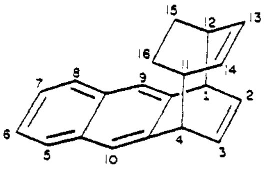
with F_2 on the signal at δ 7.5, the multiplet at δ 8.2 collapses to a doublet; with F_2 on the signal at δ 7.1, the pair of doublets at δ 6.1 collapse to a doublet; with F_2 centered on the pair of doublets at δ 6.1, the pair of doublets at δ 7.1 collapse to a doublet and the multiplet at δ 3.6 collapses to a triplet; with F_2 centered on the multiplet at δ 5.9, the multiplet at δ 5.7 collapses to a broad singlet; with F_2 centered on the multiplet at δ 5.7, the multiplet at δ 5.9 simplifies and the multiplet at δ 3.4 collapses to a triplet; with F_2 centered on the multiplet at δ 3.4, the multiplet at δ 5.7 simplifies, the multiplet at δ 3.6 collapses to a doublet, and the quintet at δ 3.1 collapses to a quartet); UV (acetonitrile) λ_{max} 362 nm (ϵ = 382 M^{-1} cm^{-1}), 344 (527), 317 (15 300), 304 (17 800), 260 (40 200) (λ (ϵ) used for UV analyses are 317 nm (1.53 × 10^4 M^{-1} cm^{-1}), 319 (1.64 × 10^4), 318 (1.51 × 10^4), 320 (1.59 × 10^4) for acetonitrile, benzene, cyclohexane, and pyridine, respectively). Chemical analysis. Found: C, 73.33; H, 4.97; Cl, 21.63.

1,4,11,12,15,16-Hexahydro-9,10-dichloro-1,4[1′,4′]-benzenoanthracene (1,4-adduct): ^1H NMR (270 MHz, $CDCl_3$) δ 1.2–1.5 (m, 4 H, H_{15}, H_{16}), 3.1–3.2 (br s, 2 H, H_{11}, H_{12}), 4.5–4.6 (m, 2 H, H_1, H_4), 6.0–6.1 (dd, 2 H, H_{13}, H_{14}), 6.3–6.4 (dd, 2 H, H_2, H_3), 7.5–7.6 (dd, 2 H, aromatic), 8.2–8.3 (dd, 2 H, aromatic) (Proton assignments referring to the numbering scheme are supported by the following spin–spin decoupling observations: with F_2 centered on the multiplet at δ 8.3, the multiplet at δ 7.6 collapses to a singlet; with F_2 centered on the multiplet at δ 7.6, the multiplet at δ 8.3 collapses to a singlet; with F_2 centered on the multiplet at δ 6.4, the multiplet at δ 4.5 collapses to a doublet); UV (cyclohexane) λ_{max} 326 mm (ϵ = 390 M^{-1} cm^{-1}), 301 (5.07 × 10^3), 292 (6.58 × 10^3).[72]



Note Added in Proof: Professor N. C. Yang has informed us that the 1,2-adduct, though not detected in benzene,[4a] was isolated and characterized in his laboratory when acetonitrile was used as irradiation solvent. For a description of this work see Srinivasachar, K. Ph.D. Dissertation, University of Chicago, 1975.

Registry No. DCA, 605-48-1; CHD, 592-57-4; DCA·CHD (9,10 adduct), 83929-13-9; DCA·CHD ((2 + 4) adduct), 83929-14-0; DCA·CHD (1,2 adduct), 83929-15-1; DCA·CHD (1,4 adduct), 83929-16-2.

Supplementary Material Available: Table I-S, a more detailed version of Table II; Tables II-S and III-S, more detailed versions of Table III; Tables IV-S–VII-S, DCA fluorescence quenching by CHD, AZ, and molecular oxygen (8 pages). Ordering information is given on any current masthead page.

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(72) Cf. ref 40, p 335, for comparison with UV spectrum of 2,3-dimethylnaphthalene.

Template Effects. 4.[1] Ion Pairing of Aryloxide Ions with Alkali Cations in 99% Me_2SO: Influence on the Rate of Formation of Benzo-18-crown-6 and of Other Williamson-Type Reactions

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Received April 5, 1982

Abstract: The effect of alkali metal ions on the rate of formation of benzo-18-crown-6 in 99% Me_2SO by cyclization of the conjugate base of *o*-hydroxyphenyl 3,6,9,12-tetraoxa-14-bromotetradecyl ether has been quantitatively accounted for according to a scheme involving separate contributions from free (k_i) and cation-paired (k_{ip}) phenoxide ion. The study has included several additional intra- and intermolecular alkylations of phenoxide ions as reference reactions to provide a set of 25 equilibrium constants for the association of five different phenoxides with the five alkali cations. Both Coulombic interaction and coordination with the neutral oxygen donors are important in determining ion pair stability, but the order in all cases is dominated by Coulombic interaction. This suggests contact interaction in the phenoxide–cation pairs, which is also consistent with evidence from the UV spectra. Whereas the rate of formation of B18C6 is depressed by Li^+ ($k_{ip}/k_i < 0.01$), the effect of the other alkali cations is rate enhancing, the maximum catalytic effect being exhibited by K^+ ($k_{ip}/k_i = 100$). In contrast, in the reference reactions the ion pairs with the alkali cations are either negligibly reactive or much less reactive than the free anions. The association constants of the alkali cations with B18C6 have been determined under the same conditions. A comparative analysis of the extent of interaction of the cations with the reactant, transition state, and reaction product of the crown ether forming reaction shows that the transition state binds cations more strongly than either the reactant or reaction product and reveals that cation interaction with both the negative charge and the neutral donors bear significant contributions to the stability of the ion pair transition state. A rationale for the template effect is presented in terms of proximity effects and chemical effects arising from interaction of the cations with the nucleophilic site of the reactant.

That alkali and alkaline earth cations may greatly facilitate the formation of crown ethers in Williamson-type reactions is a well-recognized phenomenon (template effect), which arises from complexation of the crown's precursor around the metal ion leading to what has been called a "pre-crown" complex.[2] In large ring formation, loss of the conformational entropy due to internal rotations around the single bonds of the bifunctional chain precursor provides a major contribution to the free energy of acti-

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(1) For Part 3, see ref 4. A preliminary account of a part of this work has been presented at the Fourth International Symposium on Physical Organic Chemistry, September 4–8, 1978, York, U.K.

(2) As a general reference, see: Reinhoudt, D. N.; de Jong, F. In "Progress in Macrocyclic Chemistry"; Izatt, R. M., Christensen, J. J., Eds.; Wiley: New York, 1979; Vol. 1, p 176.

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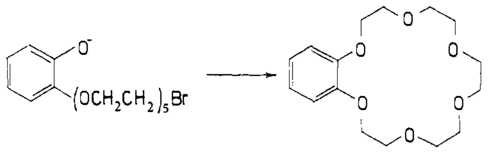
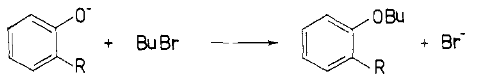
vation.[3] Reduction of the conformational entropy upon multiple coordination of the polyoxa chain with the metal ion should result in a greater "proximity" of the chain ends in the metal-associated chain than in the unassociated one. This is believed to be the basis for the template effect.[4]

In the presence of metal ions, reaction 1 is part of a more complex picture involving association equilibria with the metal ions as well as parallel noncatalyzed and metal ion catalyzed kinetic paths. A detailed analysis of the reaction requires the evaluation of equilibrium and rate constants for which the choice of the appropriate solvent seemed to be essential. The preceding papers[4,5] have described the reaction in protic solvents. We now present more far-reaching results that involve the use of 99% Me_2SO. Since in this medium the reactions are conveniently fast, we were able to carry out a complete kinetic analysis and to gain additional insight into the basic features of the template reaction. The kinetic investigation has been extended to a number of test reactions (eq 2 and 3) involving substrates **2**–**5**, whose structural variations relative to **1** contributed to an understanding of the factors at work in the association of the anionic polyether ligand **1** with the alkali cations as well as to an estimate of the nucleophilicity decrease due to ion pairing. Furthermore, we have carried out the determination of the association constants of the alkali cations with B18C6 under the same conditions and a comparative analysis of the extent of interaction of the cations with the reactant, transition state, and reaction product.



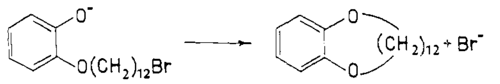
(1)

1 B18C6



(2)

2, R = H
3, R = OCH_3
4, R = $(OCH_2CH_2)_4OCH_3$



(3)

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Results

Rate and equilibrium measurements were carried out in Me_2SO–water (99:1, v/v) at 25.0 °C. The fixed water content (0.56 M) in the solvent allowed the composition of the solvent to be constant and the results to be reproducible in view of the hygroscopic character of Me_2SO and minimized the effect on the reaction rate of small changes in water content due to the added base, the rate increasing by a factor of 2.7 from 99% Me_2SO to neat Me_2SO. The water concentration in the solvent was markedly higher than that of the added salts in nearly all cases, so that possible specific hydration of the bromide ion should not alter the water content in the bulk solvent significantly, with the possible exception of the highest concentrations used (0.1–0.2 M).

The rates of intra- and intermolecular alkylations of the phenoxide reactants have been determined spectrophotometrically by monitoring the disappearance of the phenoxides on very dilute substrate solutions (ca. 1×10^{-4} M). The intermolecular reactions were run in the presence of a large excess of butyl bromide. Reactions with half-lives less than ca. 10 s were followed by a stopped-flow technique. The aryloxide ions were quantitatively generated from solutions of the parent phenols by addition of the stoichiometric amount of tetramethylammonium hydroxide. The influence of the metal cations (M^+) was studied with the whole series of alkali metals. These were added as bromides over a wide concentration range up to 0.2 M. The effect of added tetraethylammonium bromide was also studied for comparison purposes. The metal ions caused a shift of the absorption maxima of the aryloxide ions to lower wavelengths. This is shown in detail in Figure 1 in the case of compound **4**. Similar effects were observed with the other substrates.

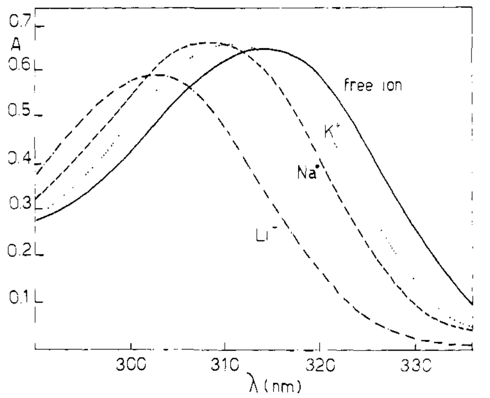

Figure 1. Effect of alkali metal bromides (0.2 M) on the UV spectrum of the tetramethylammonium salt of anion **4** (1.28×10^{-4} M) in 99% Me_2SO (cell path 10.0 mm). The spectra in the presence of rubidium and cesium bromides are practically superposable to that in the presence of potassium bromide: λ_{max} nm 302.8 (Li^+), 308.5 (Na^+), 310.9 (K^+), 311.4 (Rb^+), 311.6 (Cs^+), 314.4 (free ion).

The rate measurements were carried out at wavelengths in the neighborhood of the absorption maxima, and in all cases the absorbance decay obeyed first-order kinetics up to high conversions. A limitation in the procedure adopted was experienced with the intermolecular reactions 2 and consisted of a side reaction of the alkyl bromide with the solvent[6] that produced an acidic species. It prevented measurement of second-order rate constants lower than ca. 2×10^{-2} M^{-1} s^{-1} with reasonable accuracy.

The observed rate constants k_{obsd} are reported in detail in the Experimental Section and are graphically shown as a function of the cation concentration in Figures 2 and 3. The k_{obsd} values are virtually independent of the Et_4N^+ concentration in the whole concentration range and are quite close to the value obtained when the stoichiometric Me_4N^+ ion is the sole cation present. Hence, the k_{obsd} values in the absence of added salt may be taken with confidence as the rate constants k_i for the reactions of the free anions.

In sharp contrast with what is observed with the model reactions 2 and 3, whose rates are depressed by all alkali cations (Figure 2), the crown ether forming reaction 1 shows the unique feature that the reaction rate is markedly enhanced by all cations except Li^+ (Figure 3). The catalytic efficiency is in the order $K^+ > Rb^+ > Cs^+ > Na^+$, the maximum acceleration being 100-fold. On increasing the metal ion concentration, the k_{obsd} values increase steeply first and then tend to reach a plateau suggesting a saturation phenomenon. Downward drifts start to appear at the highest concentrations. They were especially evident when the more soluble potassium and sodium perchlorates rather than the bromides were used up to concentration as high as 1 M in occasional check experiments. Up to 0.1 M, the data are very similar whether the bromide or the perchlorate is the counterion, strongly suggesting extensive dissociation of the salts in the given concentration range.[7] The rate-depressive effect of the lithium ion is appreciable even at very low concentrations; the drop in rate

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[3] Illuminati, G.; Mandolini, L. *Acc. Chem. Res.* **1981**, *14*, 95.

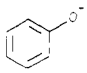
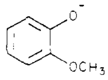
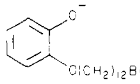
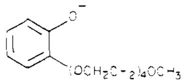
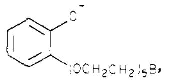
[4] Ercolani, G.; Mandolini, L.; Masci, B. *J. Am. Chem. Soc.* **1981**, *103*, 2780.

[5] Mandolini, L.; Masci, B. *J. Am. Chem. Soc.* **1977**, *99*, 7709.

[6] Galli, C.; Illuminati, G.; Mandolini, L. *J. Am. Chem. Soc.* **1973**, *95*, 8374.

[7] The conductance behavior of $NaClO_4$ and $KClO_4$ in Me_2SO has been reported to be that of typical strong electrolytes. See: Sears, P. E.; Lester, G. R.; Dawson, L. R. *J. Phys. Chem.* **1956**, *60*, 1433.

Table I. Log K_{O^-} Values for the Association of the Aryloxide Ions with Alkali Metal Ions in 99% Me_2SO at 25 °C

ArO^-	formula number	Li^+	Na^+	K^+	Rb^+	Cs^+
	2	2.47	1.6	~1	~1	~1
	3	3.26	2.64	1.7	1.6	1.6
	5	3.25	2.31	1.6	1.4	1.4
	4	3.06	2.85	2.43	2.37	2.21
	1	3.05	2.62	2.51	2.41	2.26

is 45-fold at 0.1 M, with no tendency toward a saturation phenomenon.

Treatment of Kinetic Data. The influence of alkali metal ions on the rate of the investigated reactions can be quantitatively accounted for by the hypothesis that the overall reaction rate is given by independent contributions from the free anion ArO^- and the ion pair ArO^-M^+, according to eq 4, which holds for the

$$v = k_i[ArO^-] + k_{ip}[ArO^-M^+] \tag{4}$$

intramolecular reactions. The intermolecular reactions require v to be replaced by $v/[BuBr]$. Equation 4 can be converted into eq 5, where k_{obsd} is given by $v/[ArO^-]_{tot}$ or $v/[BuBr][ArO^-]_{tot}$ for

$$k_{obsd} = k_i \frac{1 + (k_{ip}/k_i)K_{O^-}\gamma_\pm^2[M^+]}{1 + K_{O^-}\gamma_\pm^2[M^+]} \tag{5}$$

the intra- and intermolecular reactions, respectively, and K_{O^-} is the thermodynamic equilibrium constant for ion pairing:

$$K_{O^-} = \frac{[ArO^-M^+]}{[ArO^-][M^+]\gamma_\pm^2} \tag{6}$$

If eq 5 is rearranged into eq 7, the K_{O^-} and k_{ip} constants can be

$$k_{obsd} = k_{ip} - \frac{k_{obsd} - k_i}{K_{O^-}\gamma_\pm^2[M^+]} \tag{7}$$

evaluated from the least-squares slope and intercept, respectively, of the plot of k_{obsd} vs. $(k_{obsd} - k_i)/[M^+]\gamma_\pm^2$.

The mean activity coefficient $\gamma_\pm$ was calculated from eq 8, which was derived as reported in the Appendix.

$$\log \gamma_\pm = -1.12\mu^{1/2} + 1.65\mu \tag{8}$$

The term $[M^+]$ that appears in eq 5 and 7 refers to free ion concentration. On the basis of the assumption of complete dissociation of the alkali bromides, $[M^+]$ could be set equal to the added salt concentration whenever the latter was much greater than $[ArO^-]_{tot}$. But even when the added salt concentration was comparable to or lower than $[ArO^-]_{tot}$, it can be a posteriori verified that in no case is the fraction of cation sequestered by the reactant (and in the case of reaction 1 also by the product) greater than one-tenth. Therefore the total salt concentration is in all cases a reasonable approximation for $[M^+]$. Nevertheless, the least-squares treatment was carried out with the exclusion of the k_{obsd} values at too low salt concentrations where, also, large relative errors on the $(k_{obsd} - k_i)$ differences make the procedure less reliable, as well as of those in the downward drift regions.

The log K_{O^-} values were obtained for the interaction of the aryloxide ions with all the alkali cations (Table I), whereas the k_{ip} values for reactions 1 and 2, R = $(OCH_2CH_2)_4OCH_3$, could be obtained with Na^+, K^+, Rb^+, and Cs^+ ions but not with Li^+ (Table II). For Li^+, the intercepts of the plots of eq 7 were not significantly different from zero. This was also found to be the case for all the remaining reactions with the whole series of alkali cations.[8] This means that in all these cases the quantity $(k_{ip}/k_i)K_{O^-}\gamma_\pm^2[M^+]$ of eq 5 is negligible with respect to one even at the highest cation concentrations. The experimental data are well described by the lines calculated on the basis of eq 5 (Figures 2 and 3) except at the higher salt concentrations with reaction 1[9] (Figure 3). Since in the reference reaction 2, R = $(OCH_2CH_2)_4OCH_3$, saturation would be observed at concentrations in the order of 1 M, only limited portions of the predicted sigmoid-shaped profiles could be observed. The k_{ip} values, though presumably not highly precise, are nevertheless believed to reflect a real phenomenon.

Table II. Reactivity of Ion Pairs in Reactions 1 and 2, R = $(OCH_2CH_2)_4OCH_3$

	reaction 1			reaction 2, R = $(OCH_2CH_2)_4OCH_3$		
cation[a]	k_{ip}, s^{-1}	k_{ip}/k_i	log $K_\ddagger$	$k_{ip} \times 10^2$, $M^{-1}\,s^{-1}$	k_{ip}/k_i	log $K_\ddagger$
Na^+	0.0494	6.1	3.50	0.77	0.035	1.39
K^+	0.812	100	4.51	1.45	0.065	1.24
Rb^+	0.349	43	4.04	1.58	0.071	1.22
Cs^+	0.156	19	3.54	1.54	0.069	1.05

[a] In the case of Li^+, k_{ip} was negligibly small in both cases. For this cation, k_{ip}/k_i can be estimated to be no greater than 0.01; i.e., log $K_\ddagger < 1$.

Scheme I

$$\begin{tikzcd}
ArO^- \arrow[r, shift left, "K_i^{\neq}"] \arrow[d, shift right, "+M^+"'] & {[ArO^-]^{\neq}} \arrow[l, shift left] \arrow[d, shift right, "+M^+"'] \\
ArO^-M^+ \arrow[u, shift right, "K_{O^-}"'] \arrow[r, shift left, "K_{ip}^{\neq}"] & {[ArO^-M^+]^{\neq}} \arrow[l, shift left] \arrow[u, shift right, "K_{\neq}"']
\end{tikzcd}$$

Although in a strict sense eq 5 predicts no influence on k_{obsd} not only when K_{O^-} is very small but also when $k_{ip} = k_i$ even if K_{O^-} is very large, we believe it more reasonable to interpret the lack of any significant influence of added Et_4N^+ ion as indicative of a negligible association with the aryl oxide ions. This interpretation is in agreement with available evidence from conductance data indicating that tetraalkylammonium salts behave as strong electrolytes in Me_2SO solution,[10] with the notable exception of tetrabutylammonium dibenzoylmethide for which an association constant of 160 M^{-1} has been reported.[11]

According to the transition-state theory, eq 5 is equivalent to

$$k_{obsd} = k_i \frac{1 + K_\ddagger\gamma_\pm^2[M^+]}{1 + K_{O^-}\gamma_\pm^2[M^+]} \tag{9}$$

where $K_\ddagger$ given by eq 10 has the meaning of the equilibrium

$$K_\ddagger = (k_{ip}/k_i)K_{O^-} \tag{10}$$

constant[12] for conversion of the transition state that does not contain M^+ into the one that contains M^+ (Scheme I). It is a quantity that will prove useful for discussion of structural effects

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[8] As Figure 3 clearly shows, the investigated concentration range reduces sometimes to a very limited one. The extreme case is the reaction of the unsubstituted phenoxide in the presence of the heavier cations, where a very meager portion of the profiles is experimentally accessible. We have assumed by analogy with reaction 3 that also in these cases the ion pair contribution to the overall rate is negligibly small and have calculated the K_{O^-} values accordingly.

[9] We suspect that this phenomenon is due to conversion of the ion pairs into less reactive triplets or higher aggregates, but other factors may play a role.

[10] (a) Arrington, D. E.; Griswald, E. *J. Phys. Chem.* **1970**, *74*, 123. (b) Jha, J. S.; Singh, S.; Gopal, R. *Bull. Chem. Soc. Jpn.* **1975**, *48*, 2782.

[11] De Palma, V. M.; Arnett, E. M. *J. Am. Chem. Soc.* **1978**, *100*, 3514.

[12] Hammett, L. P. "Physical Organic Chemistry", 2nd ed.; McGraw-Hill: New York, 1970; Chapter 5.

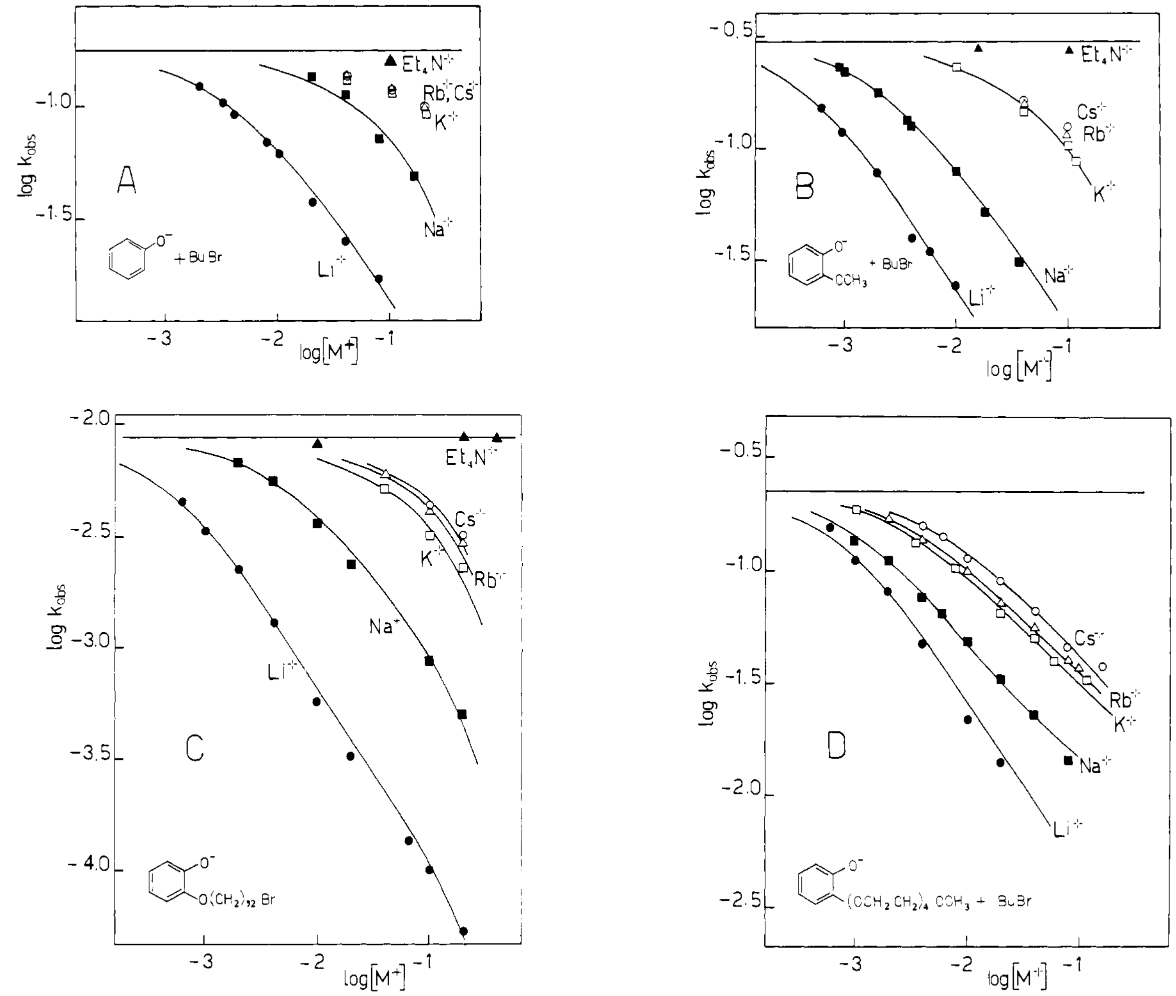

Figure 2. Effect of tetraethylammonium and alkali metal bromides on the rate of the reference reactions in 99% Me_2SO at 25.0 °C: (A) reaction 2, R = H, k_{obsd} in M^{-1} s^{-1}; (B) reaction 2, R = OCH_3, k_{obsd} in M^{-1} s^{-1}; (C) reaction 3, k_{obsd} in s^{-1}; (D) reaction 2, R = $(OCH_2CH_2)_4OCH_3$, k_{obsd} in M^{-1} s^{-1}. The horizontal lines represent the rate coefficients in the absence of added salts. The points are experimental, and the solid lines are calculated from eq 5.

on what is commonly called reactivity of ion pairs in comparison with reactivity of free ions.[13] Whenever possible, log $K_{\ddagger}$ values have been calculated and reported in Table II. In all the remaining cases, the $K_{\ddagger}$ values can be assumed to be lower than about 10, which is the detection limit imposed in ordinary precision work to 1:1 associations by complications arising from medium effects.

Direct Determination of K_{O^-}. In order to test the reliability of the K_{O^-} values obtained by the kinetic method, we have carried out an independent determination under the same conditions. This was done for the interaction of **4** with K^+. The determination was based on the absorbance changes of the UV spectrum of **4** (Figure 1) upon addition of increasing amounts of KBr. The result of this determination was a log K_{O^-} value of 2.53, which compares well with the value of 2.43 derived from the kinetics and fully supports the validity of our analysis.

Determination of K_C. The determination of the equilibrium constants K_C for association of B18C6 with Na^+, K^+, Rb^+, and Cs^+ was based on the small but measurable changes of the UV spectrum of the crown ether arising from addition of the alkali bromides. Log K_C was found to be 1.70 for Na^+, 2.85 for K^+, 2.49 for Rb^+, 2.25 for Cs^+, and too small to measure for Li^+. These values are significantly lower than those found in MeOH[14] and in CH_3CN.[15] The lower stability in Me_2SO can be attributed to the stronger cation-solvating ability[16] of this solvent relative to MeOH and CH_3CN.

The selectivity order among cations is that generally found with 18-crown-6 ethers, i.e., K > Rb > Cs > Na >> Li, except that the position of Na is often variable.[14,17] Cation solvation energies and other factors contribute to the stability of complexes in addition to the well-recognized effect[18] of the fit to the ligand cavity size.

Discussion

Catalysis and inhibition by alkali metal ions on intra- and intermolecular alkylations of aryloxide ions have been quantitatively accounted for on the basis of a common kinetic model which is basically that proposed by Acree[19] for reactions involving separate contributions from free and associated anions and correctly fits into the modern concept of ion pairs as kinetically distinguishable chemical entities with respect to free ions.[20] The

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(13) As Hammett has pointed out, "Since the ion pair and the free ion are in mobile equilibrium, the question of the mechanism by which the transition state which contains M^+ is formed is irrelevant" (ref 12, p 213). Therefore, in a strict sense, the concept of reactive (unreactive) ion pair is ambiguous and of limited scope. We nevertheless prefer to maintain its usage as a sort of shorthand notation indicating that under a given set of experimental conditions, ion pairing in the transition state is significant (negligible). Moreover, the statement that the reactivity of the ion pair is greater or smaller than that of the free ion means that ion pairing in the transition state is stronger or weaker than that in the initial state.

(14) Ercolani, G.; Mandolini, L.; Masci, B. *J. Am. Chem. Soc.* **1981**, *103*, 7484.

(15) Hofmanova, A.; Koryta, J.; Brezina, M.; Mittal, L. *Inorg. Chim. Acta* **1978**, *28*, 73.

(16) Cox, B. G.; Hedwig, G. R.; Parker, A. J.; Wattes, D. W. *Aust. J. Chem.* **1974**, *27*, 477.

(17) Poonia, N. S.; Bajaj, A. V. *Chem. Rev.* **1979**, *79*, 389.

(18) Lamb, J. D.; Izatt, R. M.; Swain, C. S.; Christensen, J. J. *J. Am. Chem. Soc.* **1980**, *102*, 475.

(19) Acree, S. F. *Am. Chem. J.* **1912**, *48*, 352.

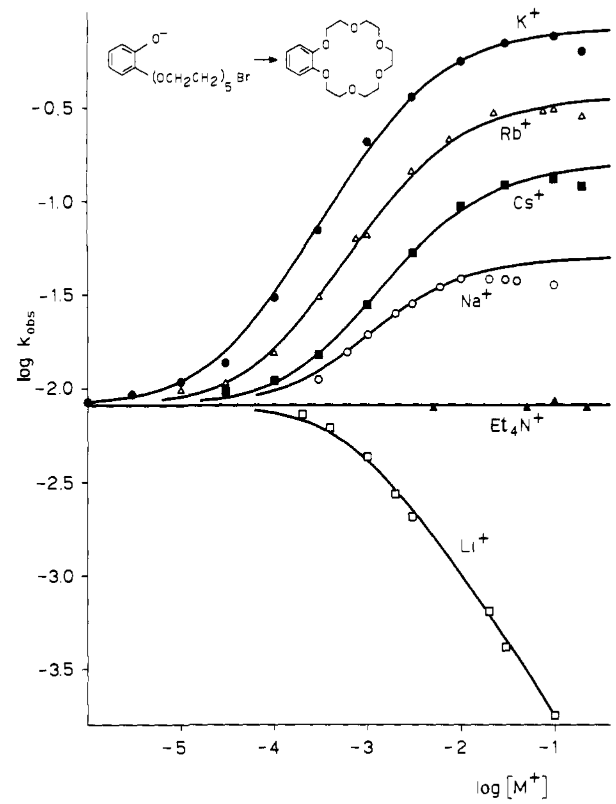


Figure 3. Effect of tetraethylammonium and alkali metal bromides on the rate of the crown ether forming reaction 1 in 99% Me_2SO at 25.0 °C. The horizontal line represents the rate coefficient in the absence of added salts. The points are experimental (k_{obsd} in s^{-1}), and the solid lines are calculated from eq 5.

basic feature of the present method is that the relative proportions of cation-associated and unassociated aryloxide ions are varied over a very wide range by virtue of the mass law effect exerted by varying amounts of added strong electrolytes. As a consequence, ion pairing effects on reaction rates become so large that their recognition is not obscured by other concentration-dependent effects such as medium effects. Self-consistency is another feature of our kinetic approach, which does not rely upon ion pairing constants from other physicochemical techniques but can in fact be regarded as a valuable tool for determination of ion pairing constants.

In the discussion that follows, we first present an analysis of structure and cation effects on ion pairing between the alkali cations and the aryloxide ions herein investigated. This will yield useful information for the quantitative treatment of the effect of ion pairing on reactivity.

Stability and Structure of the Ion Pair. The strongest associations are found for the lithium ion (Table I). For each anion the extent of ion pairing decreases in the order $Li^+ >> Na^+ > K^+ \gtrsim Rb^+ \gtrsim Cs^+$, which is apparently dominated by the stronger cation–anion interaction of the smaller cations despite the fact that the latter are more effectively solvated by Me_2SO.[21] The order is the same as that observed for the association of t-BuO^- with alkali cations in Me_2SO,[22] but the stabilities with the aryloxide ions are markedly lower and much less spaced because the negative charge is delocalized in the latter anions.

The dominance of cation–anion interactions suggests contact ion pairing in the ArO^-M^+ species. This conclusion is in accordance with the observed cation effects on the electronic spectra of the aryloxides (Figure 1). The hypsochromic shift is maximum for Li^+ and decreases to Cs^+ in the way expected on the basis of the increasing interionic distance in a contact ion pair,[23] as shown by the linear relationship of the absorption frequency with the reciprocal ionic radii (Figure 4).

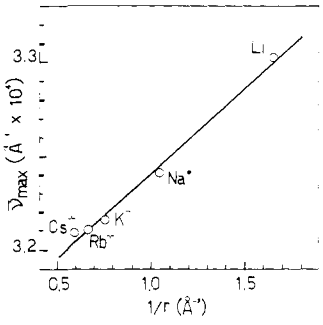
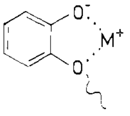


Figure 4. Plot of the UV absorption wave number of the alkali metal salts of anion 4 vs. the reciprocal ionic radii (Pauling).

There are striking differences in the nature of the ion pairs in going from MeOH[14] to 99% Me_2SO. Thus, the equilibrium constants with anion 4 follow diverse orders especially with regard to lithium, whose association along the alkali metal series is the strongest in 99% Me_2SO and the weakest in MeOH. A major factor controlling the behavior in MeOH is specific solvation (H bonding) of the aryloxide ion, which is responsible for preventing the formation of contact ion pairs. In contrast, absence of this factor in the essentially aprotic 99% Me_2SO, in which contact ion pairing occurs, is thought to allow sufficiently strong anion–cation interactions as to overcome the strong solvating ability of this solvent toward cations.

The importance of the presence of several donor sites in the anion molecule is clearly shown by the fact (Table I) that anions **1** and **4**, bearing an ortho quinquedentate side chain, associate much more strongly with all the metal ions than the unsubstituted phenoxide ion **2**, indicating that a contribution for association is provided by interaction with the ethereal oxygens. Chelation with the ether oxygen connected through the rigid o-phenylene moiety, as shown by structure **6**, is undoubtedly important with all the metal ions, as indicated by the fact that anions **3** and **5**, having such an ether oxygen as the sole neutral donor, interact more strongly with the alkali cations by 0.5 to 1.0 log unit than the unsubstituted phenoxide does. On going from the bidentate anionic ligands **3** and **5** to the sexadentate anionic ligands **1** and **4**, a further increase in ion pair stability by 0.6 to 1.0 log unit is noted with the metal ions from K^+ to Cs^+. The effect can be interpreted in terms of multiple coordination of the metal ions with the polyoxa chains, which may also be described as a built-in solvated contact pair. This is represented in structure **7**, although other rapidly equilibrating structures with lower coordination number may also be important. The stabilizing effect of multiple coordination is still appreciable for Na^+ but is apparently unimportant for Li^+. In conclusion, the tendency of multiple interaction with the side chain of the anionic ligands **1** and **4** appears to vary inversely with the solvation energies of the cations. This is not unexpected, since extensive interaction with the polyether chain requires displacement of several cation-coordinated solvent molecules.



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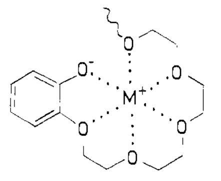

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Effect of Ion Pairing on Reactivity. The alkali metal ions are all rate depressing in the test reactions, the effect decreasing regularly from Li^+ to Cs^+. We have shown that the reactions of

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(20) Szwarc, M. In "Ions and Ion Pairs in Organic Reactions"; Szwarc, M., Ed.; Wiley-Interscience: New York, 1972; Vol. 1, Chapter 1.

(21) Burgess, J. "Metal Ions in Solution"; Ellis Horwood: Chichester, U.K., 1978; Chapter 7.

(22) Exner, J. H.; Steiner, E. C. *J. Am. Chem. Soc.* **1974**, *96*, 1782.

(23) Smid, J. In "Ions and Ion Pairs in Organic Chemistry"; Szwarc, M., Ed.; Wiley-Interscience: New York, 1972; Vol. 1, Chapter 3.

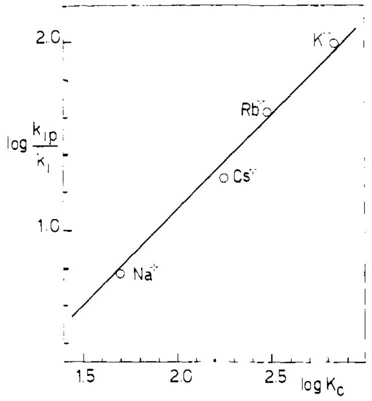
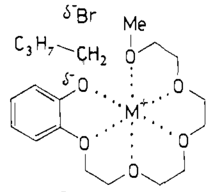


Figure 5. Catalytic efficiency of the alkali metal ions on the crown ether forming reaction 1 vs. association tendency with the reaction product, B18C6. The slope of the straight line is 1.00, and the intercept is −0.90.

2, **3**, and **5** proceed exclusively through the free ion path. As the metal ion is added, the overall rate is lowered to extents reflecting the K_{O^-} values because the equilibrium concentration of the ion pair increases at the expenses of the free ion. The low reactivity of ion pairs in S_N2 reactions between anions and neutral molecules is well documented.[11,24-27] It arises from the fact that ion pairing in the transition state is weaker, and in fact negligible in the reactions of **2**, **3**, and **5**, than that in the initial state because of extensive dispersal of the negative charge of the nucleophile on a three-atom system.

The behavior of **4** (i.e., multidentate but engaged in an intermolecular reaction), is noteworthy among the cation-inhibited reactions since it is the only one involving measurable k_{ip} values in the order $K^+ \simeq Rb^+ \simeq Cs^+ > Na^+$. Still, for the heavier metal ions, the ion pair reactivity is ca. $^1/_{15}$ as large as that of the free ion, and ca. $^1/_{30}$ in the case of sodium. Apparently, multiple coordination of the cation by the polyether chain, whose occurrence in the initial state is indicated by the K_{O^-} values, as discussed above, is still operative in the transition state, as schematically depicted in **8**. The stabilizing interaction due to multiple coordination adds to that of cation–anion interaction and renders the fraction of cation-associated transition state significant under our experimental conditions. It is noteworthy that the log $K_‡$ values (Table II) decrease regularly from Na^+ to Cs^+ as the log K_{O^-} values do. This suggests that the stability order of the ion-paired transition state is also controlled by cation–anion interaction.



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The ion pair between **4** and Li^+ is apparently unreactive ($k_{ip}/k_i < 0.01$) and behaves like the ones resulting from **2**, **3**, and **5**.

Crown Ether Forming Reaction. We now turn to the crown ether forming reaction (eq 1), which is the only one in the group whose rate is enhanced by the alkali metal ions from Na^+ to Cs^+, because the reactivities of the ion pairs are greater than that of the free ion. When compared to the test reactions, it is clear that rate enhancement is only possible when the intramolecular character is combined with the multidentate ligand character in the same reacting system. The effect is made particularly spectacular when compared to the rate-depressing influence of Li^+, whose association with the anionic reactant leads to an unreactive ion pair, as it was found to occur with all the aryloxide ions herein investigated. The catalytic efficiency (Table II, reaction 1) is at a maximum for K^+ and decreases in the order $K^+ > Rb^+ > Cs^+ > Na^+$. The order is the same as that observed for interaction of the cation with B18C6. Indeed a linear free energy relationship is observed between the related sets of data, which are plotted in Figure 5 and described by eq 11. The unit

$$\log (k_{ip}/k_i) = \log K_C - 0.90 \qquad (11)$$

slope indicates that there is a direct link between the metal ion effects observed with reaction 1 and the metal ion association constants of the reaction product, B18C6.

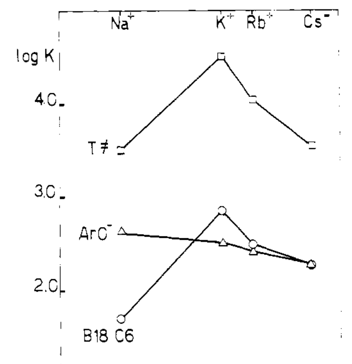
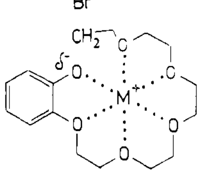


Figure 6. Log K for the association of alkali metal ions with reactant (ArO^-), transition state ($T^‡$), and reaction product (B18C6) in the crown ether forming reaction 1 in 99% Me_2SO at 25.0 °C.

Considerable insight into the transition-state structure is provided by comparison of the log K's for the associations of the reactant, transition state, and reaction product with the metal ions. These quantities are plotted in Figure 6 as a function of the ionic radius.[28] The observed difference between log $K_‡$ and log K_{O^-} for a given cation is of great significance, in view of its being equal to log (k_{ip}/k_i), see eq 10. We first note that the negatively charged ring-shaped transition state binds cations much more strongly than either the open-chain anionic reactant or the neutral cyclic product do. Furthermore, whereas the log K_{O^-} values monotonically decrease as the size of the cation increases and depend but slightly on the metal ion, both log $K_‡$ and log K_C values are markedly cation dependent and exhibit a similarly structured profile. Thus, the effect of the variation of cation on the stability of the ion-paired transition state primarily depends on those factors that make B18C6 a better ligand for, say, K^+ than for Na^+. This is because the transition state is cyclic and, therefore, closely resembles the geometry of the reaction product.

The parallelism between log $K_‡$ and log K_C is not, however, an exact one. The difference log $K_‡$ − log K_C grades regularly from Na^+ (1.80) to Cs^+ (1.29) and displays about the same spread as the log K_{O^-} values, thus indicating the importance of the cation–anion interaction in the transition state.

In summary, the transition state for the crown ether forming reaction binds the cation in much the same way as the macrocyclic sexadentate ligand B18C6 does, as depicted schematically by **9**.



9

The stability of **9** exceeds that of B18C6·M$^+$ because of the

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(24) (a) Lichtin, N. N.; Rao, K. N. *J. Am. Chem. Soc.* **1961**, *83*, 2417. (b) Lichtin, N. N.; Puar, M. S.; Wasserman, B. *Ibid.* **1967**, *89*, 6677.

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presence of the negative charge that favorably interacts with the cation. We assume that the $\log K_\ddagger - \log K_C$ difference is a measure of the stabilization due to such an interaction.

Because of dispersal of the negative charge over a three-atom system in the transition state, one expects cation–anion interaction to be weaker in the transition state than in the initial state. A reasonable estimate of cation–anion interaction in the initial state may be given by $\log K_{O^-} - \log K_{OH}$, K_{OH} being the equilibrium constant for association of the alkali metal ions with the parent phenol of anion **1**, i.e. a ligand with the same number and kind of donor atoms but devoid of the negative charge. On the basis of the above discussion, we may define α (eq 12) as the stabilization due to cation–anion interaction in the transition state relative to that in the initial state, so that $1 - \alpha$ is the fractional loss of stabilization due to cation–anion interaction on going from initial to transition state.

$$\alpha = \frac{\log (K_\ddagger/K_C)}{\log (K_{O^-}/K_{OH})} \qquad (12)$$

Combining eq 10 with eq 12, one obtains

$$\log (k_{ip}/k_i) = \log (K_C/K_{OH}) - (1 - \alpha) \log (K_{O^-}/K_{OH}) \qquad (13)$$

In agreement with our previous hypothesis,[4] eq 13 provides a basis for interpretation of the catalytic effect as resulting from two terms of opposite sign, since both K_C and K_{O^-} are greater than K_{OH} (vide infra). The positive term is the advantage of the cyclic B18C6 as a ligand over its acyclic analogue (macrocyclic effect) and therefore can be taken as a measure of the advantage of the cyclic transition state over the acyclic reactant, aside from any effect inherently bound to the presence of the negative charge. The latter is accounted for by the negative term, which is due to reduction of cation–anion interaction in the transition state and is a measure of the nucleophilicity decrease of the aryloxide ion caused by interaction with the metal ion. Consequently the positive term in the right-hand side of eq 13 is the maximum catalytic effect to be expected in a hypothetical cation-assisted reaction in which no nucleophilicity decrease due to cation interaction occurs, i.e., when $\alpha = 1$, and can therefore be taken as an estimate of the rate enhancement due to the increase of proximity of chain ends in the complexed reactant with respect to the uncomplexed one.

The K_{OH} values are not available in 99% Me_2SO, since we found no evidence for association with the parent phenol of anion **1**. However, if one makes the admittedly rough assumption that K_C/K_{OH} does not vary significantly in going from 99% Me_2SO to MeOH, on the basis of the known values in the latter solvent[14] the K_{OH} values are estimated to be nearly cation independent in 99% Me_2SO and in the neighborhood of 1 M^{-1}. Therefore to a first approximation, eq 13 reduces to the form

$$\log (k_{ip}/k_i) \approx \log K_C - (1 - \alpha) \log K_{O^-} \qquad (14)$$

which compares well with the empirical eq 11 since within the given approximations $\log K_{O^-}$ can be regarded to be constant. From the average value of 2.44 ± 0.18 for $\log K_{O^-}$, α is calculated as 0.63 ± 0.03. This shows that about one-third of the initial cation–anion interaction is lost in the transition state.

As to the rate-depressive effect of lithium, we note that in the light of eq 14, both contributing terms are unfavorable because the interaction with the anion is strongest along the series of the metal ions and even more importantly because the coordination with the polyether structure is the least and, in fact, negligible.

An independent and more straightforward way to evaluate the rate-enhancing factors due to proximity alone is obtained by correcting the observed catalytic factors for the reduced nucleophilicity of the oxide ion due to ion pairing. This is accomplished with reference to the intermolecular reaction of **4** with butyl bromide, since both **4** and **1** interact with the metal ions to very nearly the same extent (Table I) and the related transition states **8** and **9** have been inferred to have quite similar structures. It is therefore reasonable to assume that the nucleophilicity decrease of the nucleophilic site of **1** due to cation association is well mimicked by the corresponding decrease experienced by anion **4** and that for each cation the rate-enhancing factor due to proximity is given by the quantity[29]

$$\frac{(k_{ip}/k_i)_{intra}}{(k_{ip}/k_i)_{inter}} \qquad (15)$$

Introduction into this expression of the appropriate k_{ip}/k_i values from Table II yields a value (in log units) of 2.24 for Na^+, 3.19 for K^+, 2.78 for Rb^+, and 2.44 for Cs^+. Quite interestingly, such values not only vary in the same order as the $\log K_C$ values but also are similar to the latter for each individual metal cation. In view of the assumptions and approximations involved, this result strongly argues in behalf of the essential correctness of the two independent approaches. If the average values from the two sets are taken, the rate-enhancing factor due to the proximity effect can be set approximately at a level of $10^{2.0}$ for Na^+, $10^{2.4}$ for Cs^+, $10^{2.6}$ for Rb^+, and $10^{3.0}$ for K^+.

As long as any effect inherently bound to chemical change and solvation cancels with that related to the model reaction, the above factors are solely due to the fact that the cation-associated reactant can reach the transition state with a lesser entropic penalty than the unassociated reactant, because a fraction of the conformational entropy due to internal rotations around the bonds of the polyether chain of the latter is presumably lost upon multiple coordination with cations. These entropy factors calculated from the estimated rate enhancements due to proximity alone range from 9 eu for Na^+ to 14 eu for K^+. These are about one-half as large as the maximum conformational entropy effect, 26 eu, estimated[30] for the chain length under consideration, corresponding to a value of $10^{5.7}$ as upper limit for the magnitude of the proximity effect. This would mean that the polyether chain in the cation-bound reactant is roughly half way from the disordered situation occurring in the freely rotating chain of the uncomplexed reactant to the more ordered situation imposed by the close approach of chain ends in the ring-shaped transition state.

Template Effect and Effective Molarity. In the light of the present results, it seemed appropriate to work out a quantity that provides a measure of the template effect in cyclization reactions of bifunctional chains.

One possibility is simply to consider the rate enhancement produced by the metal ion on cyclization. However, since macrocyclizations are accompanied by the competing polymerization reactions of the bifunctional reactants through head-to-tail condensation and the ring-to-polymer ratio is increased not only by those factors that accelerate cyclization but also by those factors that inhibit polymerization, the metal ion effect on the latter must also be taken into account. Hence, assuming that the intermolecular reaction 2, R = $(OCH_2CH_2)_4OCH_3$, provides a reasonably good model for polymerization, an appropriate measure for the template effect, te(M^+), is given by the ratio of the metal ion effect on cyclization over the metal ion effect on the intermolecular reaction. We first note that te(M^+) is a concentration-dependent quantity. The limit TE(M^+) approached at high cation concentrations, namely,

$$\mathrm{te}(M^+) = \frac{(k_{obsd}/k_i)_{intra}}{(k_{obsd}/k_i)_{inter}} \qquad (16)$$

$$\mathrm{TE}(M^+) = \frac{(k_{ip}/k_i)_{intra}}{(k_{ip}/k_i)_{inter}} \qquad (17)$$

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[29] The advantage as a ligand of the cyclic transition-state leading to B18C6 over its acyclic analogue, i.e., the transition state of the intermolecular alkylation of **4**, is given by the ratio $(K_\ddagger)_{intra}/(K_\ddagger)_{inter}$. Since the K_{O^-} values for anions **1** and **4** are very nearly the same, the above ratio is practically coincident with $(k_{ip}/k_i)_{intra}/(k_{ip}/k_i)_{inter}$. Therefore the proximity effect can also be interpreted as the macrocyclic effect related to the association with the macrocyclic transition-state ligand.

[30] This estimate was made on a model system in which conversion of the cation-associated reactant into cation-associated transition state occurs at the sole expenses of the conformational entropy of the internal rotors of the OCH_2CH_2Br group, the remaining part of the molecule being fixed in a conformational situation equal to that occurring in the transition state.

coincides with the estimated rate enhancement due to the proximity effect. Remembering now the definition of effective molarity, EM,[31] eq 17 may be written as

$$\mathrm{TE}(\mathrm{M}^+) = \frac{(k_{\mathrm{ip}})_{\mathrm{intra}}/(k_{\mathrm{ip}})_{\mathrm{inter}}}{(k_{\mathrm{i}})_{\mathrm{intra}}/(k_{\mathrm{i}})_{\mathrm{inter}}} = \mathrm{EM}(\mathrm{M}^+)/\mathrm{EM} \qquad (18)$$

showing that the limiting value of the template effect also coincides with the ratio of the EM of the metal ion catalyzed reaction over that of the uncatalyzed one.[32] With the value of 0.08 M as the best EM value[33] for reaction 1, the following EM(M^+) values are calculated: 14 (Na^+), 123 (K^+), 48 (Rb^+), and 22 M (Cs^+). Since to a good approximation the EM represents the substrate concentration at which cyclization and polymerization occur at the same rate, we see that while in the absence of alkali cations concentration is a very critical factor in synthetic work, in the presence of alkali cations high dilution is not required as no significant competition by polymerization is predicted even at the highest attainable concentrations. Both a rate-enhancing factor on cyclization and a rate-depressing factor on polymerization bear significant contributions to the overall effect.

Experimental Section

UV spectrophotometric measurements were carried out at 25.0 ± 0.1 °C on a Beckman DB GT instrument with 1.00-cm quartz cuvettes. Fast reactions were followed on a Durrum Gibson stopped-flow spectrophotometer Model D-110, matched with a Hewlett-Packard storage oscilloscope Model 1207 B. Data were elaborated on a Hewlett-Packard 9820 A desk calculator.

Materials. Phenol (Erba), guaiacol (Merck), and butyl bromide (Erba) were purified by distillation. The parent phenols of anions **1**,[5] **4**,[14] and **5**,[34] benzo-18-crown-6,[4] and the tetraethylammonium and alkali bromides[4] were available from previous investigations. The mixed solvent (99% $\mathrm{Me_2SO}$) and the $\mathrm{Me_4NOH}$ stock solution were prepared and handled as before.[33,35]

Equilibrium Measurements. The K_{C} determination was carried out by adding increasing amounts of 0.2 M alkali bromide to 2 mL of 4.2–4.6 $\times 10^{-4}$ M benzo-18-crown-6 and recording the absorbance decrease at 289 nm. As full conversion to the complexed form could not be attained, the absorbance values A corrected for dilution were treated by the method of least squares according to the equation $(A_0 - A)/[\mathrm{M}^+] = K_{\mathrm{C}}A - K_{\mathrm{C}}A_\infty$. As a first approximation, the analytical $[\mathrm{M}^+]$ values were used to obtain K_{C} and A_∞. The latter were used to calculate the fraction of M^+ sequestered by the ligand. Corrected $[\mathrm{M}^+]$ values were then introduced again into the given equation. Convergency was readily achieved since the fraction of M^+ sequestered was in all cases very small. The mean K_{C} values (M^{-1}) from two to three independent determinations are as follows: Na^+, 50.1 ± 3.2; K^+, 708 ± 17; Rb^+, 309 ± 17; Cs^+, 178 ± 14. Correlation coefficients varied from 0.9971 to 0.9997.

The direct determination of K_{O^-} for association of anion **4** with K^+ was carried out by recording the absorbance changes at 331 nm on addition of increasing amounts of 0.2 M KBr to a 2.65×10^{-4} M solution of **4**. The latter was obtained by addition of a slight excess of $\mathrm{Me_4NOH}$ stock solution to the parent phenol. In order to prevent contamination by $\mathrm{CO_2}$, the addition of KBr into the cuvette was carried out by a septum-and-syringe technique. The cuvette was equipped with a small magnetic bar to perform stirring after each addition. The absorbance values after each addition were corrected for dilution and treated according to the equation $(A_0 - A)/[\mathrm{M}^+]\gamma_\pm^2 = K_{\mathrm{O}^-}A - K_{\mathrm{O}^-}A_\infty$. The iteration procedure described above was also used in this case.

Rate Measurements. Kinetic runs were started by fast addition of $\mathrm{Me_4NOH}$ stock solution to the thermostated solution of the reactant(s) and salt. The acidity content of the solvent was checked (typically 1.5×10^{-4} M) and accounted for.[34] As an even slight base excess altered the reaction rate at low cation concentration, probably owing to association between OH^- and M^+, the amount of added $\mathrm{Me_4NOH}$ was adjusted in order to have 80–90% conversion to the phenoxide ions. On the other hand, a slight base excess was used in the inhibited intermolecular reactions at high salt concentration in order to minimize the effect of the solvent reaction on butyl bromide. Slow conversion into the phenoxide ions was observed when adding $\mathrm{Me_4NOH}$ to the phenol solution containing Li^+ at high concentrations; this phenomenon, probably due to the association of OH^- with Li^+, did not prevent the determination of the first-order rate constants as it was relatively fast with respect to the studied reaction. Fast conversion was observed when mixing was carried out in the stopped-flow cell. Intermolecular alkylations were carried out under pseudo-first-order conditions with phenoxide ions in the range of 1 to 4×10^{-4} M and BuBr in the range of 2 to 8×10^{-2} M.

Rate constants k_{obsd} are reported in the following, at the various alkali and tetraethylammonium bromide concentrations, which are given in parentheses in M units. The correlation coefficients r of the treatment according to eq 7 are also reported:

Reaction 1; k_i = 8.14 × 10^{-3} s^{-1}. Li^+: 7.25×10^{-3} (2×10^{-4}), 6.09×10^{-3} (4×10^{-4}), 4.30×10^{-3} (1×10^{-3}), 2.70×10^{-3} (2×10^{-3}), 2.06×10^{-3} (3×10^{-3}), 6.41×10^{-4} (2×10^{-2}), 4.11×10^{-4} (3×10^{-2}), 1.78×10^{-4} (0.1); r = 0.9900.

Na^+: 1.10×10^{-2} (3×10^{-4}), 1.55×10^{-2} (6×10^{-4}), 1.92×10^{-2} (1×10^{-3}), 2.54×10^{-2} (2×10^{-3}), 2.81×10^{-2} (3×10^{-3}), 3.46×10^{-2} (6×10^{-3}), 3.82×10^{-2} (1×10^{-2}), 3.78×10^{-2} (2×10^{-2}), 3.76×10^{-2} (3×10^{-2}), 3.67×10^{-2} (4×10^{-2}), 3.50×10^{-2} (0.1); r = 0.9948.

K^+: 8.45×10^{-3} (1×10^{-6}), 9.27×10^{-3} (3×10^{-6}), 1.08×10^{-2} (1×10^{-5}), 1.36×10^{-2} (3×10^{-5}), 3.03×10^{-2} (1×10^{-4}), 6.97×10^{-2} (3×10^{-4}), 0.207 (1×10^{-3}), 0.357 (3×10^{-3}), 0.551 (1×10^{-2}), 0.690 (3×10^{-2}), 0.744 (0.1), 0.625 (0.2); r = 0.9810.

Rb^+: 9.82×10^{-3} (1×10^{-5}), 1.05×10^{-2} (3×10^{-5}), 1.53×10^{-2} (1×10^{-4}), 3.02×10^{-2} (3×10^{-4}), 6.21×10^{-2} (7.58×10^{-4}), 6.49×10^{-2} (1×10^{-3}), 0.142 (3×10^{-3}), 0.211 (7.58×10^{-3}), 0.291 (2.27×10^{-2}), 0.298 (7.58×10^{-2}), 0.304 (0.1), 0.283 (0.2); r = 0.9758.

Cs^+: 9.63×10^{-3} (3×10^{-5}), 1.09×10^{-2} (1×10^{-4}), 1.50×10^{-2} (3×10^{-4}), 2.77×10^{-2} (1×10^{-3}), 5.24×10^{-2} (3×10^{-3}), 9.33×10^{-2} (1×10^{-2}), 0.121 (3×10^{-2}), 0.130 (0.1), 0.119 (0.2); r = 0.9892.

$\mathrm{Et_4N}^+$: 7.79×10^{-3} (5×10^{-3}), 7.90×10^{-3} (5×10^{-2}), 8.54×10^{-3} (0.1), 7.85×10^{-3} (0.2).

Reaction 2, R = H; k_i = 0.178 M^{-1} s^{-1}. Li^+: 0.123 (2×10^{-3}), 0.104 (3.2×10^{-3}), 9.30×10^{-2} (4×10^{-3}), 6.95×10^{-2} (8×10^{-3}), 6.17×10^{-2} (1×10^{-2}), 3.77×10^{-2} (2×10^{-2}), 2.46×10^{-2} (4×10^{-2}), 1.70×10^{-2} (8×10^{-2}); r = 0.9972.

Na^+: 0.136 (2×10^{-2}), 0.112 (4×10^{-2}), 7.12×10^{-2} (8×10^{-2}), 4.87×10^{-2} (0.16).

K^+: 0.131 (5×10^{-2}), 0.114 (0.1), 9.21×10^{-2} (0.2).

Rb^+: 0.137 (5×10^{-2}), 0.117 (0.1), 9.82×10^{-2} (0.2).

Cs^+: 0.136 (5×10^{-2}), 0.121 (0.1), 9.83×10^{-2} (0.2).

$\mathrm{Et_4N}^+$: 0.159 (0.1).

Reaction 2; R = $\mathrm{OCH_3}$; k_i = 0.298 M^{-1} s^{-1}. Li^+: 0.150 (6×10^{-4}), 0.119 (9.67×10^{-4}), 7.63×10^{-2} (1.93×10^{-3}), 3.98×10^{-2} (4×10^{-3}), 3.38×10^{-2} (5.8×10^{-3}), 2.42×10^{-2} (1×10^{-2}); r = 0.9981.

Na^+: 0.231 (9.05×10^{-4}), 0.223 (1×10^{-3}), 0.176 (2×10^{-3}), 0.134 (3.62×10^{-3}), 0.124 (4×10^{-3}), 7.85×10^{-2} (1×10^{-2}), 5.13×10^{-2} (1.81×10^{-2}), 3.08×10^{-2} (3.62×10^{-2}); r = 0.9972.

K^+: 0.228 (1×10^{-2}), 0.146 (4×10^{-2}), 0.102 (0.1), 8.66×10^{-2} (0.118); r = 0.9879.

Rb^+: 0.157 (4×10^{-2}), 0.114 (0.1).

Cs^+: 0.163 (4×10^{-2}), 0.124 (0.1).

$\mathrm{Et_4N}^+$: 0.278 (1.59×10^{-2}), 0.272 (0.1).

Reaction 2, R = $\mathrm{(OCH_2CH_2)_4OCH_3}$; k_i = 0.223 M^{-1} s^{-1}. Li^+: 0.153 (6×10^{-4}), 0.109 (1×10^{-3}), 7.99×10^{-2} (2×10^{-3}), 4.67×10^{-2} (4×10^{-3}), 2.17×10^{-2} (1×10^{-2}), 1.40×10^{-2} (2×10^{-2}); r = 0.9958.

Na^+: 0.134 (1×10^{-3}), 0.109 (2×10^{-3}), 7.50×10^{-2} (4×10^{-3}), 6.35×10^{-2} (6×10^{-3}), 4.85×10^{-2} (1×10^{-2}), 3.26×10^{-2} (2×10^{-2}), 2.28×10^{-2} (4×10^{-2}), 1.40×10^{-2} (8×10^{-2}); r = 0.9980.

K^+: 0.183 (9.98×10^{-4}), 0.161 (1.97×10^{-3}), 0.131 (3.94×10^{-3}), 9.96×10^{-2}, (7.88×10^{-3}), 6.35×10^{-2} (1.97×10^{-2}), 4.93×10^{-2} (4×10^{-2}), 3.95×10^{-2} (5.91×10^{-2}), 3.20×10^{-2} (0.118); r = 0.9988.

Rb^+: 0.169 (2×10^{-3}), 0.135 (4×10^{-3}), 9.82×10^{-2} (1×10^{-2}), 7.02×10^{-2} (2×10^{-2}), 5.54×10^{-2} (4×10^{-2}), 4.00×10^{-2} (8×10^{-2}), 3.65×10^{-2} (0.1); r = 0.9946.

Cs^+: 0.158 (4×10^{-3}), 0.140 (6×10^{-3}), 0.112 (1×10^{-2}), 9.83×10^{-2} (2×10^{-2}), 6.59×10^{-2} (4×10^{-2}), 4.50×10^{-2} (8×10^{-2}), 3.71×10^{-2} (0.16); r = 0.9924.

Reaction 3; k_i = 8.81 × 10^{-3} s^{-1}. Li^+: 4.53×10^{-3} (6×10^{-4}), 3.38×10^{-3} (1×10^{-3}), 2.26×10^{-3} (2×10^{-3}), 1.31×10^{-3} (4×10^{-3}), 5.75×10^{-4} (1×10^{-2}), 3.30×10^{-4} (2×10^{-2}), 1.36×10^{-4} (6×10^{-2}), 1.02×10^{-4} (0.1), 5.29×10^{-5} (0.2); r = 0.9996.

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[31] The effective molarity EM is defined by the ratio $k_{\mathrm{intra}}/k_{\mathrm{inter}}$, where k_{intra} is the specific rate for cyclization and k_{inter} that for an intermolecular model reaction. For a more comprehensive definition, see ref 3.

[32] It should be noted that 2-ethoxyethyl bromide offers a more appropriate model than butyl bromide as it allows for the effect of a β-oxgen atom that is present in the bifunctional substrate **1**. Indeed we found[33] that in 99% $\mathrm{Me_2SO}$, butyl bromide alkylates the guaiacolate ion 3.2 times more rapidly than 2-ethoxyethyl bromide. This difference is immaterial to the present discussion, since we expect virtually exact cancellation in the EM(M^+)/EM ratio.

[33] The EM value of 0.08 M is based on the reaction of guaiacolate ion with 2-ethoxyethyl bromide. Illuminati, G.; Mandolini, L.; Masci, B. *J. Am. Chem. Soc.* **1981**, *103*, 4142.

[34] Mandolini, L.; Masci, B. *J. Org. Chem.* **1977**, *42*, 2840.

[35] Mandolini, L.; Masci, B.; Roelens, S. *J. Org. Chem.* **1977**, *42*, 3733.

Na^+: 6.71×10^{-3} (2×10^{-3}), 5.56×10^{-3} (4×10^{-3}), 3.59×10^{-3} (1×10^{-2}), 2.36×10^{-3} (2×10^{-2}), 8.71×10^{-4} (0.1), 5.05×10^{-4} (0.2); $r = 0.9907$.

K^+: 6.75×10^{-3} (1×10^{-2}), 5.22×10^{-3} (4×10^{-2}), 3.21×10^{-3} (0.1), 2.26×10^{-3} (0.2).

Rb^+: 5.99×10^{-3} (4×10^{-2}), 4.11×10^{-3} (0.1), 2.91×10^{-3} (0.2).

Cs^+: 5.69×10^{-3} (4×10^{-2}), 4.18×10^{-3} (0.1), 3.17×10^{-3} (0.2).

Et_4N^+: 8.12×10^{-3} (1×10^{-2}), 8.93×10^{-3} (0.2), 8.71×10^{-3} (0.4).

Appendix

Neglect of the activity coefficient term $\gamma_{\pm}^2$ led to a very poor fit of eq 5 to the data. As a first approximation, $\gamma_{\pm}$ was calculated from the Debye–Hückel limiting law

$$\log \gamma_{\pm} = -1.115\mu^{1/2} \qquad (19)$$

With the term $\gamma_{\pm}^2$ thus calculated, the fit was significantly better but not yet fully satisfactory. It was nevertheless apparent that for a given number of reactions k_{ip} was negligibly small. These were all the reactions carried out in the presence of Li^+, reactions 3 and 2 (R = H and OCH_3) as carried out in the presence of Na^+, and reactions 3 and 2 (R = OCH_3) as carried out in the presence of K^+. In all these cases, eq 7 may be rewritten in the form

$$K_{O^-}{}^{app} = \frac{k_i - k_{obsd}}{k_{obsd}[M^+]} \qquad (20)$$

where $K_{O^-}{}^{app} = K_{O^-}\gamma_{\pm}^2$ is the concentration association constant for ion pairing. Upon introduction of experimental data into eq 20 for each reaction, sets of concentration dependent $K_{O^-}{}^{app}$ values were obtained. By assuming that $\log \gamma_{\pm}$ is given by a power series in $\mu^{1/2}$,[36] with the first coefficient given by the Debye–Hückel theory for neat Me_2SO, the second coefficient C was determined from plots of the left-hand side of eq 21 against μ. The coefficient

$$\log K_{O^-}{}^{app} + 2.23\mu^{1/2} = \log K_{O^-} + 2C\mu \qquad (21)$$

C was found to vary somewhat for the varying phenoxide–cation pairs, but since no systematic trend was apparent, the average value of 1.65 ± 0.25 was assumed to apply to all ionic species including the Rb and Cs phenoxides. It is worth noting that up to $\mu \simeq 0.1$ M the $\gamma_{\pm}$ values calculated from eq 8 are indistinguishable within the precision of the data from those calculated from the extended Debye–Hückel equation

$$\log \gamma_{\pm} = -\frac{1.115\mu^{1/2}}{1 + 2.34\mu^{1/2}} \qquad (22)$$

which has been used by Kolthoff[37] and corresponds to a value of 6 Å for the adjustable parameter.

Registry No. 1, 65845-47-8; **1**·Li, 83897-22-7; **1**·Na, 83897-23-8; **1**·K, 83897-24-9; **1**·Rb, 83897-25-0; **1**·Cs, 83897-26-1; **1**·Et_4N, 83897-27-2; **2**, 3229-70-7; **2**·Li, 555-24-8; **2**·Na, 139-02-6; **2**·K, 100-67-4; **2**·Rb, 15589-78-3; **2**·Cs, 1120-91-8; **2**·Et_4N, 32580-85-1; **3**, 54976-95-3; **3**·Li, 20246-64-4; **3**·Na, 13052-77-2; **3**·K, 5633-98-7; **3**·Rb, 83897-28-3; **3**·Cs, 1194-05-4; **3**·Et_4N, 83897-29-4; **4**, 83897-41-0; **4**·Li, 83897-30-7; **4**·Na, 83897-31-8; **4**·K, 83897-32-9; **4**·Rb, 83897-33-0; **4**·Cs, 83897-34-1; **5**, 83897-39-6; **5**·Li, 83897-35-2; **5**·Na, 83897-36-3; **5**·K, 76670-16-1; **5**·Rb, 83897-37-4; **5**·Cs, 83897-38-5; **5**·Et_4N, 83897-40-9; B18C6, 14098-24-9; BuBr, 109-65-9; *o*-$BuOC_6H_4(OCH_2CH_2)_4OMe$, 83897-42-1; 2,3,4,5,6,7,8,9,10,11,12,13-dodecahydro-1,14-benzodioxacyclohexadecin, 62587-29-5; butoxybenzene, 1126-79-0; 1-butoxy-2-methoxybenzene, 51241-33-9.

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(36) Reference 12, Chapter 7.

(37) Kolthoff, I. M.; Chantooni, M. K., Jr.; Bhowmik, S. *J. Am. Chem. Soc.* **1968**, *90*, 23.

A Short-Step Entry to (±)-Quadrone

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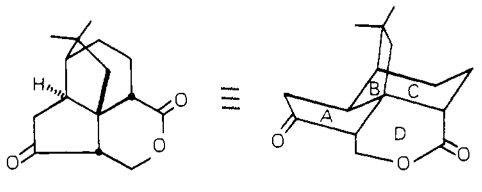
Abstract: A new synthetic route to (±)-quadrone (**1**) starting with 7,7-dimethyl-*cis*-bicyclo[4.2.0]octan-2-one (**2**) via Danishefsky's intermediate **5** is reported, in addition to the preliminary model study dealing with the synthesis of the tricyclic enone **9**. 2-(2-Propynyl)bicyclo[4.2.0]octan-2-ol (**6**) obtained from **2** was subjected to rearrangement in refluxing formic acid to produce the isomeric bicyclo[3.2.1]octanol **7** in good yield, which could have been transformed to **9** through a conventional three-step sequence of reactions in an overall yield of 47% from **2**. For the synthesis of **5**, the 3-methoxymethyl derivative of **6** derived from **2** was subjected to formolysis, yielding mainly four products: **12**–**15**. The product ratio was found to be very sensitive to the reaction conditions, and especially lowering the temperature favored increased formation of the objective compound **14**. The product mixture obtained at 25 °C was treated with PCC followed by chromatographic separation to give the [3.2.1] bicyclic ketone **17** in 31% yield from **11**. The compound **17** was then transformed to the tricyclic enone **19** according to the procedure established in the model experiment. Oxidation of the side chain of **19** to the carboxyl group by a two-step reaction afforded the key intermediate **5** in an overall yield of 4% from **2**.

Quadrone (**1**), a novel sesquiterpene reported as a fungal metabolite from *Aspergillus terreus* in 1978, exhibits inhibitory activity in vitro against human epidermoid carcinoma of the nasopharynx (KB) and in vivo against P-338 lyphocytic leukemia in mice (PS).[1] Its unique structural features embodying a quadracyclic fused ring system and its reported biological activity have received considerable attention from synthetic chemists, yielding three independent entries in recent years. The first total synthesis of (±)-**1** by Danishefsky,[2a] which was communicated in 1980, and the second one by Helquist[2b] have shared a general synthetic strategy in which the quadracyclic ring system is as-



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