

Alkali and Alkaline-Earth Metal Ion Catalysis in the Reaction of Aryl Acetates with Methoxide Ion. Effect of a Poly(oxyethylene) Side Arm¹

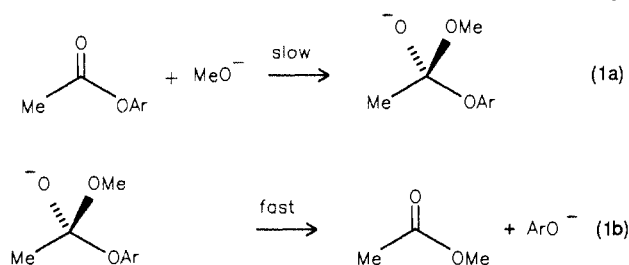
Gianfranco Ercolani* and Luigi Mandolini*

Contribution from the Centro CNR di Studio sui Meccanismi di Reazione and Dipartimento di Chimica, Università "La Sapienza", 00185 Roma, Italy. Received May 8, 1989

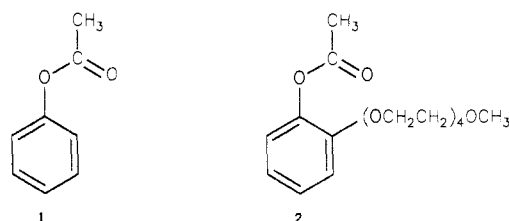
Abstract: The effect of added alkali (Na, K) and alkaline-earth (Sr, Ba) metal bromides on the rate of acyl transfer from *o*-acetoxypheyl 3,6,9,12-tetraoxatridecyl ether (**2**) to methoxide ion in methanol at 25 °C has been investigated spectrophotometrically. All of the added salts increased significantly the rate of reaction in the order $\text{Na}^+ < \text{K}^+ < \text{Sr}^{2+} < \text{Ba}^{2+}$, a maximum catalytic effect of nearly 10^2 being observed with the latter metal ion. A proper analysis of rate data afforded equilibrium constants for associations of metal ions with reactants and transition state, showing that in all cases the transition state binds metal ions much more strongly than the reactants. An analogous set of rate measurements was carried out for comparison purposes on the corresponding reaction of phenyl acetate (**1**). The fact that catalytic effects are much greater with **2** than with **1** reveals that a substantial contribution to the stability of the transition state of the metal ion assisted path arises from interaction of the metal ion with the oxygen donors of the side arm.

In recent studies of the effect of alkali and alkaline-earth metal ions on the rate of formation of benzo-crown ethers via intramolecular Williamson reaction, we found that, instead of the rate inhibitions expected for $\text{S}_{\text{N}}2$ reactions,² favorable combinations of metal ion and size of the ring being formed gave rise to remarkable rate enhancements (*template effect*).³⁻⁵ A careful analysis of the phenomenon led to the conclusion that a substantial stabilization of the transition state was provided by coordination of the metal ion with the oxygen donors of the polyether chain. Thus, the templated reactions provide noteworthy examples of homogeneous catalysis promoted by weak, noncovalent interactions.

In view of the current interest devoted to supramolecular catalysis,⁶ we have sought additional reaction systems for which rate-enhancing metal ion effects could arise from a number of suitably placed donor atoms. To this end, we have studied the acyl-transfer reaction between methoxide ion and aryl acetates, which is a two-step reaction (eq 1a and 1b) with the former step



rate determining.⁷ The underlying idea is that interaction of a metal ion with the rate-determining transition state should be enhanced by a neighboring poly(oxyethylene) chain. To test the above idea, we have carefully investigated the effect of added alkali (Na, K) and alkaline-earth (Sr, Ba) metal bromides on the rate of reaction of Me_4NOMe with phenyl acetate (**1**) and with a substituted phenyl acetate bearing in ortho position a polyether chain (**2**). The results of such an investigation are reported herein.



Results

Rate measurements were carried out in methanol at 25.0 °C on very dilute substrate solutions ($[\text{AcOAr}] \approx 5 \times 10^{-5} \text{ M}$) in the presence of excess Me_4NOMe ($4.00 \times 10^{-2} \text{ M}$) and of varying amounts of alkali (Na, K) and alkaline-earth (Sr, Ba) metal bromides. In all cases the total salt concentration was adjusted to 0.15 M with Me_4NBr . This was aimed not only at keeping the ionic strength essentially constant but also at avoiding possible complications arising from the unknown dissociation equilibria of the divalent metal bromides (vide infra).

The reaction progress was followed by monitoring the appearance of the aryl oxide absorption at 288 nm for the methanolysis of **1** and at 296 nm for the methanolysis of **2**, by either conventional or stopped-flow spectrophotometry, depending upon the time scale of the experiment. Comparison of the UV spectra of the final reaction mixtures with those of solutions of ArOH having the same ionic composition revealed that the reactions had always occurred quantitatively. In all cases first-order plots showed good linearity up to high conversions.

A preliminary set of rate measurements was carried out in the absence of metal salts in order to establish the kinetic order with respect to methoxide ion. Variations of the excess concentration of Me_4NOMe over a 10-fold range produced strictly proportional variations in the observed pseudo-first-order rate constants (see, for example, Figure 1). Since any significant association between the reactants and Me_4N^+ ion is unlikely, the second-order rate constant k_0 obtained in the presence of Me_4N^+ ion as the sole counterion was taken as a measure of the reactivity of unassociated reactants. Second-order rate constants k_{obs} for reactions carried out in the presence of metal salts were calculated from the observed pseudo-first-order rate constants and the primitive concentration of methoxide ion. The term primitive⁸ refers to the total concentration of a species, irrespective of the various forms actually present in solution through the establishment of mobile equilibria. By virtue of this definition, the quantity k_{obs} may be called the primitive value of the second-order rate constants, in that it is

(1) A preliminary account of this work was presented at the XVI Convegno Nazionale di Chimica Organica, Società Chimica Italiana, Urbino, Sept 7-12, 1986.

(2) Gordon, J. E. *The Organic Chemistry of Electrolyte Solutions*; Wiley: New York, 1975; pp 465-469.

(3) Mandolini, L. *Pure Appl. Chem.* **1986**, *58*, 1485-1492.

(4) Ercolani, G.; Mandolini, L.; Masci, B. *J. Am. Chem. Soc.* **1983**, *105*, 6146-6149.

(5) Mandolini, L.; Masci, B. *J. Am. Chem. Soc.* **1984**, *106*, 168-174. See also: *Ibid.* 3706.

(6) Lehn, J.-M. *Angew. Chem., Int. Ed. Engl.* **1988**, *27*, 89-112.

(7) Jencks, W. P. *Catalysis in Chemistry and Enzymology*; McGraw-Hill: New York, 1969; pp 508-517.

(8) Hammett, L. P. *Physical Organic Chemistry*; McGraw-Hill: New York, 1970; p 16.

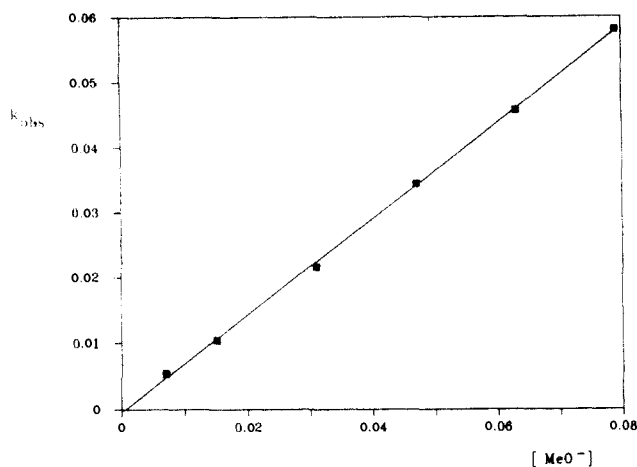


Figure 1. Plot of pseudo-first-order rate constants against $[MeO^-]$ relative to the reaction of **2** carried out in the presence of Me_4N^+ as the sole counterion.

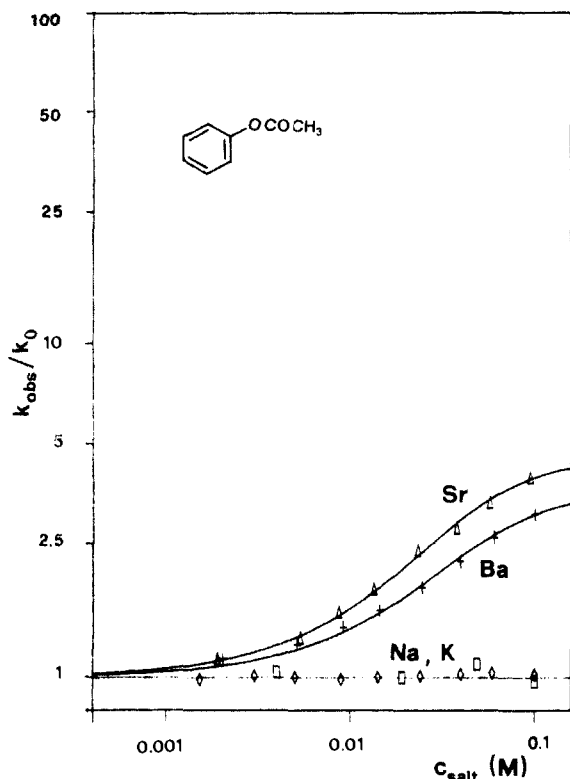


Figure 2. Logarithmic plot of catalytic effects of alkali and alkaline-earth bromides on the base-induced methanolysis of **1**. The points are experimental, and the curves for Sr^{2+} and Ba^{2+} are calculated according to eq 6.

operationally defined by relation 2, where v is the rate of reaction and c refers to primitive concentrations.

$$k_{obs} = v/c_{AcOAr}c_{MeO} \quad (2)$$

Rate data are listed in detail in the Experimental Section and are shown as log plots in Figures 2 and 3. It is apparent that the rate of attack of methoxide ion on the aryl acetates **1** and **2** is a function of cation concentration and nature, as well as of substrate structure. The reaction of the parent phenyl acetate (**1**) (Figure 2) is insensitive to the presence of the alkali metal bromides but is accelerated by the alkaline-earth metal bromides. With the poly(oxyethylene) derivative **2** (Figure 3), the observed rate-enhancing effects are much greater. In the neighborhood of 0.1 M added salt, the rate acceleration is 79 with $BaBr_2$ and 17 with $SrBr_2$. In contrast with the behavior exhibited by **1**, the reaction of **2** is significantly accelerated by KBr , and a small but clearly discernible catalytic effect is still present with $NaBr$.

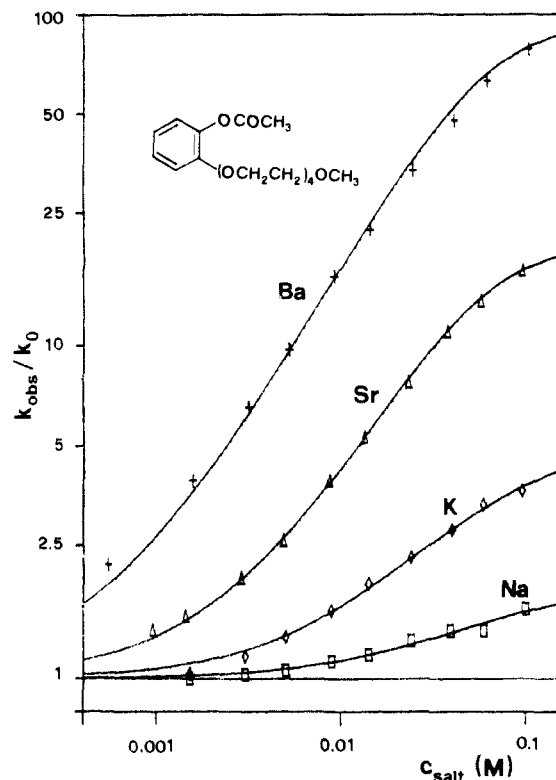


Figure 3. Logarithmic plot of catalytic effects of alkali and alkaline-earth bromides on the base-induced methanolysis of **2**. The points are experimental, and the curves are calculated according to eq 3 (Na^+ , K^+) and eq 6 (Sr^{2+} , Ba^{2+}).

A common feature of the profiles is an undeniable tendency to saturation kinetics. This is even more apparent from plots of k_{obs}/k_0 vs c_{salt} (not shown). In all cases the rate varies linearly with c_{salt} in the low concentration region, but a negative curvature appears on increasing salt concentration.

Treatment of Rate Data

The shapes of the profiles reported in Figures 2 and 3 are clearly diagnostic for significant associations of the metal ions with reactants and transition state. A derivation of the functional relation between k_{obs}/k_0 and metal ion concentration for the general case of significant associations of 1:1 stoichiometry with both reactants is presented in the Appendix.

Let us consider first the treatment of data related to the reaction of **2** in the presence of the alkali metal salts, which is inherently simpler because it is known that alkali metal ions in methanol give negligible associations with methoxide ion.⁹ This suggests eq 3 as a trial fitting equation, which is a simplified form of eq

$$\frac{k_{obs}}{k_0} = \frac{1 + K_T[M^+]}{1 + K_{AcOAr}[M^+]} \quad (3)$$

17, holding when $K_{MeO}[M^+] \ll 1$. Since the alkali metal bromides behave as strong electrolytes in methanol solution,¹⁰ and since the fraction of metal ion sequestered by the neutral substrate **2** is negligibly small in view of its low concentration, the concentration of free ion $[M^+]$ can be set equal to c_{salt} . A least-squares treatment (see the Experimental Section) of the data according to eq 3 afforded the numerical values of the parameters K_T and K_{AcOAr} listed in Table I. How closely eq 3 fits the data is shown by the curves for Na and K drawn in Figure 3.

In line with the above reasoning, the remarkable insensitivity experienced by the corresponding reactions of **1** to the added alkali metal salts implies that cation association with reactants and

(9) Barthel, J.; Justice, J.-C.; Wachter, R. *Z. Phys. Chem. (Munich)* **1973**, *84*, 100-113.

(10) Fernández-Prini, R. In *Physical Chemistry of Organic Solvent Systems*; Covington, A. K., Dickinson, T., Eds.; Plenum: London, 1973; p 568.

Table I. Association Constants Relative to the Reactions of **1** and **2** with MeO⁻ in MeOH at 25.0 °C^{a,b}

metal ion	log K_{AcOAr}	log K_{MeO}	log K_{T^*}
Compound 1			
Sr ²⁺		1.78 ± 0.15	2.45 ± 0.12
Ba ²⁺		1.64 ± 0.18	2.21 ± 0.14
Compound 2			
Na ⁺	1.24 ± 0.12		1.52 ± 0.09
K ⁺	1.23 ± 0.07		1.97 ± 0.04
Sr ²⁺		1.72 ± 0.11	3.05 ± 0.08
Ba ²⁺		1.74 ± 0.27	3.74 ± 0.19

^aThe values of the association constants not reported are to be considered significantly lower than 10 mol⁻¹ L. ^bThe association constants for the alkaline-earth cations are conditional constants that hold for solutions having the same ionic composition as that of the kinetic runs (see text).

transition state is insignificant in the whole concentration range of added salts. Stated in other words, the data closely fit the equation $k_{obs}/k_0 = 1$, which is the trivial form to which eq 17 reduces when all of the $K[M^+]$ products are negligible compared to 1, i.e., when all of the K are significantly lower than 10.

The picture is more complicated when the added salts are the alkaline-earth bromides. The difficulty arises from the fact that divalent metal ions are more strongly associated with counterions than univalent ones, the pertinent association constants in methanol solution being generally unknown.¹¹ If one considers the high concentration of Br⁻ ion in solution, it seems plausible that the alkaline-earth metal ions are mainly present as singly charged species of the type (MBr)⁺, but the existence of MBr₂ and M²⁺ cannot be excluded. It is worth pointing out, however, that since the total salt concentration was adjusted to 0.15 M with Me₄NBr, the essentially constant concentration of Br⁻ ion ensures invariance of the distribution among the various metal species in solution, the sum of which is given by \bar{c}_{salt} , which is the analytical concentration of MBr₂ less the amount of metal ion sequestered by MeO⁻; i.e., $\bar{c}_{salt} = c_{salt} - [(MeOM)^+]$. At constant [Br⁻], \bar{c}_{salt} is proportional to [M²⁺] through the constant $a = 1 + K_1[Br^-] + K_1K_{II}[Br^-]^2$, where K_1 and K_{II} are the first and the second association constants, respectively, of M²⁺ with Br⁻. It is useful to introduce the conditional constants $\bar{K}_{T^*} = [T^*M^{2+}]/[T^*]\bar{c}_{salt}$ and $\bar{K}_{MeO} = [(MeOM)^+]/[MeO^-]\bar{c}_{salt}$ coincident with K_{T^*}/a and K_{MeO}/a , respectively. For the sake of simplicity, let us consider first the reactions of **1**. Since any significant association of **1** with the metal ions is unlikely, eq 17 reduces to eq 4, in which only

$$\frac{k_{obs}}{k_0} = \frac{1 + K_{T^*}[M^{2+}]}{1 + K_{MeO}[M^{2+}]} \quad (4)$$

$$\frac{k_{obs}}{k_0} = \frac{1 + \bar{K}_{T^*}\bar{c}_{salt}}{1 + \bar{K}_{MeO}\bar{c}_{salt}} \quad (5)$$

$$\frac{k_{obs}}{k_0} = \frac{1 + (\bar{K}_{T^*}/2\bar{K}_{MeO})[-J + \{(J^2 + 4\bar{K}_{MeO}c_{salt})\}^{1/2}]}{1 + [-J + \{(J^2 + 4\bar{K}_{MeO}c_{salt})\}^{1/2}]/2} \quad (6)$$

the association with MeO⁻ ion is taken into account. Equation 4 can be immediately transformed in eq 5. Specifying \bar{c}_{salt} in eq 5 as a function of c_{salt} , c_{MeO} , and \bar{K}_{MeO} , one obtains eq 6, where $J = 1 + \bar{K}_{MeO}(c_{MeO} - c_{salt})$ and the term c_{MeO} is a known quantity (0.04 M). Equation 6 fits the data remarkably well, as shown by the curves for Sr and Ba (Figure 2) calculated with the numerical values of the quantities \bar{K}_{T^*} and \bar{K}_{MeO} listed in Table I.

As for the reactions of **2** in the presence of Sr and Ba, we found that the data could be fitted as well by eq 6 (Figure 3), with the numerical values of the parameters \bar{K}_{T^*} and \bar{K}_{MeO} listed in Table I. It is worth noting that the \bar{K}_{MeO} values coincide within any reasonable estimate of the experimental uncertainties with those obtained from the reactions of the parent phenyl acetate (**1**), which

(11) The only datum that we were able to find in the literature regards the association of Ba²⁺ with ClO₄⁻ to give (BaClO₄)⁺: $K = 425 \text{ mol}^{-1} \text{ L}$. Chantooni, M. K., Jr.; Kolthoff, I. M. *Proc. Natl. Acad. Sci. U.S.A.* **1981**, *78*, 7245–7247.

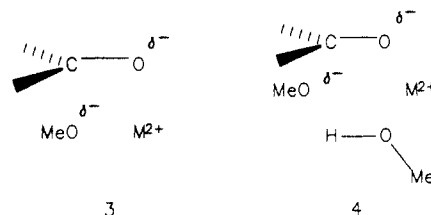
strongly indicates that, unlike the alkali metal ions, the alkaline-earth metal ions do not associate to a significant extent with the polyether ligand **2**.

Discussion

The results of the kinetic experiments described in the present work prove the soundness of our expectations that the presence of a suitably placed poly(oxyethylene) chain would enhance the effect of metal ions on the rate of acyl transfer from aryl acetates to methoxide ion. The investigated reactions provide clean-cut examples of catalysis by metal ions, which correctly fit into a kinetic model where the metal ion is involved in 1:1 associations with reactants and transition state (Table I). This is equivalent to saying that, besides the transition state T^{*} of the uncatalyzed reaction, a transition state T^{*}M²⁺ contributes to determining the rate of reaction, the contribution of the former relative to the latter being measured by the ratio $1/K_{T^*}[M^{2+}]$.

The reactions of the polyether substrate **2** illustrate well the advantages of using the transition-state language in place of the rate constant language. We found that **2** gives weak but clearly detectable associations with the alkali metal ions, but not with the alkaline-earth metal ions. In contrast, the alkali metal methoxides behave as strong electrolytes, but significant associations are found with the divalent metal methoxides. It would seem natural, therefore, to describe the reactions of **2** as occurring through reaction of a free methoxide ion with a cation–substrate complex (eq 11) in the case of the alkali metal ions and through reaction of a cation-paired methoxide ion with a free substrate molecule (eq 10) in the case of the alkaline-earth metal ions. In the language of Lefour and Loupy¹² the former reactions are under complexation control, whereas the latter are under association control. Thus, one would be faced with the unpleasant result of a dual mechanistic description of a set of reactants that are otherwise homogeneous both phenomenologically and operationally. In contrast, transition-state theory provides a unified treatment in that attention is focused on differences of chemical potential between transition state and reactants, rather than on the microscopic mechanism through which the transition state is attained. Since, as clearly pointed out by Schowen,¹³ “the entire and sole source of catalytic power is the stabilization of the transition state”, all we need for a meaningful discussion is the set of equilibrium constants listed in Table I. Accordingly, the question of the role of the metal ion on the nature and magnitude of the catalytic effect resolves itself into the comprehension of those factors that make the transition state a better ligand than the reactants. This was actually observed in all of the systems investigated, apart from the alkali metal reactions of **1**, where the relevant association constants turned out to be too small to measure under the reaction conditions.

Let us first consider the reactions of **1** as carried out in the presence of the divalent metal ions. No doubt, the structure of the rate-determining transition state T^{*} of the uncatalyzed reaction should be very similar to that of the tetrahedral intermediate apart, of course, from the extent of bond breaking, bond formation, and distribution of the negative charge. It appears therefore that an adequate structure for the transition state T^{*}M²⁺ of the metal ion assisted path is that depicted as **3**, but equally consistent with



the kinetics is **4**, where a bridging solvent molecule intervenes between the incoming nucleophile and the metal ion in a six-

(12) Lefour, J.-M.; Loupy, A. *Tetrahedron* **1978**, *34*, 2597–2605.

(13) Schowen, R. L. In *Transition States of Biochemical Processes*; Gandour, R. D., Schowen, R. L., Eds.; Plenum: New York, 1978; p 78.

membered cyclic structure. The existence of a chelate interaction in either structure **3** or **4** offers a rationale for the finding that T^* binds Sr^{2+} and Ba^{2+} ions more strongly than methoxide ion, in spite of the fact that a more localized negative charge is present in the latter anion.

If we now turn to the reactions of the polyether substrate **2**, the data listed in Table I show that in all cases the transition state binds metal ions much more strongly than the transition state of the phenyl acetate reaction, which leads to the straightforward conclusion that the polyether side arm gives a significant contribution to the complexing ability of the transition state. It also appears that the presence of the polyether chain inverts the order of catalytic efficiency $Sr > Ba$ as observed with **1**, thus indicating a certain preference of the side arm for Ba^{2+} ion. It is difficult to assign even a rough structure to T^*M^{2+} , but there is little doubt that, in addition to the negative charge localized in the reaction zone, effective binding sites for the metal ion are provided by at least some of the oxygen donors of the polyether side arm. It is worth pointing out that alkali metal ion effects are negligible in the reaction of **1** but become noticeable in the reaction of **2**, which means that the function of the side arm is that of an amplifier increasing the magnitude of both K_{T^*} and K_{AcOAr} to such an extent that catalysis is recognizable even with relatively low concentrations of added salt.

We finally note that the greater catalytic power of the alkaline-earth metal ions as compared with the alkali metal ions in the reactions investigated can hardly be explained on the basis of the rate constant model, since cation-paired nucleophiles are generally considered less reactive than unassociated ones. If one considers, however, that cation-anion electrostatic interactions are the sole driving force for association of the metal ions with the transition state of the reaction of **1**, and a major driving force in the reaction of **2**, then the greater stability of the T^*M^{2+} species with respect to the corresponding T^*M^+ species is easily understood, since coulombic interaction is expected, as actually found in model systems,¹⁴ to be much greater with the divalent metal ions.

Experimental Section

Materials. Dry methanol was obtained as previously reported.¹⁵ Alkali and alkaline-earth bromides were from a previous investigation.¹⁵ Tetramethylammonium hydroxide (20% methanol solution) was from Janssen; standard titrimetric analysis showed the presence of carbonate ion in this solution ($[CO_3^{2-}]/[MeO^-] = 0.025$). Tetramethylammonium bromide (Fluka purum) was dried under vacuum at 110 °C. AR-grade phenyl acetate (C. Erba) was used without further purification.

o-Acetoxyphenyl 3,6,9,12-tetraoxatridecyl ether (**2**) was prepared by acetylation of *o*-hydroxyphenyl 3,6,9,12-tetraoxatridecyl ether¹⁴ following a literature procedure.¹⁶ Elution of the crude product from silica gel with $CHCl_3/AcOEt$ (1:1, v/v) gave the pure title compound in 78% yield. ¹H NMR and IR spectra were as expected. Purity (>99%) was checked by vapor-phase chromatography analysis.

Rate Measurements. These were carried out either on a Varian DMS 90 or on a Durrum 110 stopped-flow spectrophotometer. The reaction solutions were freshly prepared and handled under argon to prevent contamination by atmospheric carbon dioxide. A minor correction of the analytical concentration of the added metal ions was required by the presence of carbonate ion in the Me_4NOMe stock solution, as alkali and alkaline-earth metal ions are very likely sequestered by carbonate ion in methanol solution. When precipitation of carbonate salts occurred upon mixing, the solution was decanted before addition of the aryl acetate.

Catalytic factors as measured by the ratio k_{obs}/k_0 are listed below at the various added salt concentrations, which are given in parentheses in moles per liter.

For compound **1**: $k_0 = 3.10 \text{ s}^{-1} \text{ mol}^{-1} \text{ L}$ (no added metal salts).

NaBr: 1.04 (4.00×10^{-3}), 1.00 (1.90×10^{-2}), 1.10 (4.90×10^{-2}), 0.970 (9.90×10^{-2}).

KBr: 0.984 (1.50×10^{-3}), 1.01 (3.00×10^{-3}), 1.00 (5.00×10^{-3}), 0.984 (9.00×10^{-3}), 1.00 (1.40×10^{-2}), 1.01 (2.40×10^{-2}), 1.02 (3.94

$\times 10^{-2}$), 1.03 (5.91×10^{-2}), 1.02 (9.90×10^{-2}).

SrBr₂: 1.14 ($1.92_5 \times 10^{-3}$), 1.32 (5.34×10^{-3}), 1.58 (8.75×10^{-3}), 1.85 (1.36×10^{-2}), 2.40 (2.36×10^{-2}), 2.79 (3.80×10^{-2}), 3.34 (5.80×10^{-2}), 3.98 (9.65×10^{-2}).

BaBr₂: 1.14 (2.06×10^{-3}), 1.26 (5.10×10^{-3}), 1.42 (9.20×10^{-3}), 1.60 (1.43×10^{-2}), 1.87 (2.45×10^{-2}), 2.23 (3.98×10^{-2}), 2.62 (6.00×10^{-2}), 3.08 (1.01×10^{-1}).

For compound **2**, $k_0 = 0.736 \text{ s}^{-1} \text{ mol}^{-1} \text{ L}$ (no added metal salts).

NaBr: 1.00 (1.50×10^{-3}), 1.03 (3.00×10^{-3}), 1.06 (5.00×10^{-3}), 1.13 (9.00×10^{-3}), 1.19 (1.40×10^{-2}), 1.31 (2.40×10^{-2}), 1.40 (3.90×10^{-2}), 1.40 (5.90×10^{-2}), 1.63 (9.90×10^{-2}).

KBr: 1.03 (1.50×10^{-3}), 1.17 (3.00×10^{-3}), 1.34 (5.00×10^{-3}), 1.60 (9.00×10^{-3}), 1.93 (1.40×10^{-2}), 2.32 (2.40×10^{-2}), 2.80 (3.95×10^{-2}), 3.35 (5.85×10^{-2}), 3.68 (9.55×10^{-2}).

SrBr₂: 1.41 (9.50×10^{-4}), 1.55 (1.44×10^{-3}), 2.01 (2.90×10^{-3}), 2.61 (4.85×10^{-3}), 3.97 (8.75×10^{-3}), 5.36 (1.36×10^{-2}), 7.80 (2.34×10^{-2}), 11.0₅ (3.80×10^{-2}), 13.7 (5.75×10^{-2}), 16.9₅ (9.65×10^{-2}).

BaBr₂: 2.21 (5.50×10^{-4}), 3.97 (1.58×10^{-3}), 6.58 (3.13×10^{-3}), 9.76 (5.20×10^{-3}), 16.2 (9.30×10^{-3}), 22.4 (1.45×10^{-2}), 34.2 (2.48×10^{-2}), 47.8 (4.03×10^{-2}), 63.4 (6.10×10^{-2}), 78.6 (1.02×10^{-1}).

Computational Details. Nonlinear least-squares calculations were carried out by a computer program based on the Marquardt method. In order to give a sounder weight to the experimental data, the best fit to $\log(k_{obs}/k_0)$ vs c_{salt} was sought, k_{obs}/k_0 being given by eq 3 for Na^+ and K^+ and by eq 6 for Sr^{2+} and Ba^{2+} . The data in Table I are least-squares estimates of the association constants. Standard deviations from the regressions ($s_{y,x}$) are as follows: **1**, Sr^{2+} , $s_{y,x} = 0.012$; **1**, Ba^{2+} , $s_{y,x} = 0.014$; **2**, Na^+ , $s_{y,x} = 0.012$; **2**, K^+ , $s_{y,x} = 0.017$; **2**, Sr^{2+} , $s_{y,x} = 0.013$; **2**, Ba^{2+} , $s_{y,x} = 0.035$.

Conclusion

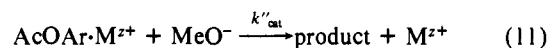
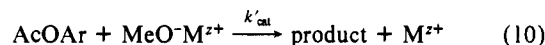
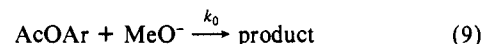
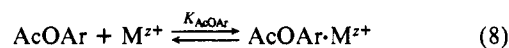
We have shown that a proximate polyether side arm significantly increases the extent of catalysis exerted by alkali and alkaline-earth metal ions on the rate of acyl transfer from phenyl acetate to methoxide ion in methanol. The reactions investigated provide remarkable examples of homogeneous catalysis by metal ions, which, in spite of their extreme simplicity, share at least some basic features with more structured supramolecular systems, in that both binding with the reactant(s) and stabilization of the transition state are provided by weak, noncovalent interactions of the metal catalyst with the oxygen donors.

Hopefully, a deep understanding of this and analogous model reactions will provide insight into more structured systems capable of enzymelike catalytic power.

Acknowledgment. We are indebted to the Ministero della Pubblica Istruzione for financial support. Stimulation by the European Economic Community (Research Contract ST2J-0215-4-I) is also gratefully acknowledged.

Appendix

An equation is developed here for the general case where the added metal ion M^{z+} gives significant associations of 1:1 stoichiometry with both reactants (eq 7 and 8). In addition to the



bimolecular pathway leading to a transition state T^* having the composition $(AcOAr \cdot MeO^-)^*$ (eq 9), two metal ion assisted bimolecular pathways can be envisaged (eq 10 and 11), which lead to transition states of the same composition $(AcOAr \cdot MeO^- \cdot M^{z+})^*$. In the mechanism of eq 10, the transition state is attained through attack of a cation-paired methoxide ion on a free substrate molecule, whereas attack of a free methoxide ion on a cation-substrate complex takes place in the mechanism of eq 11. Application of standard principles of chemical kinetics to the reaction schemes outlined by eq 7-10 and by eq 7-9 and 11 leads to eq 12 and 13, respectively, which hold for experiments carried out

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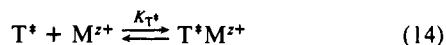
(16) Taylor, E. C.; McLay, G. W.; McKillop, A. *J. Am. Chem. Soc.* **1968**, *90*, 2422-2423.

$$\frac{k_{\text{obs}}}{k_0} = \frac{1 + (k'_{\text{cat}}/k_0)K_{\text{MeO}}[M^{z+}]}{(1 + K_{\text{AcOAr}}[M^{z+}])(1 + K_{\text{MeO}}[M^{z+}])} \quad (12)$$

$$\frac{k_{\text{obs}}}{k_0} = \frac{1 + (k''_{\text{cat}}/k_0)K_{\text{AcOAr}}[M^{z+}]}{(1 + K_{\text{AcOAr}}[M^{z+}])(1 + K_{\text{MeO}}[M^{z+}])} \quad (13)$$

at constant ionic strength and relate k_{obs}/k_0 to $[M^{z+}]$ by means of expressions containing three unknown parameters. Clearly, the two mechanisms of eq 10 and 11 are operationally indistinguishable because the corresponding kinetic equations are. It is also clear that the existence of two distinct transition states containing the metal ion cannot be operationally verified. Hence, the most reasonable assumption, actually the only viable one, is that there is only one transition state T^*M^{z+} attained through either step 10 or 11.¹⁷ The latter are, in turn, mutually exclusive, in that only one of them is necessary to populate the transition state.¹⁸

Use of transition-state theory avoids the above ambiguities. The basic assumption of the existence of an equilibrium between reactants and transition state implies that the transition state T^* is in equilibrium with the transition state T^*M^{z+} . This formal equilibrium is understood in the sense that T^* and T^*M^{z+} appear simultaneously and in proportions that are governed by $[M^{z+}]$ and by the equilibrium constant K_{T^*} (eq 14).¹⁹ Remembering that



(17) This may be viewed as a further application of the principle "Plurality is not to be assumed without necessity", which has become known as "Ockham's Razor". Nickon, A.; Silversmith, E. F. *Organic Chemistry: the Name Game*; Pergamon: New York, 1987; p 266.

(18) Thornton, E. K.; Thornton, E. R. In *Transition States of Biochemical Processes*; Gandour, R. D., Schowen, R. L., Eds.; Plenum: New York, 1978; p 18.

(19) Rudakov, E. S.; Kozhevnikov, I. V.; Zamashchikov, V. V. *Russ. Chem. Rev. (Engl. Transl.)* 1974, 43, 305-316.

k_{obs} is operationally defined in terms of primitive concentrations of the reactants (eq 2), the transition-state theory expression of k_{obs} is given by eq 15, where $c_{T^*} = [T^*] + [T^*M^{z+}]$ is the primitive

$$k_{\text{obs}} = \frac{kT}{h} \frac{c_{T^*}}{c_{\text{AcOAr}}c_{\text{MeO}}} \quad (15)$$

$$k_0 = \frac{kT}{h} \frac{[T^*]}{[\text{AcOAr}][\text{MeO}]} \quad (16)$$

$$\frac{k_{\text{obs}}}{k_0} = \frac{1 + K_{T^*}[M^{z+}]}{(1 + K_{\text{AcOAr}}[M^{z+}])(1 + K_{\text{MeO}}[M^{z+}])} \quad (17)$$

concentration of the transition state. When $[M^{z+}] = 0$, eq 15 reduces to eq 16. Combining eq 15 with eq 16 and with the expressions for the three equilibrium constants involved, eq 17 is obtained, which is clearly of the same form as eq 12 and 13. It is also apparent that K_{T^*} is related to the relevant rate and equilibrium constants through eq 18 and 19. Our preference for

$$K_{T^*} = (k'_{\text{cat}}/k_0)K_{\text{MeO}} \quad (18)$$

$$K_{T^*} = (k''_{\text{cat}}/k_0)K_{\text{AcOAr}} \quad (19)$$

eq 17 is due to the fact that it bears no relation whatsoever to the microscopic or detailed mechanism by which the transition state is attained.²⁰ The quantity K_{T^*} is a direct measure of transition-state stabilization brought about by the metal ion, to be compared with the corresponding stabilization of the reactant state, as measured by K_{AcOAr} and K_{MeO} .

Registry No. 1, 122-79-2; 2, 123903-47-9; 2 (alcohol), 57722-03-9; Me₄NOMe, 5568-08-1; KBr, 7758-02-3; SrBr₂, 10476-81-0; BaBr₂, 10553-31-8; NaBr, 7647-15-6; Sr(OMe)₂, 3214-53-7; Ba(OMe)₂, 2914-23-0.

(20) Reference 8, pp 116-117.

Vanadate Tetramer as the Inhibiting Species in Enzyme Reactions in Vitro and in Vivo

Debbie C. Crans,* Ellen M. Willging, and Steven R. Butler

Contribution from the Department of Chemistry, Colorado State University, Fort Collins, Colorado 80523. Received March 6, 1989

Abstract: Tetrameric vanadate polyanion inhibits 6-phosphogluconate dehydrogenases from human, mammalian, yeast, and bacterial sources. The inhibition by a vanadate mixture containing monomer, dimer, and tetramer was determined by measuring the rates of 6-phosphogluconate oxidation and NADP (or NAD) reduction catalyzed by 6-phosphogluconate dehydrogenase. The inhibition by vanadate is competitive with respect to 6-phosphogluconate and mixed or noncompetitive with respect to NADP or NAD. ⁵¹V NMR spectroscopy was used to directly correlate the inhibition of vanadate solutions to the vanadate tetramer. The measured inhibition constants with respect to 6-phosphogluconate for the tetramer are 0.078 mM for the human erythrocyte enzyme, 0.063 mM for the sheep liver enzyme, 0.013 mM for the yeast enzyme, and 0.24 mM for the *Leuconostoc mesenteroides*. The observed inhibition of 6-phosphogluconate dehydrogenase by vanadate tetramer is the first enzymatic activity observed of this polyanion. Our observations suggest the vanadate tetramer will be a potent inhibitor to other organic phosphate converting enzymes and preliminary results confirm this expectation. The vanadate tetramer may be an important species when considering the mechanism by which vanadium acts in biological systems in vitro and in vivo.

As a trace element in plants and mammals, vanadium has beneficial properties at low concentrations.¹ At high concentrations vanadium becomes toxic.¹ The action of vanadium is likely to vary with the oxidation state of the metal, although little is

currently understood about the mechanisms of action of vanadium in mammals or plants. The recent discoveries of vanadium-requiring enzymes illustrate the increasing interest in this element.²

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