Cation participation in nucleophilic substitution reactions promoted by complexes of polyether ligands with alkali and alkaline-earth metal salts

Alessandro Gobbi, Dario Landini, Angelamaria Maia * and Michele Penso

Centro CNR and Dipartimento di Chimica Organica e Industriale dell'Università, Via Golgi 19, I-20133 Milano, Italy

Cation electrophilic catalysis has been studied in nucleophilic substitution reactions of octyl methanesulfonate (1) promoted by complexes of macrocyclic polyethers 2–5 with alkali and alkaline-earth metal salts in chlorobenzene. The catalytic effect increases with increasing Lewis acid character of the cation, in the order $Cs^+ \sim Rb^+ \sim K^+ < Na^+ < Li^+$ and $Ba^{2+} < Sr^{2+} < Ca^{2+}$, and is mainly related to the ability of the polyether to shield the metal ion charge. Kinetic data clearly indicate that crown ethers 2–4 allow the metal ion participation in the activation process, whereas the cryptand [2.2.2,C_{10}] (5), which more effectively binds the cation, inhibits catalysis. The lower reactivity of the complexes of alkaline-earth metal salts with both crown ethers and cryptands is most likely due to a higher interaction of the divalent cation with the anion in the ion-pair.

Macrocyclic polyethers (crown ethers, cryptands) represent a particularly attractive class of synthetic ligands due to their analogy with the naturally occurring ionophores such as valinomycin, nonactin.[1,2] They are able to promote the extraction and the transport of the ions in biological and liquid–liquid membranes and to form stable inclusion complexes $(M^{n+} \subset Lig)nY^-$ with a number of alkali and alkaline-earth metal salts even in solvents of low polarity.[1,2] The reactivity of these complexes is found to increase in the order: open chain ligand ≤ crown ether ⋘ cryptand, according to the ability of the ligand to bind effectively the cation and hence to activate the associated anion.[1b,3]

Cryptates, where the metal cation is fully wrapped in the cavity of the polyether which replaces its first sphere of solvation, give rise to very reactive 'solvent-separated' ion pairs. By contrast, in the crown ether complexes the ligand induces a lower cation–anion separation, resulting in reduced anion activation.[1b,3]

The topology of the ligand also plays a major role in reactions that involve metal ions in the activation process. In early studies we revealed 'cation electrophilic catalysis' in nucleophilic substitution reactions of alkylsulfonates promoted by complexes of alkali iodides [reaction (1)].[4] In particular, our results showed that whereas cryptands, which effectively 'sequester' metal ions, inhibit catalysis, less efficient complexing agents, like crown ethers or polyethylene glycols (PEGs), allow cation participation in reaction (1).[4]

In order to ascertain whether metal ion catalysis is specific for these cations, or is a more general feature, the study has been extended to other alkali (Rb^+, Cs^+) iodides, as well as to alkaline-earth cations (Ca^{2+}, Sr^{2+}, Ba^{2+}), in consideration of the fundamental role that the latter ions are found to play in biological processes.[2,5–7] A larger number of ligands, specific for the different cations, have also been examined.

Results

Kinetics were measured by reacting octyl methanesulfonate (1) ($0.5–2 \times 10^{-2}$ mol dm^{-3}) with comparable amounts of preformed $(M^{n+} \subset Lig)nY^-$ complex ($0.4–2 \times 10^{-2}$ mol dm^{-3}) in chlorobenzene at 50, 60 and 70 °C [reaction (1)].

Rates have been evaluated by potentiometric titration of the complexed nucleophile Y^-. Under these conditions the reactions follow regular second-order kinetics [eqn. (2)] up to at least two half-lives (Fig. 1). Results are reported in Tables 1–3.

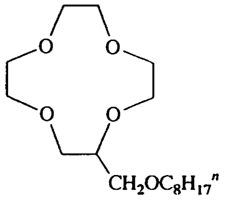
$$\underset{\mathbf{1}}{nC_8H_{17}OSO_2Me} + (M^{n+} \subset Lig)\,nY^- \xrightarrow{PhCl} nC_8H_{17}Y + (M^{n+} \subset Lig)\,nMeSO_3^- \qquad (1)$$

n = 1, 2

$M^{n+} = Li^+, Na^+, K^+, Rb^+, Cs^+, Ca^{2+}, Sr^{2+}, Ba^{2+}$

$Y^- = Cl^-, Br^-, I^-$

Lig = 12-crown-4, $CH_2OC_8H_{17}{}^n$ (**2**), PHB15-crown-5 (**3**), PHDB18-crown-6 (**4**), [2.2.2, C_{10}] (**5**)



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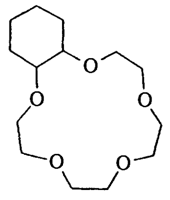

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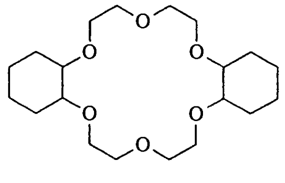

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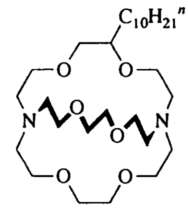

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$$\text{rate} = k[\text{substrate}][\text{complexed } Y^-] \qquad (2)$$

The activation parameters, $\Delta H^{\ddagger}$ (kJ mol^{-1}) and $\Delta S^{\ddagger}$ (J mol^{-1} K^{-1}), were calculated in the temperature range 50–70 °C for the reaction of octyl methanesulfonate (1) with the complexes $(Ca^{2+} \subset Lig)\,2I^-$ and $(Sr^{2+} \subset Lig)\,2I^-$, where Lig = PHDB18C6 (4) and [2.2.2, C_{10}] (5) (Table 2) and for sake of comparison with the complexes $(M^+ \subset PHDB18C6)\,I^-$, where M = Li, Na, K (Table 1), and $Hexyl_4N^+\,I^-$ (Table 2).

Table 1 Second-order rate constants and activation parameters for the nucleophilic substitution reaction of octyl methanesulfonate (**1**) with ($M^+ \subset$ Lig) I^- complexes in chlorobenzene, at various temperatures[a]

			$k^b/10^{-3}$ dm^3 mol^{-1} s^{-1}				$\Delta H^{\ddagger}$/kJ mol^{-1}	$\Delta S^{\ddagger}$/J mol^{-1} K^{-1}
Cation	ρ/Å^{-1}	T/°C	12C4,$CH_2OC_8H_{17}$ **2**	PHB15C5 **3**	PHDB18C6 **4**	[2.2.2,C_{10}] **5**	PHDB18C6 **4**	PHDB18C6 **4**
Li^+	1.28	50			11.2			
		60	129	126	26.3	15.3	72.2	−59.08
		70			56.8			
Na^+	1.02	50			7.7			
		60	12.6	21.5	19.0	14.6	74.14	−56.06
		70			40.6			
K^+	0.75	50			4.5			
		60		17.8	10.2	14.5	78.78	−46.53
		70			26.4			
Rb^+	0.67	60			10.8	15.0		
Cs^+	0.61	60			10.9			

[a] A chlorobenzene solution (30–50 cm^3) of the substrate (0.5–2 × 10^{-2} mol dm^{-3}) and of the ($M^+ \subset$ Lig) I^- complex (0.4–2 × 10^{-2} mol dm^{-3}).
[b] Average of at least two determinations. The error in these values is estimated to be 5%.

Table 2 Second-order rate constants and activation parameters for the nucleophilic substitution reaction of octyl methanesulfonate (**1**) with ($M^{2+} \subset$ Lig) $2I^-$ complexes in chlorobenzene, at various temperatures[a]

		$k^b/10^{-3}$ dm^3 mol^{-1} s^{-1}		$\Delta H^{\ddagger}$/kJ mol^{-1}		$\Delta S^{\ddagger}$/J mol^{-1} K^{-1}	
Cation	T/°C	PHDB18C6 **4**	[2.2.2,C_{10}] **5**	PHDB18C6 **4**	[2.2.2,C_{10}] **5**	PHDB18C6 **4**	[2.2.2,C_{10}] **5**
Ca^{2+}	50	9.7	2.6				
	60	21.0	9.0	68.86	99.91	−71.0	14.72
	70	45.9	24.2				
Sr^{2+}	50	2.7	3.5				
	60	7.2	9.4	77.28	88.24	−55.23	−19.37
	70	15.4	25.0				
Ba^{2+}	60	4.0	8.7				
$Hexyl_4N^+$	50		2.7				
	60		8.8	95.52		1.21	
	70		22.9				

[a] For reaction conditions see Table 1, footnote *a*. [b] Average of at least two determinations. The error in these values is estimated to be 5–7%.

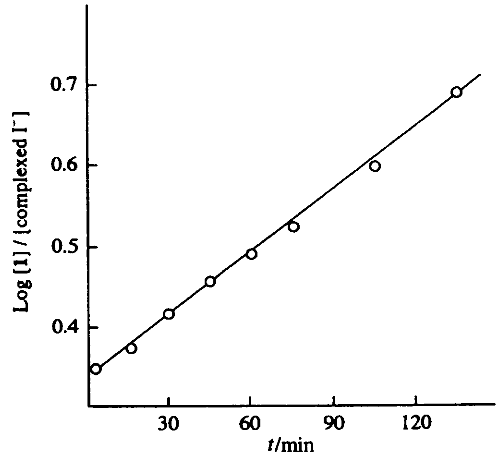


Fig. 1 Second-order plot for the reaction of octyl methanesulfonate (**1**) (0.815 × 10^{-2} mol dm^{-3}) with ($Ca^{2+} \subset$ PHDB18C6) $2I^-$ (0.365 × 10^{-2} mol dm^{-3}) in chlorobenzene, at 60 °C

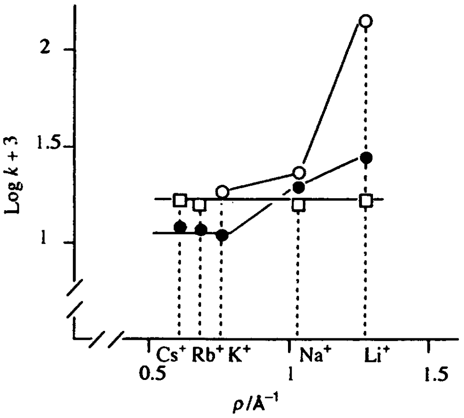


Fig. 2 Correlation between second-order rate constant k/dm^3 mol^{-1} s^{-1} and density charge ρ/Å^{-3} of the cation in the reaction (**1**) with complexes ($M^+ \subset$ Lig) I^-, where $M^+ = Li^+$, Na^+, K^+, Rb^+, Cs^+; Lig = PHB-15-crown-5 (**3**) (○), PHDB-18-crown-6 (**4**) (●), [2.2.2,C_{10}] (**5**) (□)

As reported in Tables 1 and 2, the second-order rate constants k (dm^3 mol^{-1} s^{-1}) promoted by the complexes of cryptand [2.2.2,C_{10}] (**5**) are independent of the cation M^{n+}. By contrast, values of k depend on the metal ion complexed to crown ethers **2**–**4** following the order: $k_{Li^+} > k_{Na^+} > k_{K^+} \sim k_{Rb^+} \sim k_{Cs^+}$ and $k_{Ca^{2+}} > k_{Sr^{2+}} > k_{Ba^{2+}}$. In addition, the cation being the same, the rate constants increase by diminishing the hole size of the complexing agent in the order: $k_{PHDB18C6} < k_{PHB15C5} \sim k_{12C4,CH_2OC_8H_{17}}$ as shown in Fig. 2, where the rate constants are plotted against the cation charge density (ρ) defined as 'charge : ionic radius' ratio.[8,9]

Discussion

The results as a whole highlight cation participation in the nucleophilic substitution reaction (**1**) promoted by the complexes of crown ethers **2**–**4** with both alkali (Li^+, Na^+, K^+, Rb^+, Cs^+) and alkaline-earth (Ca^{2+}, Sr^{2+}, Ba^{2+}) metal iodides.

In the series of alkali iodides (Table 1) the second-order rate constants k increase (from 2.5-fold up to more than 10-fold) in the order: $k_{Cs^+} \sim k_{Rb^+} \sim k_{K^+} < k_{Na^+} < k_{Li^+}$. The highest enhancement of reactivity is observed with the crown ether 12C4,$CH_2OC_8H_{17}$ (**2**) passing from the sodium to the corres-

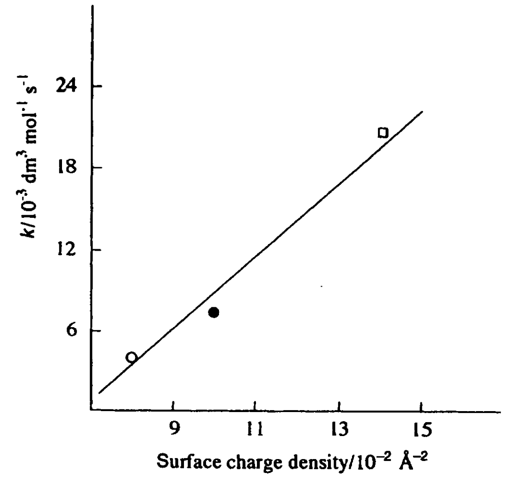


Fig. 3 Correlation between second-order rate constant k/dm^3 mol^{-1} s^{-1} and surface charge density/Å^{-2} in reaction (1) with complexes ($M^{2+} \subset$ PHDB18C6) $2I^-$, where $M^{2+} = Ba^{2+}$ (○), Sr^{2+} (●), Ca^{2+} (□) ($r = 0.992$)

ponding lithium salt (Table 1). Such a trend was explained on the basis of a concerted 'push–pull' mechanism†,[10] in which the complexed cation ($M^+ \subset$ Lig) assists the departure of the leaving group ($CH_3SO_3^-$) while favouring at the same time the attack of the iodide anion on the carbon in the transition state.[4] Indeed, the sequence found (Table 1) reflects the increasing interaction of the leaving group with the metal cation, increasing its charge density ρ.[8,9] The results show that when potassium is replaced by the slightly larger Rb^+ or Cs^+ the rate constants are practically unchanged, in line with the very close ρ values of these cations (0.67 and 0.61 Å^{-1} for Rb^+ and Cs^+, respectively)[9] (Table 1). The increasing reactivity observed, for a given cation, in the series of the crown ethers **2**–**4** is most likely due to the less efficient shielding of the metal ion charge by diminishing the number of ether oxygens resulting in higher electrophilic catalysis.[4]

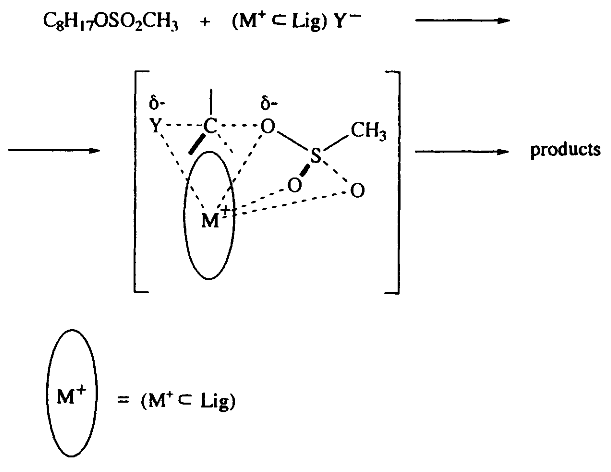
A similar trend was observed with alkaline-earth iodides MI_2 (M = Ca, Sr, Ba) (Table 2).‡ The rate constants progressively increase (up to more than five-fold), in the order $Ba^{2+} < Sr^{2+} < Ca^{2+}$, and linearly correlate with the surface charge density of the cation (see Fig. 3). The transition state does not substantially differ from that previously proposed for alkali metal ions[4] (Scheme 1) as confirmed by the activation parameters (Tables 1 and 2). The $\Delta H^\ddagger$ and $\Delta S^\ddagger$ values found for Ca^{2+} and Sr^{2+} show metal ion participation in the transition state which is more pronounced (lower enthalpy and more negative entropy) in the case of the cation with the highest charge density (Ca^{2+}) (Table 2).§

Conversely, with [2.2.2,C_{10}] cryptand (**5**) the reactivity does not appreciably change with the metal ion, M^+ or M^{2+} (Tables 1 and 2) and is, for Ca^{2+}, Li^+ and Na^+, lower than that of the corresponding complexes with crown ethers. Since cryptands efficiently shield cations and hence are excellent anion activators the lower reactivity found clearly indicates that, in this case, the participation of the cation in reaction (1) is inhibited. In addition, the same reactivity observed in the series of alkali and alkaline-earth iodides confirms that, in these complexes, the cation–anion interaction is minimised. As shown in Table 2, the activation parameters obtained with the cryptates of CaI_2 and SrI_2 are in this case very similar and comparable to those of the quaternary ammonium iodide $Hexyl_4N^+I^-$, where metal ion catalysis can be excluded.[4] The reactivity of the cryptates of divalent cations [$M^{2+} \subset (2.2.2,C_{10})$] $2I^-$ is about 1.5-fold lower than that of the complexes of alkali metal iodides [$M^+ \subset (2.2.2,C_{10})$] I^- (Tables 1 and 2). Such a difference can be attributed to a slightly higher interaction of the divalent cation with the anion in the ion pair, as suggested by the solid-state structures of these complexes.¶,[11]

Table 3 Second-order rate constants for the nucleophilic substitution reaction of octyl methanesulfonate (**1**) with ($M^{n+} \subset$ Lig) $n\mathrm{Hal}^-$ complexes ($n = 1, 2$) in chlorobenzene, at 60 °C[a]

	$k^b/10^{-3}$ dm^3 mol^{-1} s^{-1}			
$MHal_n$	PHDB18C6 **4**	k_{rel}	[2.2.2,C_{10}] **5**	k_{rel}
LiI	26.3	17.5	15.3	1
LiBr	12.8	8.5	43.0	2.8
LiCl	1.5	1	—	—
KI	10.2	1.2	14.5	1
KBr	13.0	1.5	36.6	2.5
KCl	8.6	1	50.8	3.5
CaI_2	21.0	525	9.0	1
$CaBr_2$	0.54	13.0	29.0	3.2
$CaCl_2$	0.04	1	37.5	4.2

[a] For reaction conditions see Table 1, footnote *a*. [b] Average of at least two determinations. The error in these values is estimated to be 5–7%.



Scheme 1

The data confirm that in the cryptates the cation–anion interaction, even if minimised in comparison with other ligands, is still present.[1b] The different behaviour of alkali and alkaline-earth cations is much more evident if we compare the reactivity of their complexes with crown ethers. These macrocycles are known not to realise a large cation–anion separation; in this case the complexed cation is still accessible for interaction with the anion in a 'crown-separated' ion-pair. By increasing the charge density of the cation and/or the anion the ion-pair becomes progressively more intimate and hence less

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† Pregel and Buncel proposed an analogous mechanism in reactions of alkali metal ethoxides with sulfonate and phosphinate esters in ethanol.[10]

‡ Unfortunately no kinetic measurements were possible with MgI_2 due to the insolubility of the complexes in weakly polar solvents.

§ A quantitative evaluation of metal ion participation in terms of difference of free energy of activation, could also be provided by the values of ΔG_{cat} (kJ mol^{-1}) obtained from eqn. (3),[10] for the complexes

$$\Delta G_{cat} = \Delta G_{cat}{}^\ddagger - \Delta G_{uncat}{}^\ddagger = -RT \ln(k_{crown}/k_{crypt}) \qquad (3)$$

of crowns **3** and **4** with alkali and alkaline-earth iodides, by assuming that the rate constant of the cryptate corresponds to the uncatalysed reaction and that of the complex with the crown to the catalysed reaction. The following ΔG_{cat} (kJ mol^{-1}) values are obtained. ($M^{n+} \subset$ PHDB18C6): Li^+ (−1.5); Na^+ (−0.60); K^+ (+0.97); Ca^{2+} (−2.4); Sr^{2+} (+0.74). ($M^+ \subset$ PHB15C5): Li^+ (−5.84); Na^+ (−1.07); K^+ (−0.57).

¶ Solid-state structures, determined by Weiss and co-workers,[11] have shown that whereas the metal ion does not appreciably interact with the anion in the alkali metal cryptates of [2.2.2], in the complex [$Ba(SCN)(H_2O) \subset (2.2.2)$]$^+$ the cation is still partially hydrated and in strong interaction with the anion.

reactive.[3] This is the main reason for the narrow nucleophilicity sequence ($Br^- \sim I^- \sim Cl^-$) found in the series of potassium halides (Table 3). The trend is even reversed ($I^- > Br^- > Cl^-$) when cations with higher charge density like Li^+ ($\rho = 1.28$ Å^{-1}) and Ca^{2+} ($\rho = 2.02$ Å^{-1}) are used. With these cations changing from I^- to Cl^-, the k values decrease 17.5-fold in the case of lithium and more than 500-fold for calcium halides.

Comparison with the corresponding complexes of [2.2.2,C_{10}] (**5**) (Table 3) shows that the second-order rate constants obtained with iodides are mainly due to cation electrophilic assistance whereas those with harder anions, like Br^- and Cl^-, reflect the deactivation of the anion in the ion-pair, in the order $Cl^- > Br^-$. The effect is particularly evident in the ($Ca^{2+} \subset$ Lig) $2Cl^-$ complex where a dramatic increase in reactivity of *ca.* 10^3 is observed when crown ether PHDB18C6 (**4**) is replaced by the [2.2.2,C_{10}] cryptand (**5**) that induces a much larger cation–anion separation (Table 3).

Conclusions

The kinetic data show cation electrophilic assistance in reaction (1) promoted by complexes of polyethers **2–4** with alkali and alkaline-earth metal iodides. The catalytic effect increases with increasing the Lewis acid character of the cation, in the order $Cs^+ \sim Rb^+ \sim K^+ < Na^+ < Li^+$ and $Ba^{2+} < Sr^{2+} < Ca^{2+}$, and is mainly related to the ability of the ligand to shield the metal ion charge. Whereas crown ethers **2–4** allow metal ion participation in the transition state of the reaction, the cryptand [2.2.2,C_{10}] (**5**), which more effectively binds the cation, inhibits catalysis. The lower reactivity of the complexes of alkaline-earth metal salts with both cryptands and crown ethers is most likely due to a higher interaction of the divalent cation with the anion in the ion pair.

Experimental

General methods

Potentiometric titrations were carried out with a Metrohm 670 Titroprocessor by using a combined silver electrode isolated with a potassium nitrate bridge. Karl-Fisher determinations were carried out with a Metrohm 684KF coulometer. ^{1}H NMR spectra were recorded on a Bruker AC300 spectrometer using tetramethylsilane as external standard.

Materials and solvents

Inorganic salts, AnalaR grade commercial products, were first ground then dehydrated in an oven at 110–120 °C under vacuum for several hours. In all cases water content is ≤0.05 mol per mol of salt. AnalaR grade chlorobenzene was carefully dried (Karl-Fisher titration showed a water content ≤30 ppm) by standard methods[12] and stored over molecular sieves under nitrogen. Octyl methanesulfonate (**1**) (bp 112–114 °C/2 Torr; n_D^{20} 1.4398) was prepared according to the literature (lit.,[13] bp 110–114 °C/2 Torr; n_D^{20} 1.4392). Ligands **4** and **5** were utilised as purchased. Perhydrobenzo-15-crown-5 (**3**) was obtained by catalytic hydrogenation of the commercially available benzo-15-crown-5, following a previously described procedure.[14]

2-Octyloxymethyl-12-crown-4 (**2**) was prepared from the commercially available 2-hydroxymethyl-12-crown-4 as follows.

2-Octyloxymethyl-12-crown-4|| (2)

A solution of 2-hydroxymethyl-12-crown-4 (2.06 g, 10 mmol) in anhydrous tetrahydrofuran (THF) (10 cm^3) was added to a stirred suspension of Bu^{t}OK (1.12 g, 10 mmol) in THF (5 cm^3) under N_2. After 10 min, a solution of 1-bromooctane (1.93 g, 10 mmol) in THF (10 cm^3) was added and the heterogeneous reaction mixture was refluxed under stirring for 5 h. The solvent was evaporated, water was added (20 cm^3) and the mixture was neutralised with concentrated HCl and extracted with CH_2Cl_2 (3 × 15 cm^3). The organic layers were dried over molecular sieves (0.03 nm) and evaporated under reduced pressure. The oily residue was purified by flash chromatography on silica gel (230–400 mesh) with a 1:4 mixture of ethyl ether–light petroleum (bp 40–60 °C) as eluent, affording crown ether **2** (2.52 g, 79%); n_D^{20} 1.4580, bp 123–125 °C/0.04 Torr (lit.[15] bp 125 °C/0.04 Torr); δ_H($CDCl_3$; 300 MHz) 0.86 (3 H, t, *J* 7.2, Me), 1.26 (10 H, br s, CH_2), 1.53 (2 H, m, $OCH_2CH_2CH_2$), 3.39–3.81 (19 H, m, ethereal H).

Kinetic measurements

In a typical procedure a standardised chlorobenzene solution (15 cm^3) of octyl methanesulfonate (**1**) (1–4 × 10^{-2} mol dm^{-3}) was added to a standardised chlorobenzene solution (15 cm^3) of complexed salt (0.8–4 × 10^{-2} mol dm^{-3}) in a 50 cm^3 flask thermostatted at 50–70 ± 0.1 °C. Samples (2–5 cm^3), withdrawn periodically, were quenched in ice-cold MeOH (50 cm^3) and the unreacted nucleophile Y^- was potentiometrically titrated with 0.01 M $AgNO_3$. The second-order rate constants were evaluated using a least-squares computer program from eqn. (4), where A = substrate and B = complexed Y^-. All rates

$$\frac{\ln([B][A]_0/[A][B_0])}{[B]_0 - [A]_0} = kt \qquad (4)$$

involved at least eight samplings and gave correlation coefficients of 0.997 or better.

The values of $\Delta H^\ddagger$ and $\Delta S^\ddagger$ in the temperature range 50–70 °C were computer generated by plotting ln k/T *vs.* $1/T$, following the Eyring equation.

The solutions of preformed complexes of **2–5** were prepared by magnetically stirring a standardised chlorobenzene solution (30 cm^3) of the ligand (0.8–4 × 10^{-2} mol dm^{-3}) with the appropriate quantity of the salt (0.5–10 mol per mol of ligand), as a solid phase, in a flask thermostatted at 50–70 ± 0.1 °C. The system was stirred for 1–2 h and then kept without stirring for an additional 10 min to allow good separation of the two phases. Aliquots (5–8 cm^3) of the organic phase were centrifuged and samples (2–5 cm^3) were withdrawn and titrated with 0.01 M $AgNO_3$. Potentiometric titrations of cryptates [$M^{n+} \subset$ (2.2.2,C_{10})] nY^- were performed in acid medium (HNO_3) in order to avoid the simultaneous titration of the free ligand.[3a]

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