the association constant and the extraction constant.[22] Thus, the higher activity of the extracted fluoride ion may be largely offset by a decrease in extractability of the complex. This effect would be far less severe for the much more readily extracted thiocyanate anion.

It was felt that part of the slowness of these reactions might result from failure of the lipophilic crowns and hydrophilic potassium fluoride to find each other and form the crown–cation complex that would be the actual phase-transfer agent. To test this idea, the preformed dicylohexano-18-crown-6–KBr complex was used as the catalyst (runs 53 and 54, Table III). There appeared to be some improvement but reproducibility was poor.

Solid–liquid phase transfer was also studied using the reaction of potassium iodide with allyl bromide in chlorobenzene. Within a few minutes a precipitate of crown–potassium bromide coated the solid particles and the kinetics was found not to be first order. Oxidation of the crown–potassium iodide complex to the corresponding triiodide was also observed. Consequently, no extensive study of solid–liquid systems was carried out.

Summary and Conclusions

This work has shown that both metal–ligand complex stability and lipophilicity have an effect on the performance of crown ethers in extractive processes. Furthermore, common crown ethers are already sufficiently lipophilic that further increases in their hydrophobic bulk provide little, if any, improvement in their performance. In a series of liquid–liquid phase transfer reactions catalyzed by substituted dibenzo-18-crown-6 compounds, the lipophilicity of the substituents was found to be unrelated to catalyst activity. Apparently, the partition of dibenzo-18-crown-6 and its potassium complex is already so large in favor of the organic phase that little improvement is possible. Once partitions have been maximized, the only relatively major factor affecting performance of the crown ethers as phase-transfer catalysts is the stability of the crown–metal ion complex.

A secondary effect was also observed. As the length of the substituent attached to the benzene ring of the crown ether was increased, the catalytic activity of the crown ether decreased. This effect was found to be linearly related to the number of carbon

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[26] For example, according to the 1979/1980 "Aldrich Handbook/Catalog of Fine Chemicals", 18-crown-6 costs $1.00/g while Adogen 464 (a commerical ammonium salt) costs 2.8¢/g and Carbowax 20M costs 3.2¢/g.

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atoms in the normal alkyl chain of the substituent. Bis(n-alkylcyclohexano)-18-crown-6 compounds exhibited the same phenomenon. The longer substituents are believed to interfere with the approach of the substrate to the crown-metal salt complex.

The fluoride ion was extremely difficult to extract into the organic phase. The hydrated fluoride ion is apparently unable to penetrate the chloroform phase to allow complexation to occur. On the other hand, ligands that are water soluble enough to enter the aqueous phase are insufficiently lipophilic to draw the fluoride back into the organic phase so that reaction can occur. Nevertheless, the use of a liquid-liquid phase transfer system with a hard anion is impractical since solid-liquid systems have been found to perform satisfactorily with these types of anions.[31]

Crown ethers, no matter how modified, do not appear to be the catalysts of choice for phase-transfer catalysis. In liquid-liquid systems where the anion is soft, onium salts were found to be just as effective as the crown ethers and poly(ethylene glycol) was found to be satisfactory. Both of these are less expensive than crown ethers and are just as convenient to use. Although cryptand compounds were superior catalysts, they were not found to be cost effective since they cost 30-150 times that of the crown ethers. In solid-liquid systems, other researchers have already shown that crown ethers offer no particular advantage over onium salts when high dielectric constant solvents like acetonitrile are used.[18] Furthermore, glymes and poly(ethylene glycol) have also been shown to be effective, even in nonpolar solvents.[32-38]

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Formation and Hydrolysis of Lactones of Phenolic Acids

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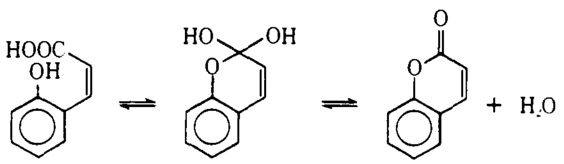
Abstract: The lactonization of 2′-hydroxybiphenyl-2-carboxylic acid to 3,4-benzocoumarin has been studied in aqueous solution, 30 °C, in the range of pH 0-6.5. As with simpler coumarinic acids, the rate-determining step changes from the breakdown of tetrahedral intermediates in the neutral or weakly acidic pH range to formation of intermediates below pH 2. In contrast, the lactonization of methyl-substituted dihydrocoumarinic acids shows no evidence for a change in rate-limiting step over a wide pH range. The hydrolysis of 8-hydroxy-1-naphthoic acid lactone in the range of pH 0-10 also does not undergo a transition in rate-limiting step. These results suggest that conjugation of the phenolic oxygen with the carbonyl carbon atom through an extended double-bond system may be necessary for the expulsion of water from a cationic tetrahedral intermediate and hence for the change in rate-determining step. Revision of the rate constants for the acid-catalyzed lactonization of dihydrocoumarinic acid and of 4,4,5,7-tetramethyldihydrocoumarinic acid indicates that the rate-enhancing effect of the "trimethyl lock" is significantly smaller than previously believed.

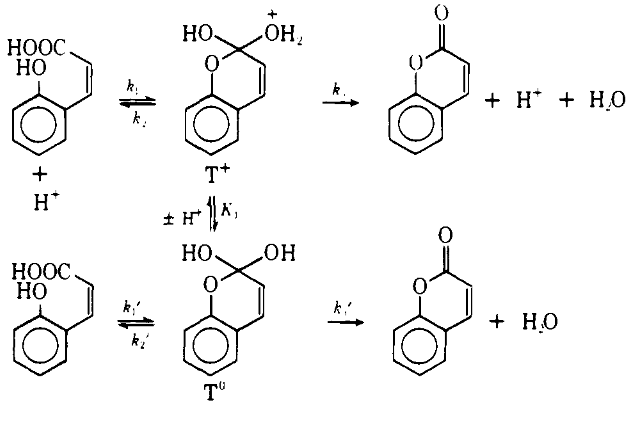
The lactonization of coumarinic acids proceeds via the formation of kinetically detectable tetrahedral addition intermediates (eq 1).[1,2] With most coumarinic acids, the rate-determining step for



(1)

lactonization changes from formation of the intermediate at low pH to breakdown of the intermediate at somewhat higher pH.[1-3] This behavior is believed to result from the different partitioning of the several ionic species of the tetrahedral intermediate between reactants and products (Scheme I). It is thought that the cationic intermediate T^+ expels mainly water ($k_3 \gg k_2$), while the neutral intermediate T^0 breaks down with predominant departure of phenol ($k_2' \gg k_3'$). In contrast, ^{18}O-exchange studies of the hydrolysis of phenyl acetate in 1.5 N HCl indicate that the ratio of the hydrolysis and exchange rates has a value of 120, so that the rate of expulsion of phenol is considerably greater than that of water, even in fairly acidic medium.[4] In addition, the lactonization of the dihydrocoumarinic acid **3** (expressed in terms of the neutral acid) in acidic aqueous solution is reported to obey the simple rate law of eq 2 and thus shows no evidence for a change in rate-limiting step with changing pH.[5]

Scheme I



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