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Alkali-metal-ion-assisted $B_{AL}2$ cleavage of 2-(methoxycarbonyl)-1,3-xylylene-18-crown-5 by benzenemethanethiolate anion

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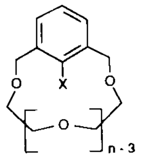
Abstract. $B_{AL}2$ demethylation of 2-(methoxycarbonyl)-1,3-xylylene-18-crown-5 by benzenemethanethiolate anion in dimethylformamide (+1.6M water) at 35°C is significantly promoted by alkali-metal counterions, the efficiency order being $Na^+ > K^+ > Cs^+ > Li^+$. The contrasting behaviour of the model compound, methyl 2,6-dimethylbenzoate, whose demethylation reaction is in fact slightly inhibited by metal ions, points to the crucial role played by the polyether bridge of the crown ether substrate. In line with previous work from this laboratory, selective transition-state stabilisation in the metal-ion-promoted cleavage of the crown-ether substrate is ascribed to a favourable combination of electrostatic binding of the metal ions with the negative charge being transferred from the nucleophile to the convergent methoxycarbonyl group and coordinative binding to the neutral donors of the polyether bridge.

Introduction

Complexation of metal ions by macrocyclic polyethers 2-X-3nC(n−1) can strongly affect the reactivity of the convergent functional group X in the 2-position of the aromatic nucleus[1-3].

Our quantitative investigations of acetyl transfer from crown-ether aryl acetates (X = $MeCO_2$, n = 5–9) to alkoxide ions[1], and of methyl transfer from crown ether anisoles (X = OMe, n = 6, 8) to benzenemethanethiolate anion[2], have shown that both nucleophilic addition to carbonyl and nucleophilic substitution at saturated carbon, respectively, are efficiently promoted by hard metal ions. In order to widen the scope of our studies of hard metal ions as electrophilic catalysts in reactions of functionalized crown ethers, we have investigated the effect of counterions on $B_{AL}2$ [a] methyl-transfer reactions from 2-(methoxycarbonyl)-1,3-xylylene-18-crown-5 (2-MeO_2C-18C5) [b] to alkali-metal (Li^+, Na^+, K^+, Cs^+) benzenemethanethiolates in dimethylformamide (DMF) (+1.6 M H_2O) at 35°C (Eqn. 1). For comparison, the corresponding reactions of the model compound methyl 2,6-dimethylbenzoate were also considered.



2-X-3nC(n − 1)

Results

Demethylation was carried out by reacting a 0.03M solution of substrate with the alkali-metal benzenemethanethiolates (0.14 M) generated *in situ* by partial neutralisation of the parent benzenemethanethiol (0.20 M) in DMF with a calculated amount of a 5M solution of the corresponding alkali-metal hydroxide in H_2O.

Reactions of the crown-ether derivative 2-MeO_2C-18C5 were followed by HPLC monitoring of the disappearance of the reactant ester and of the accumulation of the acid 2-HO_2C-18C5 produced[4]. At any time, the sum of the ester and acid was equal to the initial concentration of ester, showing that the only process taking place under the reaction conditions is that shown in Eqn. 1. Demethylation with sodium and potassium benzenemethanethiolates, which are the fastest of the series, proceeds quantitatively within the time range of about 4 h chosen for the HPLC measurements (Figure 1). Clean second-order time dependence is shown by close adherence of the experimental points to the best fit curves calculated from the integrated second-order rate equation. By analogy, second-order kinetics were assumed for the slower reactions, and the experimental data treated accordingly (Figure 1). With the slow reactions of methyl 2,6-dimethylbenzoate, the technique of choice was determination of initial rates by means of GLC monitoring of the production of benzyl methyl sulphide (Figure 2). Initial rates were translated into second-order rate constants. Suitable reference reactions for both systems were provided by kinetic runs, where 1.3 equiv. of the metal ion sequestering agent

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[a] Nucleophilic alkyl-oxygen cleavage of esters of the S_N2-type.

[b] IUPAC name: methyl 3,6,9,12,15-pentaoxabicyclo[15.3.1]heneicosa-1(21), 17, 19-triene-21-carboxylate

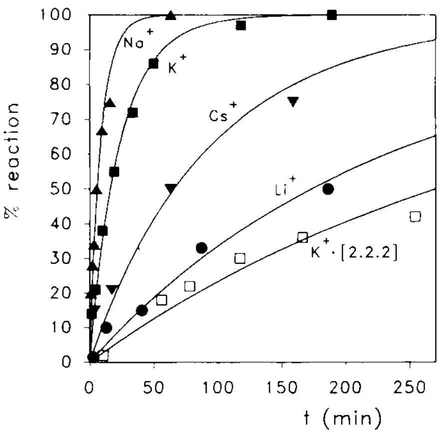


Fig. 1. Demethylation of 2-MeO$_2$C-18C5 by alkali-metal benzenemethanethiolates in DMF (+ 1.6M H$_2$O) at 35°C as monitored by HPLC. Curves are calculated from integrated second-order equation and k values listed in Table I.

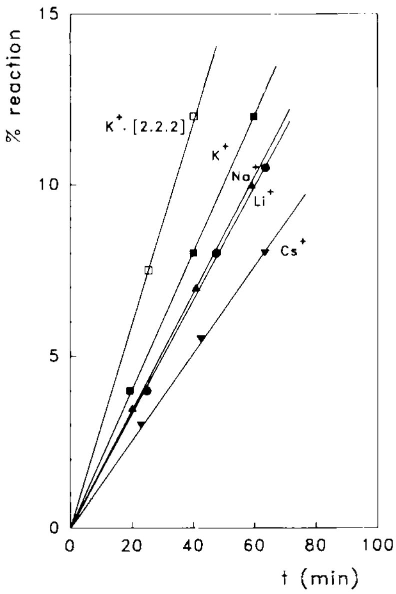


Fig. 2. GLC determination of initial rates for demethylation of methyl 2,6-dimethylbenzoate by alkali metal benzenemethanethiolates in DMF (+ 1.6M H$_2$O) at 35°C.

cryptand 222 [a] were added to potassium benzenemethanethiolate. The corresponding rate constants were taken to represent the inherent reactivities of benzenemethanethiolate, free from influence of the alkali-metal ions. Second-order rate constants for the investigated reactions are collected in Table I.

Discussion

The reactions reported in this work provide clean-cut examples of $B_{AL}2$-type methyl-transfer processes from methoxycarbonyl to a thiolate nucleophile, which are in line with the general behaviour of sterically hindered esters in reactions with nucleophiles[5].

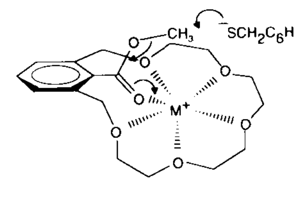
As shown in Table I, demethylation of the model compound methyl 2,6-dimethylbenzoate is invariably inhibited by alkali-metal counterions. These rate-depressing effects are consistent with the concept that ion pairs are less reactive than free ions in S_N2 reactions[6]. This is equivalent to saying that metal-ion interaction with the negative charge of the anionic nucleophile is more efficient in the reactant state than in the transition state, because in the latter the negative charge is more spread and, consequently, less available for electrostatic binding to the metal ion. It is worth pointing out that rate depressing effects on the cleavage of 2,6-dimethylbenzoate are small and nearly cation-independent, the reaction of the unassociated thiolate being only about twice as fast as the reactions of the alkali-metal thiolates. A possible interpretation of the above findings is based on weak and non-specific pairing of the hard alkali metal ions with the soft benzenemethanethiolate anion. Rate-depressing effects of comparable magnitude have been reported in the demethylation of anisole and 2,6-dimethylanisole by alkali-metal benzenemethanethiolates under closely similar conditions[2]. On the other hand, much more pronounced rate-depressing effects due to strong pairing to alkali metal ions have been found in reactions of hard nucleophiles, such as alkoxides[6b], aryloxides[7], enolates[8], and carboxylates[9] in dipolar aprotic solvents.

Table I Effects of metal ions on cleavage of methyl 2,6-dimethylbenzoate [a] and 2-MeO$_2$C-18C5 [b] by $C_6H_5CH_2S^-$ M^+ in DMF (+ 1.6M H$_2$O) at 35°C.

M^+	$k(M^{-1}\cdot s^{-1})$	k_{rel}
Methyl 2,6-dimethylbenzoate		
$K^+\cdot[2.2.2]$ [c]	$3.5\cdot10^{-4}$	1
Li^+	$1.9\cdot10^{-4}$	0.54
Na^+	$2.0\cdot10^{-4}$	0.57
K^+	$2.3\cdot10^{-4}$	0.66
Cs^+	$1.5\cdot10^{-4}$	0.43
2-MeO$_2$C-18C5		
$K^+\cdot[2.2.2]$ [c]	$3.2\cdot10^{-4}$	1
Li^+	$4.8\cdot10^{-4}$	1.5
Na^+	$1.5\cdot10^{-2}$	47
K^+	$5.4\cdot10^{-3}$	17
Cs^+	$1.4\cdot10^{-3}$	4.4

[a] From GLC determinations of initial rates. [b] From HPLC measurements. [c] 1.3 equiv of cryptand 222 added to 1 equiv of $C_6H_5CH_2SK$.

Let us now turn to the crown-ether benzoate 2-MeO$_2$C-18C5. Our first observation was that the intrinsic reactivity of this substrate is virtually the same as that of the simple model, as shown by the nearly identical rate constants measured in the presence of the $K^+\cdot$cryptand-222 counterion (Table I). Two important differences, however, emerge from comparison of reactions carried out in the presence of alkali-metal counter-ions. First, demethylation of the crown ether substrate is promoted rather than inhibited by alkali-metal ions. Secondly, the observed rate enhancements are markedly dependent upon the nature of the cation, as graphically shown in Figure 3. The most reactive salt is sodium benzenemethanethiolate, which is nearly 50 times as reactive as the free nucleophile. The potassium salt, which ranks next, is in turn more reactive than the cesium salt. A small, but clearly discernible rate enhancement of 1.5 is still present with the lithium salt, which is the least reactive of the four salts. The reactivity order, namely $Na^+ > K^+ > Cs^+ > Li^+$ suggests the importance of host–guest interactions between the crown-ether portion of the substrate and metal ions. As shown in the schematic picture of the transition state **TS** of the metal-



TS

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[a] IUPAC name: 4,7,13,16,21,24-hexaoxa-1,10-diazabicyclo[8.8.8]hexacosane

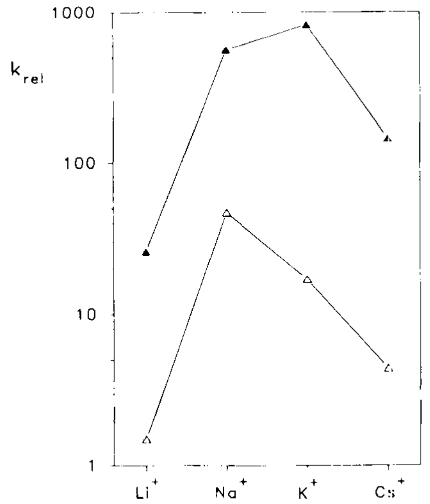

Fig. 3. Selectivity in demethylation of 2-MeO$_2$C-18C5 in DMF (+ 1.6M H_2O) at 35°C (△) and 2-MeO-18C5 in DMF (+ 3.3M H_2O) at 60°C (▲) by alkali-metal benzenemethanethiolates. Data from present work (△) and from Ref. 2 (▲).

ion-assisted demethylation, the negative charge which accumulates on the carboxylate-leaving group causes much stronger binding of the hosted metal electrophile to the altered substrate in the transition state than to the unaltered substrate in the reactant state. The present data again emphasize the importance of a synergic action of coordinative and electrostatic binding.

It is of interest to compare counter-ion effects on the cleavage of 2-MeO$_2$C-18C5 with analogous data reported for the S_N2 cleavage of 2-MeO-18C5 ($X = MeO$, $n = 6$) carried out with alkali-metal benzenemethanethiolates under similar reaction conditions[2]. The pertinent data are graphically shown in Figure 3. It is apparent that the highest reactivity in the demethylation of 2-MeO-18C5 is exhibited by the potassium salt, whereas sodium is the most efficient counter-ion in the demethylation of 2-MeO$_2$C-18C5. The importance of the match of the cation diameter to the size of the cavity defined by the crown ether bridge and the functional group undergoing nucleophilic attack is a possible explanation for the different selectivities exhibited by the two substrates. Since the convergent MeO$_2$C-group is larger than MeO-, a wider cavity is available for hosting a metal ion in the reactions of 2-MeO-18C5. As a consequence, potassium fits the cavity of the crown-ether anisole better than sodium, but the reverse holds for the crown-ether methyl benzoate.

We further note that counter-ion effects are about an order of magnitude larger in the demethylation of 2-MeO-18C5. In the reactions of 2-MeO-18C5, the negative charge transfers from sulphur to the methoxyl oxygen, but to both oxygens of the methoxycarbonyl group in the reactions of 2-MeO$_2$C-18C5. Since it seems likely that metal ions can interact only with the fractional negative charge being transferred to the carbonyl oxygen, electrostatic binding to the metal electrophile and the resulting rate enhancements should be significantly lower than those found in the reactions of 2-MeO-18C5, where all of the negative charge transferred from sulphur is essentially localised on a single oxygen atom.

Experimental

^{1}H-NMR spectra were taken on a Bruker WP-80SY spectrometer. Gas-liquid-chromatography (GLC) analyses were performed on a Varian 3400 gas chromatograph with a flame-ionisation detector, fitted with 10 m×0.53 mm HP-5 (cross-linked 5% phenyl silicone) fused-silica capillary column (2.6 μm film thickness). HPLC analyses were performed on an HP 1050 instrument with a UV-Vis detector operating at 230 nm, equipped with an HP 3394A integrator and fitted with a 25 cm×4.6 mm ID Supelcosil LC8 column.

Materials

N,N-Dimethylformamide (Carlo Erba) was thoroughly purged with argon before use. Benzenemethanethiol (Fluka) was distilled under vacuum. Other chemicals were used as received. Concentrated solutions of alkali-metal hydroxides in H_2O were prepared from the corresponding alkali-metal hydroxide and titrated with standard hydrochloric acid. 1-Naphthalenemethanol was from a previous investigation[10]. Methyl 2,6-dimethylbenzoate was prepared in quantitative yield by esterification of 2,6-dimethylbenzoic acid (Janssen) with diazomethane, bp 133°C (20 Torr), lt.[11] b.p. 109°C (19 Torr). 2-(Methoxycarbonyl)-1,3-xylylene-18-crown-5 (m.p. 52.0–53.5°C, lit.[12] oil) and 2-carboxy-1,3-xylylene-18-crown-5 (m.p. 103.0–103.5°C, lit.[12] m.p. 100–101°C) were prepared according to published procedures. All spectral data were in agreement with those already reported.

Kinetics

All operations were carried out under argon in order to minimise air oxidation of the thiolate nucleophile. Solutions of alkali-metal benzenemethanethiolates were generated *in situ* by partial neutralisation of the parent benzenemethanethiol in DMF with a calculated amount of a 5M solution of the corresponding alkali-metal hydroxide in H_2O. After mixing, the concentration of the benzenemethanethiolate anion was 0.14 M and that of the parent thiol was 0.06 M. The reactions of 2-MeO$_2$C-18C5 and methyl 2,6-dimethylbenzoate were monitored by HPLC and GLC techniques, respectively.

2-MeO$_2$C-18C5. Rate measurements were carried out by sampling of the reaction mixture at time intervals. After quenching with excess dilute hydrochloric acid, a known amount of 1-naphthalenemethanol (internal standard) was added and the mixture was thoroughly extracted with methylene chloride. The solvent was removed under reduced pressure and the residue was dissolved in MeOH/H_2O (60:40). The sample was analysed on a Supelcosil LC8 column with MeOH/H_2O (60:40) as eluent, at a flow rate of 1 ml/min. Under these conditions, retention times of 4.3, 6.3, 8.2, 10.2, and 13.2 min were observed for 2-HO$_2$C-18C5, 2-MeO$_2$C-18C5, 1-naphthalenemethanol, benzenemethanethiol, and benzyl methyl sulphide, respectively. The progress of the reaction was monitored by determining the amount of 2-MeO$_2$C-18C5. Non-linear least-squares fit of the analytical data to the standard second-order equation was carried out with the programme Sigma Plot (Jandel Scientific).

Methyl 2,6-dimethylbenzoate. Rate measurements were carried out by sampling of the reaction mixture at time intervals. After quenching with excess dilute hydrochloric acid, a known amount of 1,3,5-tri-*tert*-butylbenzene (internal standard) was added and the mixture was thoroughly extracted with hexane. The reaction progress was determined by analysing the solution for the amount of benzyl methyl sulphide produced. Data collected in the first 8–12% reaction gave initial rates which were converted into second-order rate constants.

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