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CATALYSIS BY ALKALI AND ALKALINE-EARTH METAL IONS IN NUCLEOPHILIC ATTACK OF METHOXIDE ION ON CROWN ETHERS BEARING AN INTRA-ANNULAR ACETOXY GROUP

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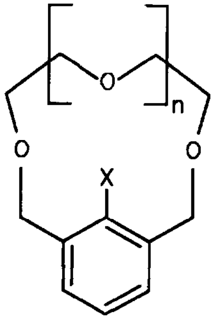
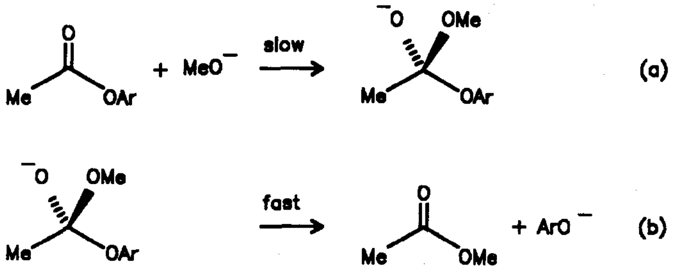
Abstract - Rates of reaction of methoxide ion with crown ethers bearing an intra-annular acetoxy group are markedly enhanced by alkali and alkaline-earth metal bromides as a result of much stronger interactions of the metal ions with transition states than with reactants.

Macrocyclic polyethers (1) containing a 1,3-xylyl unit in the macrocycle backbone plus a substituent attached to the 2-position of the aromatic moiety have attracted much attention as examples of host molecules whose binding properties can be modulated within wide limits by the intra-annular functional group in the 2-position.[1,2]



(1)

Being currently interested in the general properties and applications of macrocyclic ligands[3,4] and, more specifically, in the effect of association with metal ions on the reactivity of bound species,[5,6] we have studied the acyl transfer reaction between methoxide ion in methanol and macrocyclic ligands (1, X = OAc), where the acetoxy group is held in close proximity of a polyoxyethylene bridge of varying size (Scheme I). The simple idea underlying the present investigation was that a multidentate ligand bearing a negative charge should bind cations more strongly than a neutral ligand of similar structure.[7] Thus, the expectation was that the complexing power of the crown ether aryl acetates (1, X = OAc) should increase during the activation process leading to the rate-determining tetrahedral intermediate (Scheme 1,a), as a result of the negative charge transferred from the anionic nucleophile to the neutral acetoxy group. Were such synergism to occur, it should give rise to rate-enhancing metal ion effects, like those actually observed in a related system.[8]



Scheme I

Here we report the results of a kinetic investigation of the effect of added alkali (Na, K, Cs) and alkaline-earth (Sr, Ba) metal bromides on the rate of the second-order reaction of Me_4NOMe with 2-acetoxy-1,3-xylyl-15-crown-4 (1, X = AcO, n = 2) and 2-acetoxy-1,3-xylyl-21-crown-6 (1, X = AcO, n = 4), referred to as 2-AcO-15C4 and 2-AcO-21C6, respectively. For comparison purposes, the reaction of the parent phenyl acetate $CH_3CO_2C_6H_5$ was included as well.

RESULTS AND DISCUSSION

Rate measurements were carried out in methanol at 25.0 °C under pseudo-first-order conditions on very dilute substrate solutions (*ca.* 1×10^{-4} M) using an excess of the strong electrolyte Me_4NOMe (0.01 M) as a source of methoxide ion either in absence or in presence of metal bromides. The kinetics were followed by monitoring the appearance of the aryloxide ion absorption in the appropriate wavelength region either by conventional or stopped-flow spectrophotometry. Strictly first-order behaviour was observed in all cases up to high conversions. The results are expressed as second-order rate constants measured in presence (k_{obs}) and in absence (k_o) of added salt, respectively. These are listed in detail in the Experimental, and graphically shown in Figure 1 A-C as log plots of k_{obs}/k_o against the concentration of added salt.

It is apparent that the outcome of the kinetic experiments largely fulfils our expectations. The contrast between the rate profiles exhibited by the reference reaction of the parent phenyl acetate and those of the crown ether substrates is striking. Whereas the former (Figure 1A) is insensitive to the presence of the alkali metal ions and is accelerated only slightly by the alkali metal bromides, the latter are accelerated by all of the added salts, in a way that is a marked function of salt identity and concentration as well as of substrate structure. Observed accelerations range over nearly three orders of magnitude, the largest effects being found in all cases with the divalent metal salts. It is worth noting that whereas with 2-AcO-15C4 the k_{obs} values monotonically increase on increasing the metal salt concentration (Figure 1B), rate maxima are apparent in all of the rate profiles related to 2-AcO-21C6 (Figure 1C).

In all cases the variation of rate constants was well fitted by equation (1), which can be easily derived from transition state theory[9] and applies to bimolecular reactions where the metal ion gives significant

$$\frac{k_{obs}}{k_o} = \frac{1 + K_T\#\gamma^2[M^{z+}]}{(1 + K_{AcOAr}[M^{z+}])\ (1 + K_{MeO}\gamma^2[M^{z+}])} \qquad (1)$$

associations of 1:1 stoichiometry with both reactants. The mean activity coefficient was evaluated from the extended Debye-Hückel equation $\log \gamma = -1.90\ \sqrt{\mu}\ (1 + 3.06\ \sqrt{\mu})^{-1}$, which corresponds to a value of 32.6 for the dielectric constant of methanol and one of 6 Å for the Bjerrum distance.[10] Equation (1), which in Connors' terminology[11] might be called a

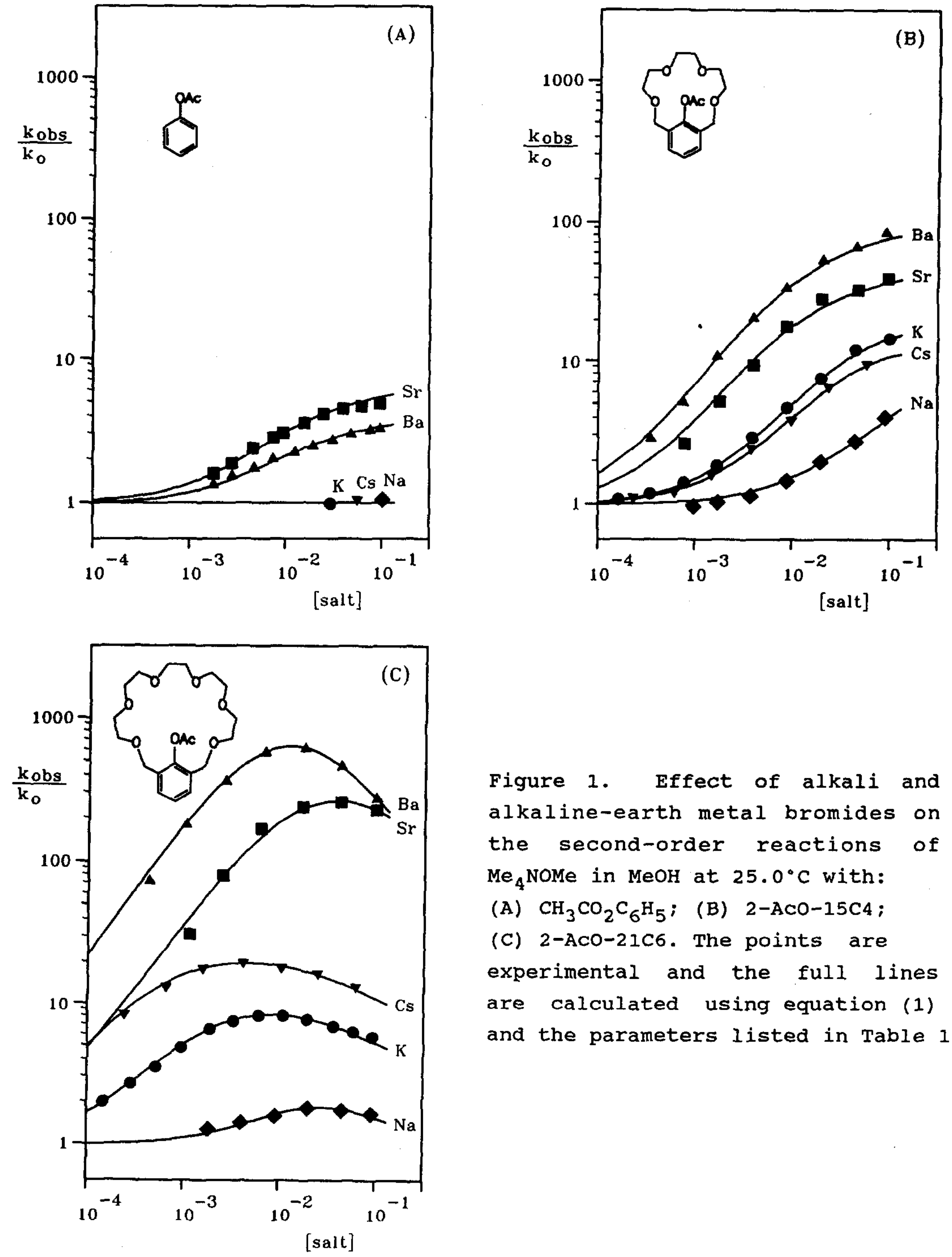


Figure 1. Effect of alkali and alkaline-earth metal bromides on the second-order reactions of Me_4NOMe in MeOH at 25.0°C with: (A) $CH_3CO_2C_6H_5$; (B) 2-AcO-15C4; (C) 2-AcO-21C6. The points are experimental and the full lines are calculated using equation (1) and the parameters listed in Table 1

nonhyperbolic isotherm, relates the measured quantity k_{obs}/k_o to the concentration of metal ion by means of a relation which contains three unknown quantities. These are the equilibrium constants for association of the metal ion with the aryl acetate (K_{AcOAr}) and with methoxide ion (K_{MeO}), and the corresponding quantity for the formal conversion of the transition state which does not contain M^{z+} into one which contains M^{z+} ($K_T\#$).[9]

The experimental data were elaborated according to standard curve-fitting procedures, where the above equilibrium constants were treated as adjustable parameters. These are summarized in Table 1.

Application of equation (1) to the reaction catalysed by the alkali metal ions was straightforward, since the alkali metal methoxides and bromides behave as strong electrolytes in methanol solution.[12] This allowed to set the concentration of free ion $[M^+]$ equal to the concentration of added salt, as well as to neglect the binomial containing K_{MeO} (i.e., $1 >> K_{MeO}\gamma^2[M^+]$), which reduces equation (1) to a simpler form containing only two adjustable parameters.

In line with expectations, the K_{AcOAr} values (Table 1) for association of the 21-membered macrocyclic ligand 2-AcO-21C6 with the alkali metal ions are much larger than those of the 15-membered analogue 2-AcO-15C4. For the latter ligand the K_{AcOAr} value determined with either K^+ and Cs^+ ion is close to the lower limit of detection, but it is too small to measure with Na^+ ion.[13] An independent determination of K_{AcOAr} was carried out by means of a direct spectrophotometric technique for the interaction of 2-AcO-21C6 with K^+ under the same conditions. The result was a K_{AcOAr} value of 770 M^{-1}, which compares well with the value of 700 M^{-1} reported in Table 1, and fully supports the validity of our kinetic analysis.

Treatment of rate data as obtained in the presence of the alkaline-earth metal salts required the usual approximation,[6] possibly a very rough one, of considering these salts as strong 1:1 electrolytes of the $(MBr)^+Br^-$ type and neglecting any possible dissociation of the $(MBr)^+$ species. Curve-fitting of the data related to the reactions of the parent phenyl acetate was carried out by means of a simplified form of equation (1), since any association of this substrate with the metal ions is unlikely (i.e., $1 >> K_{AcOAr}[M^{2+}]$). We also found that the data related to the reactions of 2-AcO-15C4 could be treated under the same approximation, since associations of this compound with the alkaline-earth metal ions turned out to be negligibly small. On the other hand, for the reactions of 2-AcO-21C6 the complete form of equation (1) had to be used. For the sake of internal consistency, and with the aim at simplifying the curve-fitting procedure, the average K_{MeO} values as obtained from the reactions of $CH_3CO_2C_6H_5$ and 2-AcO-15C4 were used for the reactions of 2-AcO-21C6. Accordingly, the

Table 1. Equilibrium Parameters[a] for Association with Alkali and Alkaline-Earth Metal Ions in Methanol at 25.0 °C.

Metal Ion	K_{MeO}[b]	K_{AcOAr}	K_{T}#	$s(f)$[c]
		$CH_3CO_2C_6H_5$		
Na^+	-	-	-	
K^+	-	-	-	
Cs^+	-	-	-	
Sr^{2+}	$1.3x10^2$	-	$8.9x10^2$	0.020(0.047)
Ba^{2+}	$1.3x10^2$	-	$5.4x10^2$	0.017(0.038)
		2-AcO-15C4		
Na^+	-	-	$1.3x10^2$	0.023(0.053)
K^+	-	8	$1.1x10^3$	0.010(0.024)
Cs^+	-	8	$8.0x10^2$	0.015(0.034)
Sr^{2+}	$1.3x10^2$	-	$6.5x10^3$	0.052(0.119)
Ba^{2+}	$1.3x10^2$	-	$1.3x10^4$	0.040(0.092)
		2-AcO-21C6		
Na^+	-	5.5x10	$3.9x10^2$	0.014(0.033)
K^+	-	$7.0x10^2$	$1.6x10^4$	0.014(0.032)
Cs^+	-	$2.1x10^3$	$1.0x10^5$	0.015(0.035)
Sr^{2+}	$1.3x10^2$	1.0x10	$7.8x10^4$	0.061(0.139)
Ba^{2+}	$1.3x10^2$	7.9x10	$4.2x10^5$	0.027(0.062)

a) All equilibrium constants in M^{-1} units. Vacancies indicate equilibrium constants which are too low to affect the kinetics, i.e., much lower than 10 M^{-1}.

b) Average values determined from the reactions of $CH_3CO_2C_6H_5$ and 2-AcO-15C4. It should be noted that the coincidence of the K_{MeO} values for Sr^{2+} and Ba^{2+} is purely incidental.

c) Defined by equation (3) and (5), respectively. It should be noted that the data for the alkali metal reactions are fitted by equation (1) with a precision which is comparable to the probable error of 3-5% of the experimental estimation of (k_{obs}/k_o).

binomial expressions $(1 + K_{MeO}\gamma^2[(MBr)^+])$ were calculated and introduced into equation (1) as known quantities, which left only two unknown parameters to be evaluated.

Consistent with the behaviour exhibited with the alkali metal ions, we found (Table 1) that also with the alkaline-earth metal ions 2-AcO-21C6 is better a ligand than 2-AcO-15C4. Because of the rough approximation involved, a word of caution is needed in the interpretation of the numerical values of the equilibrium constants for association with the alkaline-earth metal ions. Not surprisingly, the goodness of fit to the data, as measured by the standard deviations listed in Table 1, is somewhat better with the monovalent cations than with the divalent ones. In spite of such difficulties as this, we believe that the reported values provide a measure for binding of the various species with the divalent metal ions, no matter what their precise structure in solution is, and that the whole set of equilibrium constants listed in Table 1 provides a valuable and consistent basis for discussion of catalytic effects as observed in the investigated reactions.

In a mechanically descriptive picture of the catalytic phenomenon, one might envisage a rate-determining attack of the ion-paired $CH_3O^-M^{2+}$ species to a free substrate molecule as occurring *via* a four-centered transition state or, alternatively, a rate-determining attack of a free MeO^- ion on a metal ion complexed substrate.[14] In the former case one should speak of a reactive ion pair, whereas in the latter an example of electrophilic catalysis is easily recognized. But it is clear that for quantitative treatment, or even for qualitative discussion, it suffices to refer to the standard potential of the transition state and the sum of the standard potentials of the reactants, and to differences between these quantities.[15] It is also clear that $K_T\#$ is a measure of transition state stabilization brought about by the metal ion, whereas K_{MeO} and K_{AcOAr} are the corresponding quantities for the reactants. It appears therefore that the data listed in Table 1 lend themselves to an illustration of the so-called principle of transition state stabilization,[16,17] as well as of the relation between catalysis and binding. According to equation (1), catalysis ($k_{obs}/k_O > 1$) is observed whenever condition (2) holds, i.e., when the transition state $T^\#$ binds cations much more strongly than either reactant does. Inspection of Table 1 shows that condition (2) is largely

$$K_T\# > K_{MeO} + K_{AcOAr} + K_{AcOAr}\,K_{MeO}\,\gamma^2[M^{2+}] \qquad (2)$$

fulfilled in the reactions of 2-AcO-15C4 and 2-AcO-21C6. The transition state $T^\#$ is far the best ligand out of the three species MeO^-, AcOAr, and

$T^{\#}$ for all of the metal ions, the $K_T\#$ values ranging from two to more than five orders of magnitude. It appears plausible therefore, to picture the transition states for the reactions of 2-AcO-15C4 and 2-AcO-21C6 as macrocyclic polyether ligands where the presence of a negative charge provides an additional driving force for binding metal ions.

That the transition state retains some of the selectivity features of the corresponding reactant is shown by the fact that for the reaction of 2-AcO-21C6 the $K_T\#$ values increase in the same order $Na^+ < K^+ < Cs^+$ and $Sr^{2+} < Ba^{2+}$ as the K_{AcOAr} values, and that a similar parallelism is found for the alkali metal ion reactions of 2-AcO-15C4. It is worth noting that the $K_T\#$ values show the tendency to vary more rapidly than the corresponding K_{AcOAr} values, which implies that the $K_T\#/K_{AcOAr}$ ratios, which are a measure of the maximum acceleration in the absence of association of M^{2+} with MeO^- ion and of ionic strength effects, vary in the same order as the K_{AcOAr} values. Stated in different words, this means that there is a relation between catalysis and substrate binding. A closer inspection of the data reveals, however, that the relation between binding and catalysis is not so simple. In fact, 2-AcO-21C6 binds the alkali metal ions much more strongly than 2-AcO-15C4, yet the extent of catalysis is comparable (Cs^+) or even larger (Na^+ and K^+) for the latter substrate.

CONCLUSIONS

The data reported in the present work provide evidence that remarkable rate-enhancing effects can be obtained with such a simple catalyst as an alkali or alkaline-earth metal ion. The investigated systems are simple enough as to allow a complete analysis to be carried out in terms of cation binding in the transition state and in the reactant state. It is argued that transition state stabilization results from a favourable combination of weak, noncovalent interactions of the catalyst both with the negative charge dispersed in the reaction zone and with at least some of the oxygen donors of the polyether chain.

It is hoped that the basic information gained from this and analogous studies of simple model systems will assist in the comprehension and design of more complex systems capable of displaying supramolecular catalytic activity.

EXPERIMENTAL

Materials. 2-AcO-15C4 and 2-AcO-21C6 were prepared by acetylation of the parent phenols[18] with CH_3COCl and EtOTl according to a published procedure.[19] Purification was carried out by flash chromatography on silica gel (230-400 mesh) using AcOEt/MeOH 30:1 (2-AcO-15C4) or 25:1 (2-AcO-21C6) as eluent. Purity was found to be >99% by GLC analysis. ^1H NMR and mass spectra were as expected.[2]

Methanol (Erba RP) was fractionally distilled over magnesium methoxide and stored in an automatic burette under nitrogen. NaBr (Erba RP) and KBr (Erba RP) were crystallized from water and dried under vacuum at 200 °C. CsBr (Merk Suprapur) was dried under vacuum at 200 °C. $SrBr_2 \cdot H_2O$ (Erba RP) and $BaBr_2 \cdot 2H_2O$ (Riedel de Haën) were used as such, since attempted drying was unsuccessful. The bromide content of the methanolic solutions was checked by argentometric titration.

A special attention was devoted to the choice of the stock solution of tetraalkylammonium methoxide in methanol, because of the extreme sensitivity of the investigated reactions to the minute amounts of alkali metal ions usually contained in the commercially available samples. We found by atomic absorption analysis that a commercial sample of $Me_4NOH \cdot 5H_2O$ (Fluka) was practically free from alkali metal ions. The water contained in the solid sample was removed by repeated azeotropic distillations with benzene under vacuum. The residue was then repeatedly taken up with anhydrous methanol and evaporated to dryness, and eventually dissolved in a calculated amount of dry methanol. All operations were carried out under argon. Titration of the stock solution with hydrochloric acid showed the absence of carbonate ions. The suitability of the above stock solution for the rate measurements was showed by the fact that the rate of the reaction of 2-AcO-21C6 in the absence of added salt was unaffected by the addition of [2.2.2]cryptand.

Equilibrium and Rate Measurements. UV spectral measurements were carried out on a Cary 219 instrument. Fast kinetics were followed on a Durrum-Gibson stopped-flow spectrophotometer model D-110.

The equilibrium constant for association of K^+ with 2-AcO-21C6 was carried out spectrophotometrically as previously described.[7]

The kinetic runs were started by rapidly adding the calculated amount of Me_4NOMe stock solution to a solution of the reactant and added salt.

Second-order rate constants (in $l\ mol^{-1}s^{-1}$) are reported in the following, at the various alkali and alkaline-earth metal bromide concentrations, which are given in parentheses in M units:

PhOAc: k_o = 2.41 ± 0.02

NaBr: 2.60 (0.100)

KBr: 2.37 (3.00×10^{-2})

CsBr: 2.57 (5.44×10^{-2})

$SrBr_2 \cdot H_2O$: 3.98 (1.80×10^{-3}); 4.68 (2.85×10^{-3}); 5.78 (4.75×10^{-3}); 6.97 (7.60×10^{-3}); 7.54 (9.50×10^{-3}); 8.96 (1.66×10^{-2}); 10.0 (2.59×10^{-2}); 11.0 (3.99×10^{-2}); 11.8 (6.58×10^{-2}); 12.1 (9.97×10^{-2}).

$BaBr_2 \cdot 2H_2O$: 3.32 (1.89×10^{-3}); 3.83 (2.99×10^{-3}); 4.36 (4.99×10^{-3}); 4.99 (7.98×10^{-3}); 5.62 (1.30×10^{-2}); 6.25 (1.99×10^{-2}); 6.85 (3.19×10^{-2}); 7.40 (4.99×10^{-2}); 7.77 (7.98×10^{-2}); 7.90 (9.97×10^{-2}).

2-OAc-15C4: k_o = 0.104 ± 0.01

NaBr: 0.104 (1.00×10^{-3}); 0.110 (1.81×10^{-3}); 0.123 (3.98×10^{-3}); 0.153 (9.18×10^{-3}); 0.201 (2.04×10^{-2}); 0.287 (4.49×10^{-2}); 0.431 (9.18×10^{-2}).

KBr: 0.110 (1.63×10^{-4}); 0.124 (3.57×10^{-4}); 0.145 (7.89×10^{-4}); 0.192 (1.74×10^{-3}); 0.307 (4.02×10^{-3}); 0.489 (8.72×10^{-3}); 0.802 (1.96×10^{-2}); 1.27 (4.47×10^{-2}); 1.53 (9.81×10^{-2}).

CsBr: 0.117 (2.43×10^{-4}); 0.125 (6.43×10^{-4}); 0.169 (1.58×10^{-3}); 0.263 (4.00×10^{-3}); 0.409 (1.01×10^{-2}); 0.682 (2.43×10^{-2}); 1.01 (6.07×10^{-2}).

$SrBr_2 \cdot H_2O$: 0.286 (7.95×10^{-4}); 0.574 (1.80×10^{-3}); 1.04 (4.02×10^{-3}); 1.91 (9.01×10^{-3}); 2.92 (2.01×10^{-2}); 3.49 (4.53×10^{-2}); 4.16 (9.54×10^{-2}).

$BaBr_2 \cdot 2H_2O$: 0.304 (3.60×10^{-4}); 0.542 (7.91×10^{-4}); 1.17 (1.75×10^{-3}); 2.19 (4.00×10^{-3}); 3.60 (8.86×10^{-3}); 5.69 (2.05×10^{-2}); 7.06 (4.51×10^{-2}); 9.10 (9.27×10^{-2}).

2-OAc-21C6: k_o = 7.43 ± 0.10 x 10^{-2}

NaBr: 9.31×10^{-2} (1.78×10^{-3}); 0.107 (3.96×10^{-3}); 0.120 (8.88×10^{-3}); 0.135 (2.00×10^{-2}); 0.131 (4.51×10^{-2}); 0.124 (8.83×10^{-2}).

KBr: 0.150 (1.48×10^{-4}); 0.202 (2.77×10^{-4}); 0.268 (5.07×10^{-4}); 0.365 (9.23×10^{-4}); 0.496 (1.85×10^{-3}); 0.561 (3.20×10^{-3}); 0.605 (5.86×10^{-3}); 0.615 (1.06×10^{-2}); 0.588 (1.95×10^{-2}); 0.537 (3.55×10^{-2}); 0.481 (5.68×10^{-2}); 0.440 (8.88×10^{-2}).

CsBr: 0.627 (2.42×10^{-4}); 1.00 (6.42×10^{-4}); 1.35 (1.57×10^{-3}); 1.48 (3.99×10^{-3}); 1.37 (1.01×10^{-2}); 1.25 (2.42×10^{-2}); 1.03 (6.05×10^{-2}).

$\underline{SrBr_2 \cdot H_2O}$: 2.31 ($1.10 \times 10^{-3}$); 6.02 ($2.50 \times 10^{-3}$); 12.5 ($6.25 \times 10^{-3}$); 18.3 ($1.62 \times 10^{-2}$); 19.7 ($4.00 \times 10^{-2}$); 17.3 ($9.27 \times 10^{-2}$).

$\underline{BaBr_2 \cdot 2H_2O}$: 5.43 ($4.16 \times 10^{-4}$); 13.7 ($1.04 \times 10^{-3}$); 27.9 ($2.60 \times 10^{-3}$); 44.7 ($6.50 \times 10^{-3}$); 47.2 ($1.69 \times 10^{-2}$); 34.4 ($4.16 \times 10^{-2}$); 20.9 ($9.63 \times 10^{-2}$).

Computational Details. Non-linear least-squares calculations were carried out by the programme "Eureka: The Solver" (Borland International Inc.). Curve-fitting was carried out on the logarithmic scale in order to give a sounder weight to the data. The standard deviation *s* from the regression line was calculated as

$$s = \sqrt{\frac{\sum_i (Y_{exp} - Y_{calc})_i^2}{n-2}} \qquad (3)$$

where $Y = \log (k_{obs}/k_o)$, the subscripts exp and calc refer to experimental and calculated quantities, respectively, n is the number of experimental points, and the summation is taken over all values of the running index i from 1 to n. Since for small x

$$\Delta \log x = 2.303\ \Delta x/x \qquad (4)$$

the quantity *f* calculated as

$$f = 2.303\ s \qquad (5)$$

represents the fractional standard deviation between experimental and calculated (k_{obs}/k_o) values.

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