

ALKALI METAL ION-ASSISTED CLEAVAGE OF CROWN ETHER ANISOLES BY TOLUENETHIOLATE ANION

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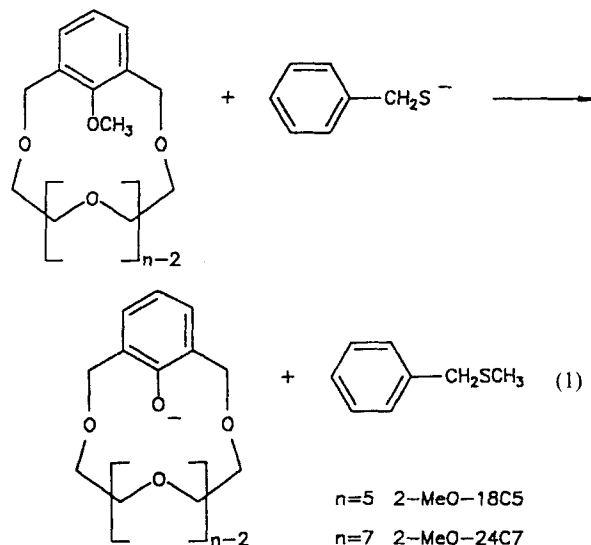
The effect of alkali metal ions (Li^+ , Na^+ , K^+ , Cs^+) on the reactivity of toluenethiolate anion in the demethylation of 2-methoxy-1,3-xylyl-18-crown-5, 2-methoxy-1,3-xylyl-24-crown-7 and the model compounds anisole and 2,6-dimethylanisole was investigated in dimethylformamide (+3.3 M water) at 60°C. It was found that the metal ion effects are markedly influenced by the presence of the polyether chain in the reaction system. Whereas reactions of the model compounds are slightly inhibited by the presence of alkali metal ions, the latter strongly enhance rate of demethylation of the crown ether derivatives, the observed catalytic factors ranging over nearly three orders of magnitude. These remarkable rate-enhancing effects are ascribed to a strong transition-state stabilization by metal ions through cooperation of electrostatic binding with the negative charge developing on the oxygen atom of the methoxy group undergoing nucleophilic attack and coordinative interaction with the polyether chain.

INTRODUCTION

In recent investigations of acyl transfer reactions from aryl acetates to alkoxide ions,^{1–4} we found that the extent of rate enhancement brought about by hard (alkali and alkaline earth) metal ions is greatly magnified by polyether chains strategically placed in close proximity of the acetoxy group undergoing nucleophilic attack. In the investigated systems, efficient binding of metal ions to transition states was ascribed to a favourable combination of electrostatic interaction with the negative charge of the anionic transition state and coordinative interaction with the neutral oxygen donors.

Since the question of selective transition state stabilization in small model systems is crucial to the understanding and design of more complex supramolecular systems capable of displaying enzyme-like catalytic activity, we felt it worthwhile to investigate the effects of metal ions on reactions belonging to mechanistic types other than nucleophilic addition to carbonyl. To this end we considered methyl transfer from crown ether anisoles to toluenethiolate anion [equation (1)] as an example of $\text{S}_{\text{N}}2$ reaction. Cleavage of aralkyl ethers by alkali metal salts of thiolate and other soft nucleophiles is well preceded for preparative purposes,⁵ but kinetic investigations are generally unavailable.

In this paper we report on a kinetic study of the



demethylation reaction of 2-methoxy-1,3-xylyl-18-crown-5 and 2-methoxy-1,3-xylyl-24-crown-7 (2-MeO-18C5 and 2-MeO-24C7, respectively) with the alkali metal salts of toluenethiolate anion in *N,N*-dimethylformamide (DMF) (+3.3 M H_2O) or in *N,N*-dimethylformamide- d_7 (DMF- d_7) (+3.3 M D_2O). For comparative purposes demethylations of the model compounds anisole and 2,6-dimethylanisole were also included.

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EXPERIMENTAL

^1H NMR spectra were taken on a Bruker WP-80SY spectrometer. Gas-liquid chromatographic (GLC) analyses were performed on a Hewlett-Packard (HP) 5830A gas chromatograph with a flame ionization detector, equipped with an HP 3392A integrator and fitted with a $15\text{ m} \times 0.53\text{ mm}$ SPB-1 fused-silica capillary column ($1.5\text{ }\mu\text{m}$ film thickness).

Materials. *N,N*-Dimethylformamide (Carlo Erba) and *N,N*-dimethylformamide- d_7 (Aldrich) were thoroughly purged with argon before use. Tolueneithiol (Fluka), anisole (Carlo Erba) and 2,6-dimethylanisole (Aldrich) were distilled under vacuum. Other chemicals were used as received. Concentrated solutions of alkali metal hydroxides in H_2O or D_2O were prepared from the corresponding alkali metal hydroxide and titrated with standard hydrochloric acid.

2-Methoxy-1,3-xylyl-18-crown-5 (m.p. $50.0\text{--}50.5^\circ\text{C}$, lit.⁶ m.p. $50.0\text{--}50.5^\circ\text{C}$) and 2-hydroxy-1,3-xylyl-18-crown-5 (m.p. $50.5\text{--}51.5^\circ\text{C}$, lit.⁶ m.p. $49.0\text{--}51.0^\circ\text{C}$) were prepared as described.⁶ 2-Methoxy-1,3-xylyl-24-crown-7 was prepared in low yield from 2,6-bis(bromomethyl)anisole⁶ and hexaethyleneglycol,⁷ according to an extension of the procedure used for the lower homologue.⁶ This compound had m.p. $44.5\text{--}46.5^\circ\text{C}$; ^1H NMR (CDCl_3), δ (ppm) $3.5\text{--}3.8$ (m, 24 H, OCH_2), 3.93 (s, 3 H, OCH_3), 4.61 (s, 4 H, ArCH_2), $7.0\text{--}7.45$ (m, 3 H, ArH). Analysis: calculated for $\text{C}_{21}\text{H}_{34}\text{O}_8$, C 60.85, H 8.27; found, C 60.90, H 8.34%. Demethylation⁶ of the above compound afforded a 38% yield of 2-hydroxy-1,3-xylyl-24-crown-7 as a waxy solid melting at room temperature. All spectral data were in agreement with those reported in the literature.⁸

Kinetics. Solutions of alkali metal tolueneithiolates were generated *in situ* by partial neutralisation of the parent tolueneithiol (0.5 M in DMF or DMF- d_7) with a calculated amount of a 5 M solution of the appropriate alkali metal hydroxide in H_2O or D_2O . After mixing the concentration of the tolueneithiolate salt was typically in the range $0.24\text{--}0.30\text{ M}$. All operations were carried out under argon in order to minimize air oxidation of the thiolate nucleophile.

Rates of the fastest reactions ($k > 1 \times 10^{-5}\text{ l mol}^{-1}\text{ s}^{-1}$) were determined by continuous assay by ^1H NMR. Reactions which were inconveniently slow for the NMR technique ($k \leq 1 \times 10^{-5}\text{ l mol}^{-1}\text{ s}^{-1}$) were analysed in the early stages by GLC after appropriate quenching and work-up.

^1H NMR technique. Kinetic runs were carried out in an NMR tube and were started by addition of a small volume of a concentrated alkali metal hydroxide solution in D_2O to a solution of substrate and tolueneithiol in DMF- d_7 thermostated at 60°C . Initial concen-

trations after mixing were substrate 0.06 M , alkali metal tolueneithiolate 0.30 M and tolueneithiol 0.20 M . The progress of the reaction was determined by monitoring the disappearance of the signal due to the benzylic protons of the crown anisole at $\delta\ 4.5\text{ ppm}$ and the appearance of the corresponding signal of the product at $\delta\ 4.4\text{ ppm}$. Non-linear least-squares fit of the analytical data to the standard second-order equation was carried out with the program Sigma Plot (Jandel Scientific).

GLC technique. Reactions were carried out in sealed ampoules which were analysed periodically. Initial reactant concentrations were substrate 0.80 M , alkali metal tolueneithiolate 0.24 M and tolueneithiol 0.26 M . After quenching with excess of hydrochloric acid, a known amount of cyclododecane (internal standard) was added and the mixture was thoroughly extracted with diethyl ether. The progress of the reaction was determined by analysing the ether solution for the amount of benzyl methyl sulphide. Analysis of data collected during the first 10% of reaction afforded the initial reaction rates, which were converted into second-order rate constants.

Occasional checks of the concentration of tolueneithiolate anion in the time course of the reactions were carried out by adding excess of butyl bromide to the reaction mixtures, which were allowed to react for 30 min at 60°C and eventually analysed, after standard work-up, by GLC (cyclododecane as internal standard) for the amount of benzyl butyl sulphide. Whenever tested, the concentration of the tolueneithiolate anion was as expected, showing that side-reactions leading to its consumption were unimportant under the reaction conditions.

RESULTS

The tolueneithiolate anion in aqueous DMF proved to be a convenient demethylating agent for the purposes of this work. Rate measurements were carried out at 60°C , which was the lowest temperature compatible with the inherent slowness of the demethylation process. At this temperature the slowest reactions afforded conversions, after reaction times of the order of 1 week, of only a few percent, which could be determined by GLC analysis of the benzyl methyl sulphide produced. However, the fastest reactions gave, after a few hours, moderate to high conversions, which were conveniently determined by continuous assay by ^1H NMR (Figure 1). In no case were significant amounts of undesirable by-products detected.

Measurements by ^1H NMR spectroscopy required the use of DMF- d_7 ($+3.3\text{ M D}_2\text{O}$) instead of DMF ($+3.3\text{ M H}_2\text{O}$). On the assumption that the change from the light to the heavy mixed solvent has a limited influence, if any, on the reactions at hand, the two sets of rate data are strictly comparable.

The Na^+ and K^+ reactions of 2-MeO-18C5, which

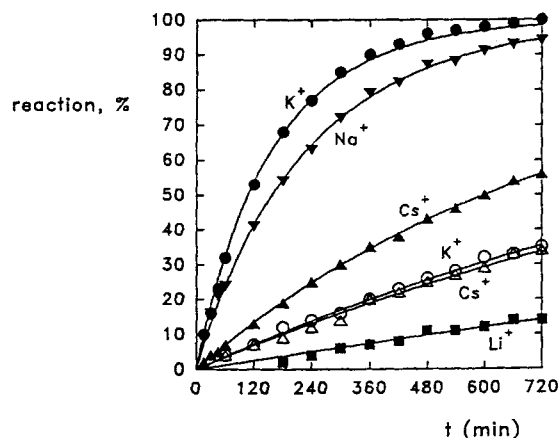


Figure 1. Demethylation of crown anisoles by alkali metal toluenethiolates in DMF- d_7 (+3.3 M D_2O) at 60 °C as monitored by 1H NMR. Closed symbols, reactions of 2-MeO-18C5; open symbols, reactions of 2-MeO-24C7. The curves are calculated from the integrated second-order equation and the k values listed in Table 1

are the fastest of those considered, proceeded very nearly to completion within the time range of 6 h chosen for the 1H NMR observations (Figure 1). These reactions display a clean second-order time dependence,

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

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

^a Rate constants higher than $1 \times 10^{-5}\ l\ mol^{-1}\ s^{-1}$ were determined by continuous assay by 1H NMR in DMF- d_7 (+3.3 M D_2O). The others were from GLC determinations of initial rates in DMF (+3.3 M H_2O).

^b 1.05 equiv. of [2.2.2]-cryptand added to 1 equiv. of $C_6H_5CH_2SK$.

as shown by the good fit to the curves calculated from the second-order integrated rate equation. Second-order behaviour was therefore assumed for all of the investigated reactions, and the experimental data were treated accordingly.

Second-order rate constants for all of the investigated reactions are collected in Table 1. The entries marked as $K^+ \cdot [2.2.2]$ refer to runs where 1 equiv. of [2.2.2]-cryptand was added as a K^+ -sequestering agent. On the reasonable assumption that the $C_6H_5CH_2SK + [2.2.2]$ -cryptand system represents the reactivity of free thiolate ion, the k_{rel} values listed in Table 1 provide a genuine measure of the effect of alkali metal ions on the investigated reactions.

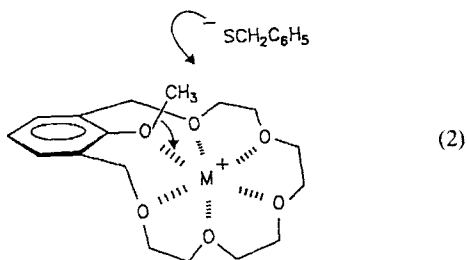
DISCUSSION

Before discussing the influence of metal ions on the reactions of the crown anisoles, we shall consider briefly the reactions of the simple substrates anisole and 2,6-dimethylanisole. The first observation is that the alkali metal salts are in all cases less reactive than the unassociated nucleophile. This finding is in keeping with the notion that nucleophilicity of ion pairs in S_N2 reactions is lower than that of free ions.⁹ The rate-depressing effects are rather small, presumably on account of weak associations of the hard alkali metal ions with the soft thiolate nucleophile. Much stronger rate-depressing effects due to pairing of alkali metal ions with harder nucleophiles such as aryl oxides,^{10,11} enolates¹²⁻¹⁴ and carboxylates¹⁵ have been reported in dipolar aprotic solvents. We further note that in addition to being small, the observed effects are nearly independent of the nature of the cation. No trace is found in the present data of the presumed superiority of the small Li^+ ion as a Lewis acid catalyst,¹⁶ nor any indication of the exceptional properties to which caesium thiolates in DMF solution have been ascribed.¹⁷

Finally, it is worth noting that the intrinsic reactivities of anisole and 2,6-dimethylanisole are not too different from each other, or from those of the crown substrates, showing that the presence of bulky groups in the *ortho* positions has only a modest influence on rates of methyl transfer and, consequently, that transition-state structures including charge distributions are not dramatically different throughout the series investigated. It appears, therefore, that the striking sensitivity to metal ions of the reactions of the crown substrates as compared with those of the simple anisoles (Table 1) are ascribable to the presence of the polyether bridges.

The rate-enhancing effects observed with the former compounds are not only exceptionally large in many cases, but also highly dependent on the particular substrate-cation combination. Thus potassium toluenethiolate demethylates 2-MeO-18C5 nearly three orders of magnitude more rapidly than the unassociated nucleophile, and about 30 times more rapidly than the

corresponding lithium salt. Sodium ion is very effective in the reaction of 2-MeO-18C5 but hardly at all in that of 2-MeO-24C7. The order of catalytic efficiency observed with 2-MeO-18C5 is $K^+ > Na^+ > Cs^+ > Li^+$ and with 2-MeO-24C7 it is $K^+ \approx Cs^+ \gg Na^+$. Further, the Na^+ and K^+ reactions of 2-MeO-18C5 are much faster than the corresponding reactions of 2-MeO-24C7, whereas the Cs^+ reactions of the two substrates proceed at comparable rates. All these effects are clearly of a kind which demonstrates that a host-guest interaction between the crown ether reactant and metal cation plays a central role. The basic mechanistic picture which emerges from the data is one in which the negative charge being transferred from sulphur to the methoxyl oxygen [equation (2)] is responsible for a



much stronger binding of the metal ion catalyst to the altered substrate in the transition state than to the unaltered substrate in the reactant state. Stated in a different way, the metal ion which, by virtue of the crown ether bridge, becomes complexed to the oxygen of the methoxy group increases what is sometimes called the nucleofugality¹⁸ of the aryl oxide group in the nucleophilic displacement from methyl. It appears, therefore, that the transition state for methyl transfer from the crown anisoles can be roughly depicted as a lariat ether with a short side-arm bearing a partial negative charge and having the proper geometric arrangement to effect metal ion complexation.

CONCLUSION

We have found that rates of methyl transfer from crown anisoles to toluenethiolate are greatly enhanced by alkali metal ions. To the best of our knowledge, catalytic effects by alkali metal ions comparable in magnitude to those recorded in the reaction of 2-MeO-18C5 are unprecedented.

Strong binding of the alkali metal ions to the transition state results from a favourable combination of coordinative interaction with the polyether bridge and electrostatic interaction with the negative charge developing on the methoxyl oxygen during the activation process. Electrostatic binding alone does not stabilise the transition state to a significant extent, as is clearly shown by the behaviour of anisole and 2,6-dimethylanisole.

The results presented here coupled with previous reports from our^{1-4,10} and other laboratories¹⁹⁻²¹ show that catalysis by alkali metal ions is of much more frequent occurrence than is commonly believed.

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