

(m, 4-H, H-2a', H-2e', H-2a'', H-2e'').

Acknowledgment. Support of this research by the Deutsche Forschungsgemeinschaft, the Fonds der Chemischen Industrie, and the Behringwerke AG, Marburg, is gratefully acknowledged.

Crown Ethers as a Mechanistic Probe. 1. Inhibitory Effects of Crown Ethers on the Reactivity of Anionic Nucleophiles toward Diphenyl *p*-Nitrophenyl Phosphate

Junghun Suh* and Bong Seok Mun

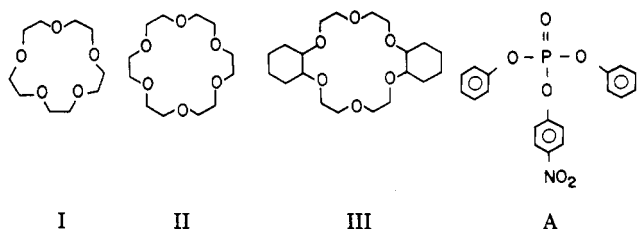
Department of Chemistry, Seoul National University,
Seoul 151-742, Korea

Received September 20, 1988

Through complex formation with cations, crown ethers affect physical and chemical behavior of both the cations and their counteranions.¹ For example, reactivities of anions are enhanced, sometimes simply due to the increased solubility of their salts in the presence of crown ethers.¹ In some cases, the intrinsic reactivity of the resultant naked anion may be raised, leading to further increases in reaction rates.² In addition, very close proximity between the catalytic group and the reaction site has been achieved with crown ether derivatives.³ Furthermore, some crown ethers are able to recognize enantiomeric differences.⁴

When a metal ion is complexed by a crown ether, its effective radius is increased, reducing the charge density.¹ This would decrease the electrostatic stabilization of the anionic centers of both the transition state and the ground state, leading to a change in the overall rate. Thus, kinetic studies in the presence of crown ethers can be used as a mechanistic probe for the characterization of the distribution of negative charges in the transition state.

In order to test whether crown ethers are generally applicable as such a mechanistic probe, we have investigated the effects of 15-crown-5 (I), 18-crown-6 (II), and dicyclohexano-18-crown-6 (III) on the rates for the reaction of anionic nucleophiles with diphenyl *p*-nitrophenyl phosphate (A) in acetonitrile. In this reaction, the *p*-



nitrophenolate of A is substituted by the nucleophiles. The anionic nucleophiles employed in the kinetic studies are phenolate (B), *p*-methoxyphenolate (C), *p*-chlorophenolate (D), 1-naphtholate (E), and ethoxide ions. The crown ethers used in the kinetic studies were chosen in view of different sizes of both the cavities and the whole molecules

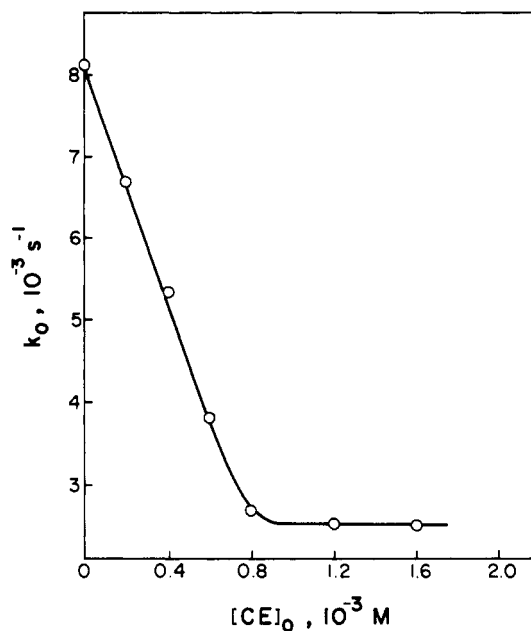


Figure 1. Dependence of the pseudo-first-order rate constant (k_0) for the reaction of 8×10^{-4} M potassium phenolate with A on the concentration of III measured in acetonitrile at 25 °C.

Table I. Parameter Values Estimated from the Kinetic Data of Nucleophilic Reactions on A in the Presence of Crown Ethers I–III^a

countercation	nucleophile	$10^2 k_0^{sp}$, s ⁻¹	$10^2 k_0^{CE}$, s ⁻¹		
			I	II	III
Na ⁺	B	4.7	1.2	0.86	0.79
Na ⁺	C	3.7	0.94	0.83	0.76
Na ⁺	E	1.0	0.38	0.30	0.27
K ⁺	B	0.81	0.54	0.38	0.25
K ⁺	C	1.0	0.76	0.54	0.43
K ⁺	D	0.88	0.50	0.43	0.26
K ⁺	ethoxide	13	5.3	2.8	2.7

^a Measured at 25 °C in acetonitrile with 0.8×10^{-3} M nucleophile.

as well as the different inductive effects imposed by the alkyl portions.¹

Results and Discussion

The degree of neutralization of the phenol derivatives with sodium or potassium ethoxide in acetonitrile was examined by measuring the UV-vis spectra of the substituted phenols (1×10^{-3} M) in the presence of sodium or potassium ethoxide [(0.2–1.7) $\times 10^{-3}$ M]. The spectral titration indicated that the phenol derivatives were completely converted into the respective phenolate ions (B–E) when 1–1.1 equiv of sodium or potassium ethoxide was added. Results of the spectral titration were not affected by the addition of crown ether II.

Nucleophiles B–E were generated in the kinetic studies by mixing sodium or potassium ethoxide (0.8×10^{-3} M) and the respective phenol (1×10^{-3} M). According to the results of the spectral titration mentioned above, the ethoxide ion is to be completely protonated by the added phenol derivatives. The reaction mixtures, therefore, contain anions B–E at the concentration of 0.8×10^{-3} M. The pseudo-first-order rate constants (k_0) measured under these conditions for the release of *p*-nitrophenol from A (initial concentration: 1×10^{-5} M) decreased as the concentration ($[CE]_0$) of initially added crown ether was raised. A typical dependence of k_0 on $[CE]_0$ is illustrated in Figure 1. From the curves for the dependence of k_0 on $[CE]_0$, the pseudo-first-order rate constant (k_0^{sp}) observed

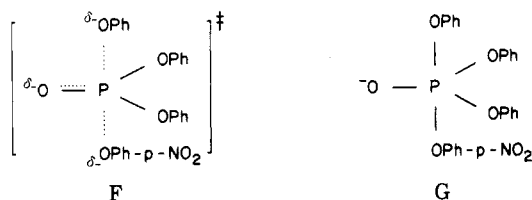
- (1) De Jong, F.; Reinhoudt, D. N. *Adv. Phys. Org. Chem.* 1980, 17, 279.
- (2) (a) Smid, J.; Varma, A. J.; Shar, S. C. *J. Am. Chem. Soc.* 1978, 100, 1426. (b) Cook, F. L.; Bowers, C. N.; Liotta, C. L. *J. Org. Chem.* 1974, 39, 3416. (c) Suh, J.; Yoon, Y. *Bull. Korean Chem. Soc.* 1985, 6, 249.
- (3) Cram, D. J.; Katz, H. E. *J. Am. Chem. Soc.* 1983, 105, 135.
- (4) Cram, D. J. *Application of Biochemical Systems in Organic Chemistry*; Jones, J. B., Sih, C. J., Perlman, D., Eds.; Wiley: New York, 1976; Part II, Chapter V.

in the absence of added crown ethers and the limiting value of the pseudo-first-order rate constant (k_0^{CE}) observed in the presence of a sufficient amount of a crown ether can be estimated. The data illustrated in Figure 1 indicate that k_0^{CE} is attained when $[\text{CE}]_0$ was similar to the concentration ($0.8 \times 10^{-3} \text{ M}$) of the added sodium or potassium salt of the phenol derivative. The values of k_0^{sp} and k_0^{CE} measured for the reaction of the phenolate anions in the presence of I-III are summarized in Table I.

The kinetic measurements were also carried out in the presence of $0.8 \times 10^{-3} \text{ M}$ potassium ethoxide and various amount of I-III without any added phenol derivative. The kinetic results are summarized in Table I.⁵

The kinetic results reveal that the rates are slower for the potassium salts of the phenolate derivatives than for the corresponding sodium salts in the presence or absence of I-III. Since the radius of potassium ion is larger than that of sodium ion, the positive-charge density of the counteraction of the anionic nucleophiles is smaller when the potassium salts were employed. In addition, rates decrease in the order of I > II > III for a given nucleophile. Considering the electronic effects and the size of the crown ethers, the charge density of the counteractions (crown ether complexed metal ions) would decrease in the order of I > II > III. Thus, the reaction rate decreases as the effective charge density of the counteraction of the nucleophile is lowered. This suggests that the electrostatic destabilization caused by the reduction of the effective charge density of the counteraction is greater for the transition state compared with the ground state.

The reactions of nucleophiles with triaryl phosphate esters may proceed through either a concerted $\text{S}_{\text{N}}2$ -like mechanism or an associative (addition followed by elimination) mechanism.⁶ In the transition states (F) for both the concerted and the associative mechanisms, the nucleophile and the leaving group occupy apical positions of the trigonal-bipyramidal phosphorus atom. In the associative mechanism, a discrete pentacovalent intermediate (G) is involved. The transition state for the associative mechanism would resemble the pentacovalent intermediate, according to Hammond's postulate.⁷



The kinetic results obtained for the phenolate nucleophiles in the presence or absence of the crown ethers indicate that a metal ion exerts greater electrostatic effects on the negative charges of the transition state compared with those of the ground state. This suggests that the negative charge is highly localized in the transition state. If the concerted mechanism is operative, the negative charge would be more delocalized in the transition state than in the ground state, on the contrary to the observed kinetic data. On the other hand, the results of the present study are compatible with the associative mechanism, for which the negative charge is considerably localized in the transition state.⁸ Thus, the inhibitory kinetic effects of

crown ethers support the associative mechanism, in agreement with other mechanistic data reported in the literature.⁶

The reactivity of ethoxide ion is only 10–20 times greater than that of B-E, although its basicity in water is about 10^6 times larger than that of B-E.⁹ If the transition state resembles G, the basicity of the nucleophiles would primarily affect the stability of the ground state. The free energy of ethoxide anion would be higher than that of anions B-E. In organic solvents, however, anions are stabilized by the counteraction. The degree of electrostatic stabilization would be greater for a more basic anion, compensating for the instability of the cation-free anion. Consequently, the difference in the energy between ethoxide ion and B-E would be much smaller in acetonitrile than in water,¹⁰ resulting in less pronounced differences in nucleophilicity.

The reactivity of ethoxide ion is also decreased by the addition of I-III. This suggests that the electrostatic interaction with a counteraction is again stronger for the negative charge developed in the transition state than for ethoxide ion.⁵

Effect of crown ethers on reactivity of anions is related to the reduction of the electrostatic interaction of the anionic nucleophile with the counteraction. Whether the consequent production of a naked anion results in acceleration or retardation of the reaction rate should depend on the anionic charge densities of both the transition state and the ground state. The present results indicate that the effects of crown ethers on reaction rates can be further used as a probe for the investigation of charge distribution in the transition state.¹¹

Experimental Section

Compound A was prepared according to the literature, mp 49–50 °C (lit 49–51 °C).¹² Phenol derivatives and crown ethers were purified by distillation or recrystallization. Acetonitrile and ethanol were dried according to the literature.¹³ Sodium or potassium ethoxide was prepared by dissolving the respective metal in ethanol.

Kinetic measurements were carried out with a Beckman Model 25 spectrophotometer by following the release of *p*-nitrophenol at 420 nm.

Temperature was controlled at 25 ± 0.1 °C with a Haake E52 circulator. Pseudo-first-order rate constants were calculated with the measured values of the infinity absorbance readings.

Acknowledgment. This work was supported by a grant from the Basic Science Research Institute Program (1988), Ministry of Education, Republic of Korea.

Registry No. I, 33100-27-5; II, 17455-13-9; III, 16069-36-6; A, 10359-36-1; B, 3229-70-7; C, 29368-59-0; D, 24573-38-4; E, 17545-30-1; ethoxide, 16331-64-9.

(8) The kinetic results suggest that the anionic oxygen linked to the phosphorus atom of pentacovalent intermediate G is stabilized by electrostatic interaction with the counteraction to a greater extent than the anionic oxygens of phenolate or ethoxide ion.

(9) Jencks, W. P.; Regenstein, J. *Handbook of Biochemistry and Molecular Biology*, 3rd ed.; Fasman, G. D., Ed.; CRC Press: Cleveland, 1976; Vol. 1, pp 305–351.

(10) The reactivities of B-E are not well correlated with the basicity⁹ measured in water. This also indicates that the reactivity of the anionic nucleophiles in acetonitrile involves some mutually compensating effects of the anions.

(11) Effect of the charge density of the counteraction on the reaction of an anionic nucleophile may be also examined by substituting the cation through the addition of salts. This is, however, accompanied by an increase in the polarity of the medium, complicating interpretation of the kinetic outcome especially when the reaction is carried out in nonaqueous media.

(12) Gulich, W. M. *J. Am. Chem. Soc.* **1966**, *99*, 2928.

(13) Perrin, D. D.; Armarego, W. L. F.; Perrin, D. R. *Purification of Laboratory Chemicals*; Pergamon: London, 1966.

(5) The values of k_0^{sp} or k_0^{CE} for the potassium salts of B-D are 6–20% of those for potassium ethoxide in the presence or absence of I-III. This excludes the possibility that the rates for B-D represent the reaction of the residual ethoxide present in the reaction mixtures.

(6) Bunton, C. A. *Acc. Chem. Res.* **1970**, *3*, 257.

(7) Hammond, G. S. *J. Am. Chem. Soc.* **1955**, *77*, 334.