Lipophilic Bis(monoazacrown ether)s as Phase-transfer Catalysts under Solid–Liquid Two-phase Conditions

Pier Lucio Anelli and Silvio Quici *
Centro CNR 'Sintesi e Stereochimica di Speciali Sistemi Organici,' Via Golgi 19, I-20133 Milano, Italy

Bis(monoazacrown ether)s (1) and (2), made lipophilic by the presence of an alkyl chain, are efficient complexing agents for alkali halides in a solid–liquid two-phase system. Under these conditions they have been studied as phase-transfer catalysts in the OMs-Y (Y = I, Br, or Cl) exchange of n-octyl methanesulphonate. Catalytic activities of (1) and (2) are much greater than those obtained with macrocyclic ligands (5)—(7) when Br⁻ or Cl⁻ is the nucleophile, suggesting that sandwich complexes are most likely formed by (1) and (2).

Crown ethers have been widely used as phase-transfer catalysts in anion-promoted reactions under liquid–liquid and solid–liquid conditions.[1,2] Catalytic activity is dependent on the extent of complexation of the crown ethers which relates to factors such as the intrinsic liopophilicity of the crown ether, the polarity of the solvent, the size of the metal cation, and the anion hydrophilicity. In non-polar solvents complexation of alkali cations by crown ethers is generally very low or zero when hydrophilic anionic counterparts (*e.g.* Br⁻, Cl⁻, F⁻, OH⁻) are involved.[3] The complexing ability of crown ethers has been improved by the introduction of secondary donor sites covalently bonded to the macrocyclic ring through a flexible arm.[4] Complexation can also be increased with ligands capable of forming sandwich complexes, which, in principle, are favoured when two macrocyclic units are connected through a suitable bridging chain.†

A number of lipophilic bis-macrocycles have been synthesized and studied for selective extraction of alkali cations or as ion carriers through membranes.[6–11] In the present paper we describe the synthesis of ligands (1) and (2), and the extent of their complexation with alkali cations. A detailed investigation of the catalytic activities of (1) and (2) under solid–liquid two-phase conditions in comparison with those of lipophilic mono-azacrown ethers (5) and (6) and dicyclohexano-18-crown-6 (7), is also reported. Some of our preliminary results have been reported.[12]

Experimental

[1]H N.m.r. spectra were recorded at 90 MHz on a Varian EM-390 spectrometer with Me₄Si as internal standard. M.p.s were measured on a Büchi 510 apparatus and are uncorrected. G.l.c. analyses were performed on a Hewlett-Packard model 5840 flame ionization instrument (6 ft × 0.125 in SE 30 10% on Chromosorb W 80—100 mesh column). Potentiometric titrations were performed with a Metrohm Titroprocessor E 636 and Metrohm Dosimat E 635. Organic and inorganic reagents, ACS grade, were used without further purification. 2-Hexadecyl-1,3-bis(tosyloxy)propane,[13] monoaza-15-crown-5,[14] monoaza-18-crown-6,[14] and n-octyl methanesulphonate[15] were prepared according to already reported procedures.

2-*Hexadecyl*-1,3-*bis*-(1,4,7,10-*tetraoxa*-13-*azacyclopenta-*

decan-13-*yl)propane* (1). A mixture of (3) (4.83 g, 22 mmol), 2-hexadecyl-1,3-bis(tosyloxy)propane (6.68 g, 11 mmol), and anhydrous sodium carbonate (11.66 g, 110 mmol) in acetonitrile (100 ml) was stirred and refluxed over 4 days. After cooling to room temperature the reaction mixture was filtered, the precipitate washed with dichloromethane, and the solvent evaporated. The residue was dissolved in dichloromethane (100 ml) and washed with water (2 × 50 ml). Evaporation of the solvent and column chromatography (neutral alumina, ethyl acetate followed by ethyl acetate–triethylamine 99:1) afforded (1) (5.56 g, 72%) as a colourless oil (Found: C, 66.4; H, 11.0; N, 4.1. Calc. for $C_{39}H_{78}N_2O_8$: C, 66.6; H, 11.2; N, 4.0%); $\delta_H(CDCl_3)$ 0.90 (t, 3 H, Me), 1.00—1.70 [m, 31 H, $(CH_2)_{15}CH$], 2.35 (m, 4 H, CHCH_2N), 2.70 (t, 8 H, CH₂CH_2N), and 3.50—3.90 (m, 32 H, CH₂O).

2-*Hexadecyl*-1,3-*bis*-(1,4,7,10,13-*pentaoxa*-16-*azacyclo-octa-decan*-16-*yl)propane* (2) was prepared in 59% yield from (4) and 2-hexadecyl-1,3-bis(tosyloxy)propane as described for (1): colourless oil (Found: C, 65.0; H, 10.85; N, 3.75. Calc. for $C_{43}H_{86}N_2O_{10}$: C, 65.3; H, 11.0; N, 3.5%); $\delta_H(CDCl_3)$ 0.90 (t, 3 H, Me), 1.00—1.70 [m, 31 H, $(CH_2)_{15}CH$], 2.35 (m, 4 H, CHCH_2N), 2.75 (t, 8 H, CH₂CH_2N), and 3.40—3.80 (m, 40 H, CH₂O).

13-*Hexadecyl*-1,4,7,10-*tetraoxa*-13-*azacyclopentadecane* (5) was prepared in 70% yield from (3) and hexadecyl bromide (1-bromohexadecane) as described for (1): colourless oil (Found: C, 70.2; H, 12.0; N, 3.3. Calc. for $C_{26}H_{53}NO_4$: C, 70.4; H, 12.1; N, 3.2%); $\delta_H(CDCl_3)$ 0.90 (t, 3 H, Me), 1.00—1.70 [m, 28 H, $(CH_2)_{14}$], 2.50 [t, 2 H, $(CH_2)_nCH_2N$], 2.75 (t, 4 H, OCH₂CH_2N), and 3.55—3.80 (m, 16 H, CH₂O).

16-*Hexadecyl*-1,4,7,10,13-*pentaoxa*-16-*azacyclo-octadecane* (6) was prepared in 55% yield from (4) and hexadecyl bromide as described for (1): colourless oil (Found: C, 68.9; H, 11.6; N, 3.0. Calc. for $C_{28}H_{57}NO_5$: C, 68.9; H, 11.8; N, 2.9%); $\delta_H(CDCl_3)$ 0.90 (t, 3 H, Me), 1.00—1.70 [m, 28 H, $(CH_2)_{14}$], 2.50 [t, 2 H, $(CH_2)_nCH_2N$], 2.75 (t, 4 H, OCH₂CH_2N), and 3.50—3.80 (m, 20 H, CH₂O).

Extent of Complexation of Ligands (1), (2), (5)—(7) *under Liquid–Liquid Conditions.*—A mixture of 12 ml of a 0.02M solution of the ligand in toluene and 9 ml of a 4M aqueous solution of the appropriate salt was stirred for 2 h in a flask thermostated at 50 °C. After standing for an additional 2 h in order to allow good separation, a 4 ml sample of the organic phase was diluted with methanol (40 ml), acidified with concentrated nitric acid (10 drops), and titrated with 0.01M aqueous silver nitrate (potentiometric titration). Results are

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† Sandwich-type complexation may occur, provided that the cation is too large to fit into the cavity of the macrocycle and that co-operative action of the two macrocyclic units is constrained by structural features as in the case of the highly loaded polymer-supported crown ethers.[5]

Table 1. Extent of complexation of ligands (1) and (2) with alkali and ammonium iodides

| | % Complexation | | | |
| | Liquid–liquid | | Solid–liquid | |
Cation	(1)	(2)	(1)	(2)
Li	8	5	7	15
Na	12	6	193	49
K	14	19	24	97
Cs	6	4	9	13
NH₄	65	31	49	102

Table 2. Extent of complexation of (1) and (2) with sodium and potassium halides: comparison with (5), (6), and (7) in solid–liquid conditions

| | % Complexation | | | | |
Salt	(1)	(2)	(5)	(6)	(7)
NaI	193	49	95	90	100
KI	24	97	8	52	73
NaBr	11	6	6	7	4
KBr	13	8	4	5	2
NaCl	9	5	—ᵃ	—ᵃ	—ᵃ
KCl	8	6	—ᵃ	—ᵃ	—ᵃ

ᵃ Not detectable.

given in Table 1 and are the average of at least four measurements. Experimental error was within ±5%.

Extent of Complexation of Ligands (1), (2), (5)—(7) *under Solid–Liquid Conditions.*—A sample of 12 ml of a 0.02M solution of the ligand in toluene was stirred in the presence of 7.2 mmol of the appropriate solid salt for 2 h. After standing for an additional 1 h, a 4 ml sample was diluted and titrated as reported above. Results are shown in Tables 1 and 2, and are the average of at least four measurements. Experimental error was within ±5%.

*Kinetic Measurements.*—A 10 ml flask equipped with a Teflon-lined screw cap and magnetic bar, thermostatted by an Exacal 200 Bath Circulator at 50 ± 0.01 °C with circulating oil, was charged with: 10 mmol of the appropriate alkaline salt, 2.0 ml of a 0.05M toluene solution of the ligand, and 1.0 ml of a 0.5M toluene solution of tetradecane as internal standard. At zero time, 2 ml of a 1M toluene solution of octyl methanesulphonate were added and the reaction mixture stirred at 1 300 ± 50 r.p.m. The reactions were followed by g.l.c. analysis. The pseudo-first-order rate constants ($k_{obs.}$) were obtained by plotting ln [substrate] vs. time and determining the slope of the straight lines.

Results and Discussion
Condensation of 2-hexadecyl-1,3-bis(tosyloxy)propane with monoazacrown ethers (3) and (4) afforded catalysts (1) and (2) in good yields.

Lipophilicity of receptors (1) and (2) is ensured by the presence of the long alkyl chain and in aqueous organic two-phase conditions they are entirely in the organic phase.

Complexing ability of receptors (1) and (2) was investigated with alkali iodides MI (M = Li, Na, K, or Cs) and NH₄I both under liquid–liquid (toluene–aqueous solution of MI) and solid–liquid (toluene–MI) two phase conditions. The extent of

(3) n = 2
(4) n = 3

(1) n = 2
(2) n = 3

(5) n = 2
(6) n = 3

(7)
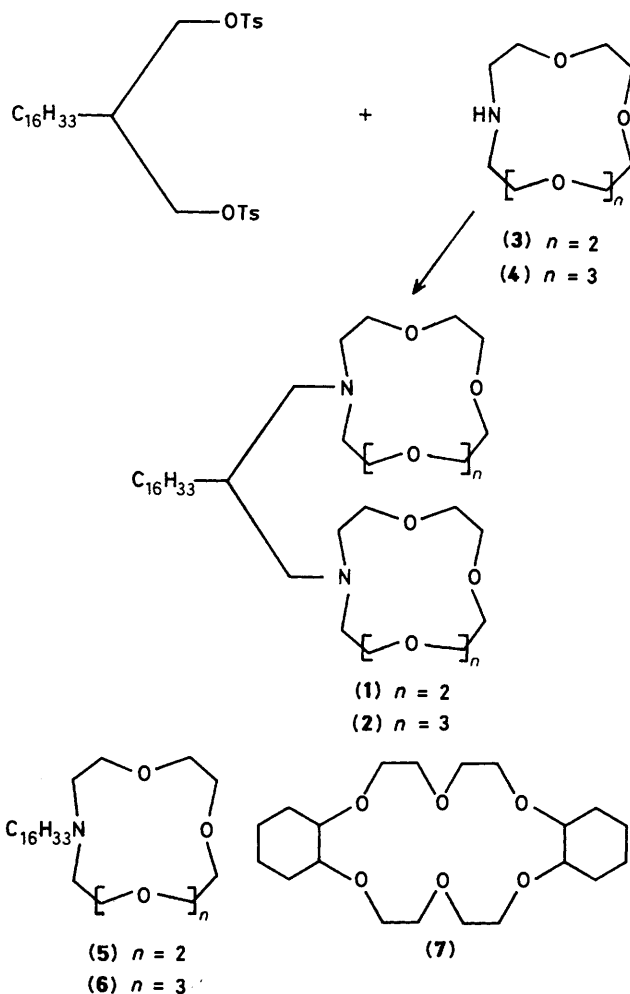
complexation (Table 1) was measured by potentiometric titration of the halide ion in the organic phase with silver nitrate.

Unexpectedly the amount of alkali iodide extracted from the aqueous into the organic phase, under liquid–liquid conditions, is modest (<20%) with both receptors. The higher values found for NH₄I [65 and 31% with (1) and (2), respectively] under aqueous–organic conditions are due to stronger hydrogen-bonding interactions between the NH₄⁺ cation and the ligands.*

The extent of complexation strongly increases for both ligands under solid–liquid conditions (Table 1); sodium iodide is complexed 193% by ligand (1) thus indicating the formation of a binuclear complex. Complexation values of KI and NH₄I with ligand (2) are 97% and 102%, respectively, suggesting that the cations may be sandwiched between the two azacrown ether units.

Results in Table 1 indicating the extent of complexation <100% do not allow speculation on the nature of the complexes formed. Lithium and caesium iodides are very poorly complexed, even under solid–liquid conditions, probably because the sizes of Li⁺ and Cs⁺ are too small and too large, respectively.

The extent of complexation of ligands (1) and (2) with Na⁺ and K⁺ under solid–liquid conditions was also measured when Br⁻ and Cl⁻ were the anions; values are reported in Table 2 together with those obtained with lipophilic monoazacrown

* Bis-macrocycles proved to be very effective ligands for alkyl-ammonium salts and an extensive n.m.r. investigation of the complexes has been reported by Sutherland.[14]
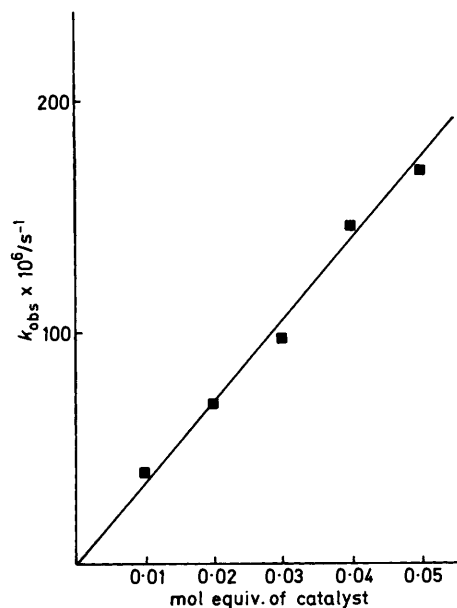
Figure. Dependence of the observed pseudo-first-order rate constants ($k_{obs.}$) on molar equivalents of ligand (2) for OMs–I exchange reaction of n-octyl methanesulphonate in solid–liquid (KI–toluene) two-phase conditions at 50 °C

Table 3. Catalytic activity of ligands (1), (2), (5)—(7) under solid–liquid two-phase conditions[a]

| Catalyst[b] | $k_{obs.} \times 10^6$ (s⁻¹) | | | | | |
	NaI	KI	NaBr	KBr	NaCl	KCl
(1)	240	82	30.3	19.8	3.4	2.8
(2)	192	170	27.7	20.7	3.1	2.8
(5)	292	20	3.3	—[c]	—[c]	—[c]
(6)	252	154	4.1	2.6	—[c]	—[c]
(7)	256	160	5.0	5.3	—[c]	—[c]

[a] For OMs–halide exchange of n-octyl methanesulphonate in toluene at 50 °C. [b] 0.05-Molar equivalents. [c] Too low to measure.

ethers (5) and (6) and the dicylohexano-18-crown-6 (7). Due to the hard character of Br⁻ and Cl⁻ the extents of complexation are smaller than those found for I⁻; furthermore they are largely independent of the cation. Interestingly ligands (1) and (2) are capable of extracting, to some extent, even Cl⁻ ions in the organic phase whereas none of this anion was detected with monocyclic analogue (5), (6), and (7). This last feature accentuates the increased complexing capability of lipophilic bis-(monoazacrown ether)s; this is in agreement with the stability constants determined by Kimura *et al.*[16] for similar systems in methanol–water.

The catalytic activity of ligands (1)—(5) was evaluated by nucleophilic substitution of n-octyl methanesulphonate by I⁻, Br⁻, and Cl⁻ under solid–liquid phase-transfer conditions.

* These results once again stress the crucial role played by the nature of the anion when different catalytic systems are compared.[17]

As pointed out by a Referee, the extent of extraction of NaI by ligand (1) under solid–liquid conditions is not in accord with the catalytic results. A possible explanation could be that one iodine atom is tightly sandwiched between two sodium cations in the complex, thus reducing the phase-transfer catalytic activity.

$$n\text{-}C_8H_{17}OMs + MY \xrightarrow[\text{toluene, 50 °C}]{\text{catalyst}} n\text{-}C_8H_{17}Y + MsOM$$
$$Y = I, Br, Cl$$
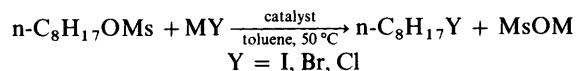
The reactions follow pseudo-first-order kinetics and the observed rate constants ($k_{obs.}/s^{-1}$) are linearly related to molar equivalents of ligand (see Figure). Values of $k_{obs.}$ are

$$\text{rate} = k_{obs.} \text{[substrate]}$$

reported in Table 3. The catalytic activity of bismacrocycles (1) and (2) is similar to that found with monocyclic ligands (5)—(7) when I⁻ is the nucleophile, whereas (1) and (2) proved to be five- to ten-fold more active than (5)—(7) when Br⁻ is involved. In MsO–Cl exchange, the catalytic activity of (1) and (2) is almost one order of magnitude lower than that found in MsO–Br exchange. In spite of this it is noteworthy that in MsO–Cl exchange the monocyclic ligands do not show any detectable reactivity.*

The very high activity found for (1) and (2) with Br⁻ and Cl⁻ can most likely be explained in terms of the formation of sandwich-type complexes with both sodium and potassium cations. As a consequence of their facile synthesis, macrocycles (1) and (2) represent an alternative to the highly efficient but more sophisticated cryptands in the activation of hydrophilic anions (*e.g.* CN⁻, OH⁻, and RO⁻).

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