

## Specific transition state stabilization by metal ions in reactions of functionalized crown ethers

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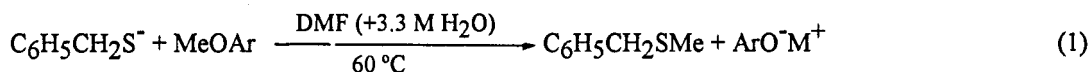
### Abstract

The reactivity of groups lying in close proximity of a crown-ether moiety where a metal ion is hosted, has been investigated in model systems. We have found that methyl transfer and acyl transfer reactions are greatly accelerated by alkali and alkaline-earth metal ions. Rate enhancements in the order of  $10^2$ - $10^3$  are commonly observed, but exceptionally high values in the order of  $10^5$ - $10^7$  are also found in some cases, which correspond to transition state stabilizations of some 7-10 kcal/mol.

A large variety of chemical phenomena are markedly and selectively influenced by coordinative interactions with alkali and alkaline-earth metal ions (ref. 1). Among these, we have been mainly interested in reaction systems where metal ion complexation is a major factor in controlling the reactivity of the complexed species. Our earlier studies dealt with the template effect exerted by alkali and alkaline-earth metal ions on the formation of crown ethers (ref. 2). It is the purpose of this lecture to review our recent work in the field, which consists of a series of kinetic investigations of metal ion effects in reactions of anionic nucleophiles with functionalized crown ethers.

### Methyl transfer reactions

The effect of alkali metal counterions ( $\text{Li}^+$ ,  $\text{Na}^+$ ,  $\text{K}^+$ ,  $\text{Cs}^+$ ) on the reactivity of toluene thiolate anion in the demethylation of a series of anisoles (eq 1) including 2-MeO-18C5, 2-MeO-24C7 and the model compounds anisole (AN) and 2,6-dimethylanisole (2,6-Me<sub>2</sub>AN) (ref. 3) illustrates well the general



strategy underlying our investigations. Rates of cleavage of the crown anisoles (Table 1) are greatly enhanced by alkali metal ions in a way that is highly dependent on the particular substrate-cation pair. When the metal ion is sequestered by [2.2.2.] cryptand, any rate-enhancing effect disappears. The importance of the crown ether bridge is clearly shown by the reactions of the model compounds AN and 2,6-Me<sub>2</sub>AN where the effect of the alkali metal ions is in fact rate-inhibiting, rather than rate-enhancing. This is in keeping with the well known concept that free ions are more nucleophilic than ion pairs in S<sub>N</sub>2 reactions. The rather small rate-depressing effects are suggestive of weak associations of the hard alkali metal ions with the soft thiolate nucleophile. More pronounced rate-depressing effects have been reported for harder nucleophiles such as aryloxides (ref. 4), enolates (ref. 5), and carboxylates (ref. 6).

The mechanistic picture which accommodates all of the observed facts is one which is based on a metal bound transition state where the negative charge being transferred from the incoming nucleophile to the

TABLE 1. Effects of metal ions on the cleavage of anisoles by  $C_6H_5CH_2S^-M^+$ .

Compound	$M^+$	$k$ ( $M^{-1} s^{-1}$ )	$k_{rel}$
2-MeO-18C5	$K^+$ , [2.2.2]	$4.6 \times 10^{-7}$	1
	$Li^+$	$1.2 \times 10^{-5}$	26
	$Na^+$	$2.6 \times 10^{-4}$	565
	$K^+$	$3.8 \times 10^{-4}$	826
	$Cs^+$	$6.7 \times 10^{-5}$	146
2-MeO-24C7	$K^+$ , [2.2.2]	$6.6 \times 10^{-7}$	1
	$Na^+$	$2.3 \times 10^{-6}$	3
	$K^+$	$3.5 \times 10^{-5}$	53
	$Cs^+$	$3.3 \times 10^{-5}$	50
AN	$K^+$ , [2.2.2]	$2.0 \times 10^{-7}$	1
	$Li^+$	$5.1 \times 10^{-8}$	0.26
	$Na^+$	$5.3 \times 10^{-8}$	0.27
	$K^+$	$5.8 \times 10^{-8}$	0.29
	$Cs^+$	$6.6 \times 10^{-8}$	0.33
2,6-Me <sub>2</sub> AN	$K^+$ , [2.2.2]	$8.9 \times 10^{-7}$	1
	$Li^+$	$2.2 \times 10^{-7}$	0.25
	$Na^+$	$3.8 \times 10^{-7}$	0.43
	$K^+$	$3.8 \times 10^{-7}$	0.43
	$Cs^+$	$3.7 \times 10^{-7}$	0.42

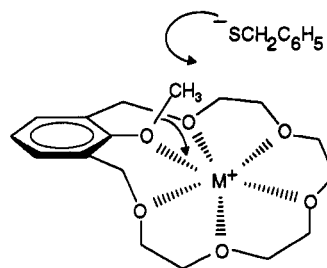
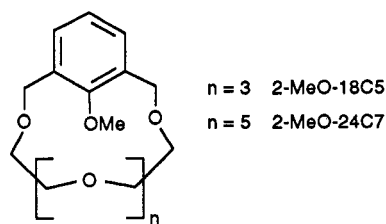
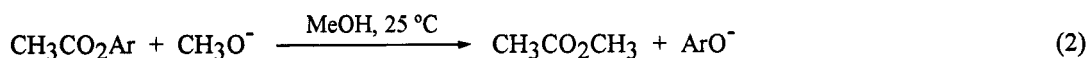


Fig. 1. Schematic picture of the transition state of the metal ion assisted demethylation of 2-MeO-18C5.

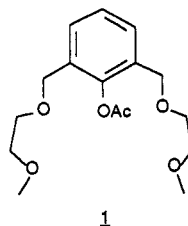
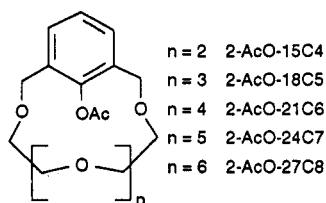
methoxyl oxygen (Fig. 1) is responsible for a much stronger binding of the metal electrophile to the altered substrate in the transition state than to the unaltered substrate in the reactant state. In other words, the transition state binds metal ions much more strongly than the neutral substrate by virtue of the simple principle that a negatively charged ligand is more effective than a neutral ligand with similar structure (ref. 7).

#### Acyl transfer reactions

Transfer to methoxide ion of the acetyl group of a series of crown ether aryl acetates ranging from 2-AcO-15C4 to 2-AcO-27C8 (eq 2) is accelerated by alkali and alkaline-earth metal ions (ref. 8).



Maximum observed accelerations range from 2 to 20 with the alkali ions and from 2 to 3 orders of magnitude with the alkaline-earth metal ions. On account of their inherent simplicity, these reactions lent themselves to an extensive investigation from which the strength of interaction of metal ions with reactants and transition states was carefully measured. Acetyl transfer reactions were carried out by reacting very dilute (*ca.* 0.1 mM) substrate solutions with excess  $Me_4NOMe$  (1-10 mM) either in the absence or presence of metal bromides over a wide concentration range. For each substrate a series of rate profiles



was obtained. The data for the alkali metal reactions were well fitted by eq 3, which is a binding isotherm for the case of 1:1 stoichiometry where  $k_{\text{obsd}}$  is the second order rate constant measured in

$$\frac{k_{\text{obsd}}}{k_0} = \frac{1 + K_{\text{T}\#}[\text{M}^+]}{1 + K_{\text{S}}[\text{M}^+]} \quad (3)$$

the presence of added salt, and  $k_0$  refers to reactions run in the presence of tetraalkylammonium ion as the sole counterion. The quantities  $K_{\text{S}}$  and  $K_{\text{T}\#}$  are defined by eq 4 and 5, respectively, where S denotes



the crown ether substrate,  $\text{T}\#$  is the transition state of the uncatalyzed path, whereas the metal ion assisted path proceeds through a transition state having the composition  $\text{T}\#\cdot\text{M}^+$ . Equation 3 can be written in the equivalent form of eq 6 where  $k_{\text{cat}}$  is the second order rate constant for reaction of methoxide

$$k_{\text{obsd}} = \frac{k_0 + k_{\text{cat}}K_{\text{S}}[\text{M}^+]}{1 + K_{\text{S}}[\text{M}^+]} \quad (6)$$

ion with the substrate fully saturated by the metal ion. The results of the treatment of rate data by means of eq. 3 (6) are summarized in Table 2. It is apparent that in all cases metal ions bind to transition states more strongly than to reactants, which is tantamount to saying that metal ions are rate enhancing in all of the reactions investigated. The data are fully consistent with the idea that transition state stabilization by metal ions occurs through cooperation of electrostatic binding to the negative charge being transferred from the incoming nucleophile and coordinative binding to the crown ether bridge. When the bridge is absent as in phenyl acetate (ref. 8a), or when the bridge is replaced by short side arms to give **1**, electrostatic binding is hardly appreciable. As for the important question of differential binding of metal ions to transition and reactant state, there is a definite tendency for  $K_{\text{T}\#}$  to increase on increasing  $K_{\text{S}}$ , which is not really surprising as the altered substrate in the transition state resembles in some way the unaltered substrate in the reactant state. But a plot of  $\log K_{\text{T}\#}$  versus  $\log K_{\text{S}}$  (Fig. 2) reveals considerable scatter, showing that the relation between binding and catalysis is not a simple one.

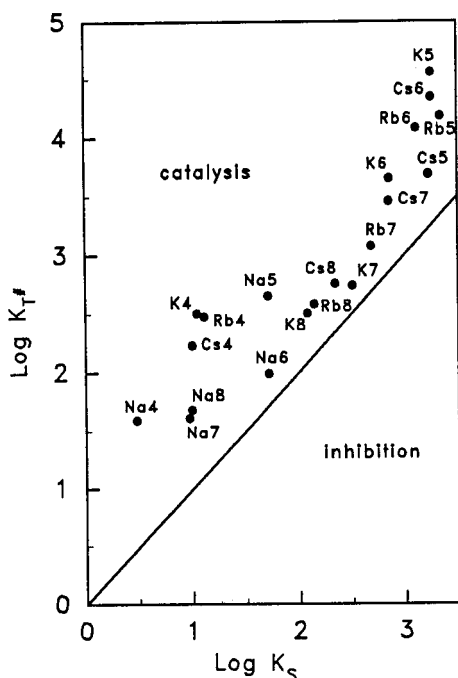


Fig. 2. Transition state stabilization vs. reactant state stabilization for the alkali metal assisted methanolysis of crown-ether aryl acetates. The numbers attached to the data points indicate the number of oxygens in the crown-ether bridge. The line which has unity slope and zero intercept is the borderline between the catalysis and inhibition domains.

TABLE 2. Alkali metal ion assisted acetyl transfer in MeOH at 25 °C.

	$K_S$ ( $M^{-1}$ )	$K_T^\#$ ( $M^{-1}$ )	$k_{cat}$ ( $M^{-1}s^{-1}$ )	$k_{cat}/k_o$
2-AcO-15C4				
Na	< 3	$3.9 \times 10$	>1.2	>12
K	11	$3.2 \times 10^2$	2.8	29
Rb	13	$3.0 \times 10^2$	2.2	23
Cs	10	$1.7 \times 10^2$	1.6	17
2-AcO-18C5				
Na	$5.1 \times 10$	$4.5 \times 10^2$	0.58	8.8
K	$1.8 \times 10^3$	$3.6 \times 10^4$	1.30	20
Rb	$2.2 \times 10^3$	$1.5 \times 10^4$	0.45	6.8
Cs	$1.7 \times 10^3$	$4.9 \times 10^3$	0.19	2.9
2-AcO-21C6				
Na	$5.2 \times 10$	$9.8 \times 10$	0.12	1.8
K	$7.2 \times 10^2$	$4.5 \times 10^3$	0.42	6.3
Rb	$1.3 \times 10^3$	$1.2 \times 10^4$	0.61	9.2
Cs	$1.8 \times 10^3$	$2.2 \times 10^4$	0.81	12
2-AcO-24C7				
Na	9.3	$4.1 \times 10$	0.30	4.5
K	$3.2 \times 10^2$	$5.5 \times 10^2$	0.12	1.8
Rb	$4.8 \times 10^2$	$1.2 \times 10^3$	0.17	2.5
Cs	$7.1 \times 10^2$	$2.9 \times 10^3$	0.27	4.0
2-AcO-27C8				
Na	9.8	$4.8 \times 10$	0.31	4.9
K	$1.2 \times 10^2$	$3.2 \times 10^2$	0.17	2.7
Rb	$1.4 \times 10^2$	$3.8 \times 10^2$	0.17	2.7
Cs	$2.2 \times 10^2$	$5.7 \times 10^2$	0.16	2.5

TABLE 3. Alkaline-earth metal ion assisted acetyl transfer in MeOH at 25 °C.

	$K_S$ ( $M^{-1}$ )	$K_{MeO}$ ( $M^{-1}$ )	$K_T^\#$ ( $M^{-1}$ )	$(k_{obsd}/k_o)_{max}^a$
<u>1</u>				
Sr		31	$2.8 \times 10^2$	7.0
Ba		23	$1.7 \times 10^2$	5.6
2-AcO-15C4				
Sr		20	$1.2 \times 10^3$	$4.0 \times 10$
Ba		16	$2.4 \times 10^3$	$9.3 \times 10$
2-AcO-18C5				
Sr		30	$9.1 \times 10^3$	$2.3 \times 10^2$
Ba		17	$2.0 \times 10^4$	$7.6 \times 10^2$
2-AcO-21C6				
Sr	~3	26	$8.5 \times 10^3$	$1.9 \times 10^2$
Ba	50	18	$3.2 \times 10^4$	$2.5 \times 10^2$
2-AcO-24C7				
Sr	8	26	$2.2 \times 10^4$	$3.5 \times 10^2$
Ba	260	18	$4.4 \times 10^4$	$1.0 \times 10^2$
2-AcO-27C8				
Sr	5	26	$1.3 \times 10^4$	$2.5 \times 10^2$
Ba	74	18	$2.6 \times 10^4$	$1.6 \times 10^2$

<sup>a</sup>Maximum observed rate enhancing effects in the investigated concentration range. Whenever a rate maximum is absent, the data refer to 0.1 M added salt.

Treatment of rate data obtained in the presence of barium and strontium bromides required an appropriate binomial accounting for association of the metal ion with methoxide ion to be included in the denominator of eq 1 to give eq 7. The latter fits remarkably well all of the kinetic data.

$$\frac{k_{obsd}}{k_o} = \frac{1 + K_T^\# c_{salt}}{(1 + K_S c_{salt})(1 + K_{MeO} c_{salt})} \quad (7)$$

The much greater catalytic power of the divalent as compared with the monovalent metals is not only due to a much larger electrostatic stabilization of the transition state, but also to a better utilization in catalysis of the binding energy due to coordinative interactions with the polyether bridges, as shown by the equilibrium parameters listed in Table 3.

In order to widen the scope of our investigations of metal ion effects on transacylation reactions, a series of new crown-ether like macrocyclic compounds (2) containing the 2,6-dibenzyl-4-nitrophenyl acetate substructure have been synthesized (ref. 9).

These macrocyclic compounds may be regarded as possessing a section of a 1,3-crowned calix[4]arene. At first the results were highly disappointing, as small rate enhancements due to barium and strontium ions were measured in MeOH solution. But later on transacylations were carried out in EtOH solution, where remarkably high catalytic factors and novel kinetic features were observed (ref. 9). In the MeO<sup>-</sup>/MeOH base-solvent system used in previous studies association of barium and strontium ions with MeO<sup>-</sup> was far

from being complete and had to be taken into account in the kinetic treatment. In the EtO<sup>-</sup>/EtOH base-solvent system, on the other hand, evidence was obtained that the ethoxide ion is completely bound to the divalent metal, as shown in eq 8. This led to a much simpler kinetic treatment, as the metal-bound ethoxide



species can be treated kinetically as a single species, as shown in eq 9.

$$v = k_M [\text{EtOMBr}] [\text{S}] \quad (9)$$

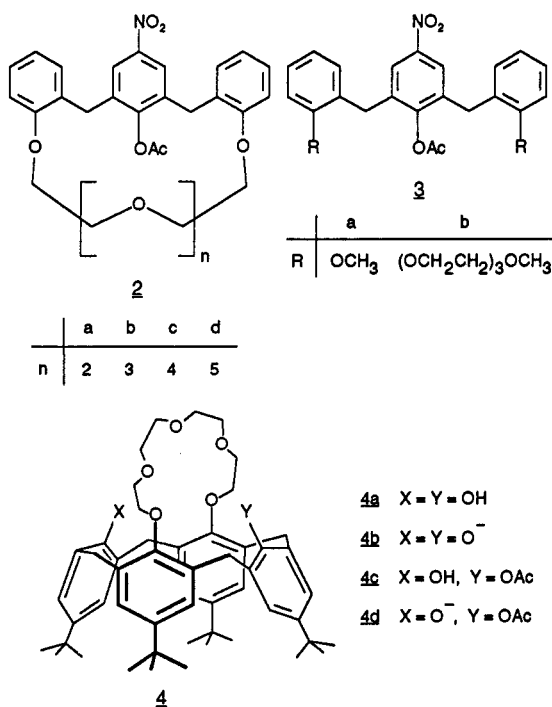
Rate data were obtained for the ring compounds 2 a-d and for the open chain model *p*-nitrophenyl acetate pNPOAc and 3 a,b (Table 4). It is apparent that the divalent metals are rate-enhancing in all of the studied reactions, but more favourable situations are found in the more flexible macrocycles 2c and 2d, as well as in the open-chain analogue 3b. These data point once more to the importance of a polyether chain which is available for complexation with the metal ion, and pose the question of why the divalent metals are more efficient in EtOH than in MeOH. To give an answer to the latter question, acyl transfer reactions of 2-AcO-15C4, 2-AcO-18C5, and 2-AcO-21C6 were reinvestigated in EtO<sup>-</sup>/EtOH (ref. 10). The conclusion was reached that both electrostatic binding and coordinative binding in the metal bound transition state are much more efficient in ethanol than in methanol solution. The rate data listed in the lower part of Table 4 clearly reveal dramatic accelerations by metal ions, the largest acceleration being displayed by 2-AcO-21C6, which reacts with EtOBaBr 500,000 times faster than with EtONMe<sub>4</sub>.

TABLE 4. Rate data for acetyl transfer reactions from aryl acetates to ethoxide ion in EtOH at 25 °C.<sup>a</sup>

Substrate	EtOSrBr	EtOBaBr
	$k_M/k_O$	$k_M/k_O$
pNPOAc	8.0	7.0
<u>3a</u>	24.8	18.5
<u>3b</u>	279	188
<u>2a</u>	16.7	14.1
<u>2b</u>	14.2	15.1
<u>2c</u>	46.6	91.3
<u>2d</u>	249	691
POAc <sup>b</sup>	62	45
2-AcO-15C4	2,300	7,200
2-AcO-18C5	48,000	46,000
2-AcO-21C6	41,000	500,000

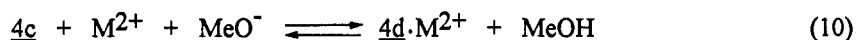
<sup>a</sup>Data from ref. 9 (upper part) and ref. 10 (lower part).

<sup>b</sup>POAc = phenyl acetate.



#### Acetyl transfer reactions in calixcrown systems

Calix[4]arenes diametrically bridged with polyether chains (e.g. 4a) are suitably preorganized hosts whose efficiency and selectivity in cation binding have found useful applications (ref. 11). The monoacetate 4c has been recently prepared *via* a metal ion controlled acetylation of 4a (ref. 12). Since the ionizable hydroxyl of 4c had the potential of providing an additional binding site for holding a metal ion in the crown ether cavity, we have investigated the basic methanolysis of 4c in the presence of barium and strontium ions (ref. 13). We found that replacement of the ionizable proton of 4c with a divalent metal (eq 10) converts a



species which proved to be very reluctant to undergo methanolysis into a very reactive one. The strontium complex of **4d** reacts with  $\text{MeO}^-$   $1.2 \times 10^6$  times more rapidly than **4c**, and with the barium complex a rate enhancement as large as  $2.1 \times 10^7$  was obtained. These huge rate enhancements provide to the best of our knowledge the most striking examples of electrophilic catalysis by these ions. They led us to the development of a novel nucleophilic catalyst with transacylase activity (ref. 14). The barium complex of **4b**, generated *in situ* from **4a** and  $\text{BaBr}_2$  in MeCN/MeOH 9:1 in the presence of diisopropylethylamine-bromide salt buffer, behaves as a nucleophilic catalyst in the methanolysis of pNPOAc. The liberation of pNPOH is characterized by an initial burst, followed by a linear portion where the overall reaction order is zero. Such a behavior is typical of a ping-pong mechanism (eq 11). Evidence was obtained that the active



forms of the catalyst (cat) and acetylated catalyst (catAc) are the barium complexes **4b**· $\text{Ba}^{2+}$  and **4d**· $\text{Ba}^{2+}$ , respectively. Independent evidence for the accumulation of the acetylated catalyst was obtained by HPLC analysis. These results constitute an important step towards our ultimate, admittedly ambitious, objective of developing synthetic catalysts with enzyme-like activity.

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