Anion Activation by the Bulky Perhydrotribenzo[2.2.2]cryptand in Aqueous–Organic Two-phase Systems and in Low Polarity Media. A Comparison with the Anionic Reactivity induced by [2.2.2,C_{14}]cryptand

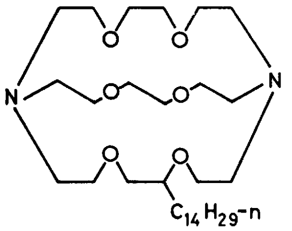
By **Dario Landini, Angelamaria Maia,* Fernando Montanari, and Franco Rolla,*** Centro CNR and Istituto di Chimica Industriale dell'Università, I–20133 Milano, Italy

In the displacement of the methanesulphonate group by a series of nucleophiles, anionic activation promoted by perhydrotribenzo[2.2.2]cryptand (2) is practically identical to that observed in the presence of the less hindered [2.2.2,C_{14}]cryptand (1), both under phase-transfer catalysis conditions and in homogeneous chlorobenzene solution. However, the stability constants of cryptates noticeably decrease on passing from (1) to (2), especially in anhydrous solutions. The latter behaviour is best explained on the basis of the greater rigidity of cryptand (2) compared with (1), whereas the reactivity data seem to indicate that an optimal ionic separation, and therefore a maximum anionic activation, is already reached with the [2.2.2]ligand.

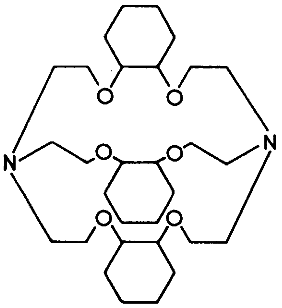
In the inclusion complexes (cryptates) of azamacrobicyclic polyethers, the cation is fully surrounded by the tridimensional ligand which replaces its solvation sphere.[1] Therefore, when cryptates are made soluble in low polarity media by long alkyl chains, the poor anion solvation and the large cation–anion separation imposed by the topology of the system give rise to high anionic activation,[1,2] probably the highest which can actually be obtained in solution.[2,3]

It seemed important to establish whether the use of bulkier macrobicyclic ligands gives rise to a further increase in the reactivity of anions. In principle, this could be realized by perhydrotribenzo[2.2.2]cryptand (2), [2.2.2,PHTB], synthesized as previously described together with preliminary data on its catalytic activity under phase-transfer conditions.[4]

In the present paper we report a kinetic study of aliphatic nucleophilic substitutions catalysed by cryptand (2) in a water–chlorobenzene two-phase system. Cryptand (2) was a mixture of inseparable diastereoisomers,† and used as such. The study has been extended to the same nucleophilic substitutions by pre-formed [K^+ (2.2.2,PHTB)]Y^- cryptates in anhydrous chlorobenzene solutions and the data have been compared with those previously obtained [2] in the presence of [K^+ (2.2.2,C_{14})]Y^- cryptates.



(1)



(2)

RESULTS

The reaction studied is the nucleophilic substitution of the methanesulphonate group in n-octyl methanesulphonate by a series of anionic nucleophiles (Cl^-, Br^-, I^-, SCN^-) in a water–chlorobenzene two-phase system, in the presence of catalytic amounts of [2.2.2,PHTB]cryptand (2) (0.08—0.005 mol per mol of substrate) and with a 5 : 1 molar ratio of inorganic salt to substrate [reaction (1)].

$$\text{n-}C_8H_{17}OSO_2Me + KY \xrightarrow[\text{PhCl-}H_2O]{[2.2.2,\text{PHTB}]} \text{n-}C_8H_{17}Y + MeSO_3K \quad (1)$$
$$Y = Cl, Br, I, SCN$$

Reactions were carried out [2] while stirring the heterogeneous system at 1 000 r.p.m., to ensure the rates are independent of ion diffusion at the interface. Reaction rates were measured by following the disappearance of the substrate by ^1H n.m.r. analysis, with phenyl benzyl ether as internal standard. The complexation percentages of ligand (2) with the inorganic salts under phase-transfer catalysis conditions were determined by potentiometric titration of the anion in the organic phase. They remained constant during the reaction and ranged from 9% for KCl to 92% for KSCN (Table 1).

By using liquid membranes [2,3,5] it was established that under phase-transfer catalysis conditions catalyst (2) is entirely dissolved in the organic phase as a free ligand and/or a cryptate. Titrimetric measurements showed that the anion associated with the cryptate is nucleophile Y^-, whereas methanesulphonate is quantitatively transferred to the aqueous phase. Thus equilibrium (2) is fully shifted to the right.

$$\{[K^+ (2.2.2,\text{PHTB})]MeSO_3^-\}_{org} + (KY)_{aq} \rightleftharpoons \{[K^+ (2.2.2,\text{PHTB})]Y^-\}_{org} + (MeSO_3K)_{aq} \quad (2)$$

This greatly simplifies the kinetics. The reactions follow the pseudo-first-order kinetic equation (3) up to at least 80% conversion, and the observed pseudo-first-order rate constants are linearly related to the concentration of the [K^+ (2.2.2,PHTB)]Y^- cryptate (Figure).

$$\text{rate} = k_{obs}[\text{substrate}] \quad (3)$$

Karl Fischer analyses of the organic phase showed that under the same conditions followed in the kinetic measurements and in the presence of non-complexable salts such as $(CH_3)_4N^+Cl^-$, free ligand (2) is associated with 2 mol equiv

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† According to the synthetic scheme [4] they are: *trans,trans,trans* (in-phase); *trans,trans,trans* (out-of-phase); *trans,trans,cis* (in-phase); *trans,trans,cis* (out-of-phase).

TABLE 1

Second-order rate constants for nucleophilic substitutions of methanesulphonate by anions (Y^-)[a] in n-octyl methanesulphonate in chlorobenzene–water two-phase system under phase-transfer conditions in the presence of [2.2.2,PHTB] (2) or [2.2.2,C_{14}] (1) cryptands at 60 °C

	[2.2.2,PHTB]cryptand[b]			[2.2.2,C_{14}]cryptand[c]		
Y	10^2k/l mol^{-1} s^{-1} [d,e]	Complexation (%)	Hydration state n of [K+ (2.2.2,PHTB)]$Y^-\cdot nH_2O$ [f,g]	10^2k/l mol^{-1} s^{-1} [d,e]	Complexation (%)	Hydration state n of [K+ (2.2.2,C_{14})]$Y^-\cdot nH_2O$
Cl	3.8 (0.8)	9	5.2 ± 0.3	3.5 (0.7)	95	5.3 ± 0.2
Br	5.5 (1.2)	42	4.3 ± 0.2	5.6 (1.2)	97	4.3 ± 0.2
I	4.5 (1.0)	89	3.2 ± 0.1	4.7 (1.0)	100	3.2 ± 0.1
SCN	0.8 (0.2)	92	2.8 ± 0.2	1.1 (0.23)	100	2.9 ± 0.2

[a] From [K^+ (2.2.2,PHTB)]Y^- or [K^+ (2.2.2,C_{14})]Y^-. [b] A chlorobenzene solution (20 ml) of substrate (6.0×10^{-1}M) and of [K^+ (2.2.2,PHTB)]Y^- (0.3—4.5×10^{-2}M), and an aqueous solution (15 ml) of potassium salt (4.2M). [c] From data previously reported.[2] [d] k is defined as $k = k_{obs}$/[cryptate]. [e] Relative rates in parentheses. [f] For the uncomplexed cryptand $n = 2.2 \pm 0.2$. [g] Average of at least three determinations.

TABLE 2

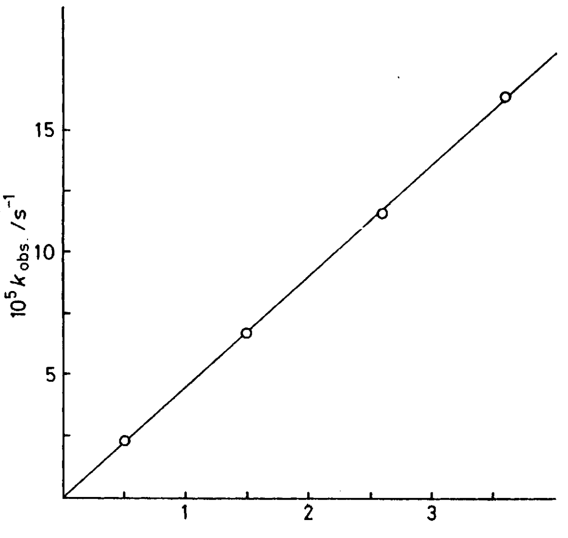
Second-order rate constants for nucleophilic substitutions of methanesulphonate by anions (Y^-)[a] in n-octyl methanesulphonate in anhydrous chlorobenzene at 60 °C

	[2.2.2,PHTB]cryptand[b]		[2.2.2,C_{14}]cryptand[c]	
Y	10^2k/l mol^{-1} s^{-1} [d,e]	Complexation (%)	10^2k/l mol^{-1} s^{-1} [e]	Complexation (%)
Cl		3	50.8 (5.8)	43
Br	37.4 (3.6)	10	36.6 (4.2)	97
I	10.5 (1.0)	93	8.7 (1.0)	100
SCN	2.3 (0.19)	100	1.5 (0.17)	100

[a] From [K^+ (2.2.2,PHTB)]Y^- or [K^+ (2.2.2,C_{14})]Y^-. [b] [substrate] 1—5×10^{-2}M; [cryptate] 0.2—4×10^{-2}M. [c] From data previously reported.[2] [d] Average of at least two runs. [e] Relative rates in parentheses.

of water. In the presence of potassium salts an additional amount of water depending on the anion (1—3 mol equiv.) is associated with the cryptate of (2) (Table 1).

Kinetic measurements in homogeneous anhydrous solutions were carried out with comparable concentrations of pre-formed cryptate (0.2—4×10^{-2}M) and substrate (1—5×10^{-2}M) [reaction (4)].



Dependence of the observed rate constants (k_{obs}/s^{-1}) on the [K^+ (2.2.2,PHTB)]I^- concentration for the reaction of n-octyl methanesulphonate with iodide ion in the PhCl–H_2O two-phase system at 60 °C. For reaction conditions see footnote b of Table 1

$$\text{n-}C_8H_{17}OSO_2Me + [K^+ (2.2.2,\text{PHTB})]Y^- \xrightarrow{\text{PhCl}} \text{n-}C_8H_{17}Y + [K^+ (2.2.2,\text{PHTB})]MeSO_3^- \quad (4)$$

$$Y = \text{Br, I, SCN}$$

Reaction rates were measured from the disappearance of the nucleophile and were found to follow second-order kinetics [equation (5)].

$$\text{rate} = k[\text{substrate}][\text{cryptate}] \qquad (5)$$

Second-order rate constants are reported in Table 2, together with the complexation percentages of cryptand (2) in anhydrous chlorobenzene. The latter were determined by stirring for 2—6 h a chlorobenzene solution of ligand (2) (2—4×10^{-2}M) in the presence of an excess of the corresponding anhydrous potassium salts as solid phase (20 mol per mol of cryptand), and potentiometrically titrating the dissolved anions. In Tables 1 and 2 the rate constants and the complexation percentages of ligand (1) measured under phase-transfer catalysis and homogeneous conditions[2] are also reported for the sake of comparison.

DISCUSSION

The experimental data indicate that the kinetic picture is identical for the reactions promoted by cryptates of (1) and (2), both under phase-transfer catalysis conditions and in anhydrous chlorobenzene. Under phase-transfer catalysis conditions the reactions occur in the organic phase. Nucleophilic attack on the substrate is the rate-determining step of the overall process, anion exchange between the two phases and re-establishment of equilibria being relatively fast steps. By using liquid membranes it was demonstrated that the anion exchange at the interface does not require the concomitant transfer of the cationic counterpart. Therefore the mechanism is the same as that already found for phase-transfer reactions catalysed by [2.2.2,C_{14}]cryptand (1),[2] by quaternary salts[5,6] and crown ethers,[3] all of them completely insoluble in the aqueous phase. It can be summarised by equation (6).

As in the case of cryptates derived from (1), under homogeneous anhydrous conditions the kinetic behaviour is that expected for a classical bimolecular nucleophilic S_N2 substitution. As shown in Tables 1 and 2, reaction rates are the same for all the anions under phase-transfer catalysis conditions and, for Br^-, in anhydrous chlorobenzene; in this solvent for I^- and SCN^- only there is a modest reactivity increase on passing from (1) to (2) (1.2 and 1.5 times, respectively),

$$\begin{tikzcd}
\mathrm{RX} + [\mathrm{K}^+ (2.2.2,\mathrm{PHTB})]\mathrm{Y}^- \arrow[r] & \mathrm{RY} + [\mathrm{K}^+ (2.2.2,\mathrm{PHTB})]\mathrm{X}^- \arrow[d] & \text{(organic phase)} \\
\mathrm{Y}^- + \mathrm{K}^+ \arrow[u] \quad + & \mathrm{X}^- & \text{(aqueous phase)}
\end{tikzcd} \qquad (6)$$

constants for all the diastereoisomers. However for any single diastereoisomer the volume of the ligand, and thus the interionic distance, cannot be very different. The diminished stability of cryptates of (2) is consistent with the low flexibility of the ligand due to the cyclohexane rings, and therefore with an internal cavity less adjustable to the cation diameter,[10] even if the stability constants of the various diastereoisomers of (2) are different from each other.*

The factors determining the narrow reactivity range and the nucleophilicity sequence under phase-transfer catalysis conditions have been discussed in previous papers.[2,3,6] The same sequence ($Br^- > I^- > Cl^- > SCN^-$) is found for (2) as the phase-transfer catalyst. It is anomalous with regard to the well known reactivity sequences in protic and in dipolar aprotic solvents,[7] and primarily depends on the specific solvation of the anion in the organic phase by a limited number of molecules of water (Table 1). It should be noted that the hydration numbers of the anions are the same, independent of the nature of the cryptate. If one takes into account the fact that uncomplexed reagents (1) and (2) both associate 2 mol. equiv. of water, the hydration numbers are equal to those previously found for quaternary salts [6,8] and complexed crown ethers.[3]

In going from the two-phase water–chlorobenzene system to the homogeneous chlorobenzene solution (Table 2), a constant reactivity increase is observed, which is a maximum for the more electronegative and/or less polarizable anions (seven and two times for Br^- and I^-, respectively). Under these conditions the reactivity scale is the same as that found [7] in dipolar aprotic solvents ($Cl^- > Br^- > I^- > SCN^-$).

Unlike the rate constants, the stability of cryptates noticeably changes on passing from (1) to (2). It dramatically diminishes in the case of Br^- and Cl^- and, for the same anions, on changing from two-phase to homogeneous conditions in which specific hydration of the anion is lacking. On the other hand, it remains constant for I^- and SCN^-.

A likely explanation of the kinetic data is that the ion separation determined by (1) is already optimal, so that a further increase of this distance in (2) due to the insertion of the three cyclohexane rings does not result in substantial variations of anionic reactivity. Indeed, from the *X*-ray analysis of $[Na^+ (2.2.2)]I^-$ cryptate,[9] it appears that, at least in the solid state, I^- is outside the spheroidal ligand of *ca.* 10 Å diameter. As already pointed out by Lehn,[1b,10] this diameter is about three times that of Cs^+, the largest inorganic cation. Cryptand (2) is a mixture of diastereoisomers, and thus the reported rate constants are a combination of the rate constants for all the diastereoisomers.

The results reported here seem to confirm the previous conclusions [2] that anion activation obtained with [2.2.2]-cryptates soluble in organic non-polar media is probably the highest actually obtainable in solution. Even if a more efficient wrapping of the cation, for example by tricyclic ligands,[12] might possibly allow a further increase of anionic reactivity, it seems unlikely that it will be significant.†

EXPERIMENTAL

^1H N.m.r. spectra were obtained on a Varian EM-390 90-MHz spectrometer with tetramethylsilane as internal standard. Potentiometric titrations were run with a Metrohm type E 576 potentiograph using silver and calomel electrodes, the latter isolated with a potassium sulphate bridge.

Materials and Solvents.—The synthesis of perhydrotribenzo[2.2.2]cryptand (2) as a mixture of diastereoisomers, has been previously reported.[4] n-Octyl methanesulphonate, b.p. 112—114 °C at 2 mmHg, n_D^{20} 1.4398, was obtained according to the literature (lit.,[13] b.p. 110—114 °C at 2 mmHg, n_D^{20} 1.4392). Inorganic salts were AnalaR grade commercial products, used without further purification, except for experiments under anhydrous conditions in which they were carefully dried and stored in a desiccator. Chlorobenzene was AnalaR grade chemical solvent, used without further purification in the kinetic measurements carried out under phase-transfer catalysis conditions. In the reactions carried on under anhydrous homogeneous conditions, it was carefully purified and dried by standard methods,[14] and stored over molecular sieves. Karl Fischer analysis showed a water content $\leqslant 50$ p.p.m.

Extent of Complexation and Distribution Coefficients.—The extent of complexation of [2.2.2,PHTB]cryptand (2) under phase-transfer catalysis conditions was measured by stirring a standardized chlorobenzene solution (20 ml) of (2) (1—5×10^{-2}M) with an aqueous solution (15 ml) of potassium salt (4.2M) in a flask thermostatted at 60 ± 0.1 °C. The system was stirred for 60 min, then kept without stirring for an additional 60—90 min to allow good separation of the two layers. Portions of the organic phase were withdrawn

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* See for example the case of the two diastereoisomers of perhydrodibenzo-18-crown-6.[11]

† The relatively modest increase of reactivity, a maximum of five-fold, observed on passing from sterically hindered quaternary salts to lipophilic [2.2.2,C_{14}]cryptand,[2] seems to agree with this conclusion.

and potentiometrically titrated with 0.01N-silver nitrate. Blank experiments showed that in all cases stirring times of *ca.* 60 min were sufficient to obtain a constant value of ligand complexation. Equilibrium (2) was studied under the same conditions described above, adding to the system potassium methanesulphonate (12 mmol) corresponding to the amount formed in reaction (1) at 100% conversion.

The percent of complexation under anhydrous conditions was determined by stirring a standardized chlorobenzene solution (20 ml) of [2.2.2,PHTB]cryptand (2) (1—5 × 10^{-2}M), thermostatted at 60 ± 0.1 °C, with anhydrous potassium salt (20 mmol) as solid phase. Portions of the solution were withdrawn at various times by stopping the stirring for 60—90 min to allow adequate separation and titrated with 0.01N-silver nitrate (potentiometric titration). This procedure was repeated until a constant value was obtained (2—6 h). Potentiometric titrations must be run in the absence of free ligand (2), since the latter is also titrated by silver nitrate. Therefore the determinations were performed in acid medium (HNO_3) in which cryptand (2) is protonated.

Hydration State of Cryptates.—The hydration state of the cryptates was determined by stirring for 1 h a standardized chlorobenzene solution (20 ml) of [2.2.2,PHTB] (2) (2—5 × 10^{-2}M) with an aqueous solution (15 ml) of the appropriate potassium salt (4.2M) in a flask thermostatted at 60 °C. Stirring was stopped and portions of the organic layer were withdrawn at intervals until a constant water content was measured (Karl Fischer analysis; 2—4 h). The concentration of complexed KY in the organic phase was determined in parallel by potentiometric titration. The hydration state of [2.2.2,PHTB]cryptand (2) was determined as described above, using an aqueous solution of tetramethylammonium chloride instead of potassium salt. Potentiometric titration of the organic phase did not detect Cl^-.

Liquid Membranes.—In a U shaped system, thermostatted at 60 ± 0.1 °C, standardized chlorobenzene solutions (A) (30 ml) of $[K^+ (2.2.2,PHTB)]Y^-$ (1—3 × 10^{-2}M) and chlorobenzene (B) (30 ml) were connected through an aqueous solution (90 ml) of the corresponding inorganic salt KY (4.2M). The system was stirred and portions of organic layers (A) and (B) were independently withdrawn at intervals by stopping the stirrer for 20 min to allow adequate separation, and titrated with 0.01N-silver nitrate. These analyses showed that no transfer of $[K^+ (2.2.2,PHTB)]Y^-$ from (A) to (B) could be detected even after several days.

Kinetic Measurements.—The apparatus used for kinetic measurements under phase-transfer catalysis conditions has been previously described.[6] In a typical run, the reaction flask, thermostatted at 60 ± 0.1 °C, was charged with an aqueous solution (15 ml) of potassium salt (4.2M) and a standardized chlorobenzene solution of cryptand (2) (2—10 × 10^{-2}M). The heterogeneous mixture was stirred for 1 h, then two portions (5 ml) of the organic layer were withdrawn, and the extent of complexation was determined by potentiometric titration. A chlorobenzene solution of n-octyl methanesulphonate (1.2M) and benzyl phenyl ether (0.8M) as internal standard, already at 60 ± 0.1 °C, was added to the flask, and stirring and timing were started. Portions of the organic phase were withdrawn at intervals by stopping the stirring for 60 s to allow adequate separation of the two phases. These were quenched by cooling and analysed by ^1H n.m.r.

Reaction rates were evaluated by following the disappearance of the triplet (CH_2-OSO_2Me) centred at δ 4.05 and using the singlet at δ 4.80 (OCH_2Ph) as standard. The pseudo-first-order rate constants (k_{obs}) were obtained by plotting log[substrate] against time and determining the slope of the straight line using a least-squares computer program. The second-order rate constants (k) were calculated by dividing k_{obs} by the cryptate concentration. In the kinetic measurements under anhydrous homogeneous conditions a standardized chlorobenzene solution (10 ml) of n-octyl methanesulphonate (5—20 × 10^{-2}M) was added at zero time to a standardized chlorobenzene solution (40 ml) of $[K^+ (2.2.2,PHTB)]Y^-$ (0.25—5 × 10^{-2}M) in a 100-ml flask thermostatted at 60 ± 0.1 °C. The solution of $[K^+ (2.2.2,PHTB)]Y^-$ was prepared as described above. Samples (3—6 ml), withdrawn at various times, were quenched in ice-cold MeOH (50 ml) in the presence of 6M-HNO_3 (3 ml) and unchanged nucleophile was measured with 0.01N-silver nitrate (potentiometric titration). The second-order rate constants were determined using a least-squares computer program, as already reported.[2,6]

[0/1538 *Received, 8th October, 1980*]

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