Synthetic Ionophores. Part 4. Phase Transfer-catalysed Synthesis of Pyridine-containing Macrocycles and Their Ionophore Character

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Phase transfer-catalysed reactions of pyridine-2,6-dicarboxylic acid dichloride and 2,6-dichloropyridine with oligo(ethylene glycols) provide macrocycles in yields higher than those reported by high dilution or transesterification methods. Extraction and transport studies of some of these macrocycles towards picrates of Li^+, Na^+, K^+, Tl^+, Mg^{2+}, Ca^{2+}, and Ba^{2+} by using chloroform as the nonpolar layer showed that two examples, the pyridino crown ethers (3a) and (5b), transport barium and thallium picrates respectively with significant selectivity.

Heterocyclic units on the periphery of macrocycles[1] impart unique chemical and biochemical properties. Pyridine is important as an additional heterocyclic unit in designing macrocyclic ionophores,[2] the dihydro derivatives of which are also effective NADH models.[3] Phase transfer-catalytic conditions[4] (PTC), which have been used advantageously for the synthesis of macrocycles containing ether, sulphide, or ether–ester units, have not been used for the synthesis of pyridine-containing macrocycles. Here, we report that pyridine-2,6-dicarboxylic acid dichloride and 2,6-dichloropyridine with diols under non-hydrolytic PTC conditions provide the respective macrocycles in moderate to high yields in a manner superior to their synthesis involving high-dilution conditions or transesterification. The metal-ion extraction and transport behaviour of some of these macrocycles using chloroform as a nonpolar layer has also been studied.

Results and Discussion

Synthesis.—Pyridine-2,6-dicarboxylic acid dichloride (1a) and tri(ethylene glycol) (3,6-dioxaoctane-1,8-diol) in dichloromethane in the presence of potassium fluoride and triethylbenzylammonium chloride (TEBA) provided (2a) (74%). It had earlier been obtained by high dilution[5] and transesterification[6] methods in 9.6 and 26% yields respectively. Similarly, (1) and tetra(ethylene glycol) (3,6,9-trioxaundecane-1,11-diol) gave (2b) in 90% yield (*cf.* reported synthesis[7] in 77% yield). In these reactions only 1:1 stoicheiometric condensations took place. Furthermore, (1a) with 4-oxaheptane-1,7-diol and 4,8-dioxaundecane-1,11-diol furnished both 1:1 and 2:2 stoicheiometric products, (3a),(4a) and (3b),(4b), respectively but the former constituted the major components.

2,6-Dichloropyridine (1b) and tri(ethylene glycol) in refluxing xylene containing potassium carbonate and TEBA furnished (5a) and (6a) in 52 and 19% yields (*cf.* reported[8,9] yields of 16 and 2%). Similarly, (1b) with 1,2-bis(2-hydroxyethoxy)benzene and tetra(ethylene glycol) gave (7),(8) *and* (5b),(6b) in moderate to very good yields (Table 1).
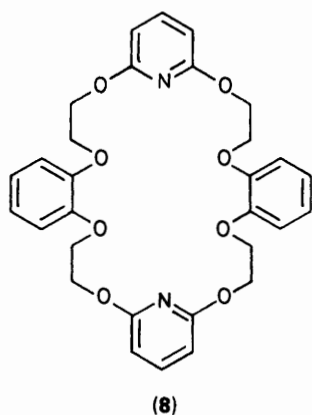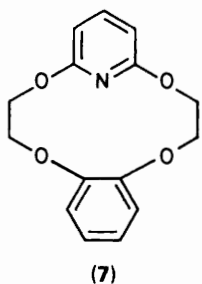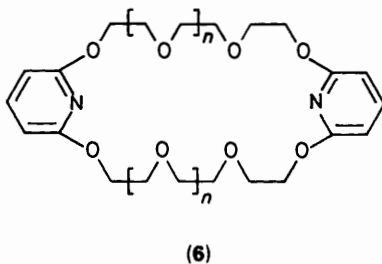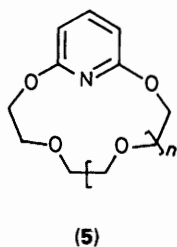
Thus, phase transfer-catalysed condensations of diols with the pyridine derivatives (1a) and (1b) proceed readily to give 1:1 stoicheiometric products as the major or sole constituents, and 2:2 products as minor components. In the reactions of (1a) with tri- and tetra-(ethylene glycols) only 1:1 condensation products are isolated.

Extraction and Transport Studies.—The restoration of the ionophoric character of dioxo-18-crown-6 to that of 18-crown-6 itself on incorporation of a pyridine moiety[10] in place of a

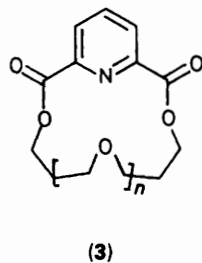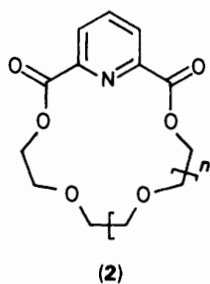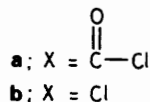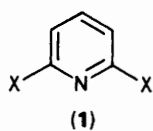–CH_2–O–CH_2– unit and use of the pyridine-containing proton-ionizable crown ethers[2a] to increase the flux and selectivity towards alkali metal ions has emphasized the importance of ionophore studies on pyridine-containing macrocycles. Also, as the process of facilitated transport of cations through a nonpolar membrane involves extraction (complexation) and release (decomplexation) of the cation,[12] extraction/association constants having direct relevance to the complexation are necessary[13] to characterize the transport properties of an ionophore. In the present study, we have determined the extraction constants and transport rates of Li^+, Na^+, K^+, Tl^+, Mg^{2+}, Ca^{2+}, and Ba^{2+} picrates with the ionophores (2b), (3a), (3b), (5a), (5b), (7), and (6a), using chloroform as the nonpolar membrane. Plots of log (extraction constant) *vs.* log (transport rate) for the monovalent cations are straight lines, indicating that the transport of cations with pyridine-containing macrocyles is primarily dependent on the ability of crown ethers to complex/extract metal picrates.

The extraction constants of ligand (3a) for the monovalent metal picrates are in the order $Tl^+ > K^+ > Na^+ > Li^+$ which is also the trend for their transport. Therefore, the 14-crown-4 derivative (3a), which has an optimum cavity size for encapsulating Li^+, transports the much larger cations K^+ and Tl^+ selectively. However, Bartsch[14] and Bradshaw[2a] have shown that 14-crown-4 ethers containing methylene groups or pendant arms and pyridino-14-crown-4- derivatives are selective complexing agents for lithium cations. Here, the increased transportation of K^+ and Tl^+ relative to Li^+ may be attributed to the formation of 2:1 sandwich type complexes by K^+ and Tl^+. Further, the presence of the soft pyridine nitrogen atom increases eightfold the extraction of the soft Tl^+ compared with K^+. The selectivity for transport of Tl^+ relative to K^+ is 15 for (3a). Alkaline earth metal ions are more efficiently transported than alkali metal ions by (3a). Barium picrate is transported 30 times faster than the similarly sized monovalent potassium picrate and 20–40 times faster than calcium and magnesium picrates. Therefore, (3a), does not follow a cavity–ion size relationship[13] for transport of barium in comparison with other metal ions.

The macrocycle (3b), containing five heteroatoms in an 18-membered ring, shows an extraction constant ratio for Na^+/K^+ of 3. However, the selectivity in transport of Na^+/K^+ is decreased to 1. Another 18-membered macrocycle, (2b), possessing six heteroatoms shows increased extraction constants and transport rates. Also, the selectivity in extraction constants for K^+/Na^+ is increased to 60, but a similar selectivity is not observed during transport across a chloroform membrane. Therefore the better complexation of (3b) with potassium

transported nearly 17 and 13 times more readily than Ca^{2+} and the similarly sized Li^+ picrates respectively. The macrocycle (**5b**), possessing six heteroatoms (5 O, 1 N) in a 16-membered ring, shows an increase in transport rates and extraction constants for Tl^+ only compared with (**5a**), and a transport selectivity for Tl^+/K^+ of 6.2, but shows poor selectivity for Na^+ in comparison with both K^+ and Li^+. Its extraction constant ratio for Tl^+/K^+ is 10.

Corey–Pauling–Koltun (CPK) models of compounds (**5**)–(**8**) show that for the three heteroatoms of the O–C–N–C–O unit either the two oxygen atoms or only the pyridine nitrogen lone pair can remain pointing inwards. As the pyridine nitrogen atom is fixed in position in the ring, the pyridine-bound oxygen atoms participate least in complexation, explaining the weak complexation of (**5**) and (**7**). Ligand (**6a**), which possesses two nitrogen and eight oxygen atoms, could be better considered as a 26-crown-6 analogue and should exhibit increased complexation with large cations. As expected, (**6a**) efficiently transports K^+, Ba^{2+}, and Tl^+, but with marginal selectivity over each other, and transports potassium picrate 33 times faster than sodium picrate.

Thus, in general, these macrocycles show greater selectivity in extraction constants than in transport constants, except for the macrocycle (**3a**). So, here, transportation primarily depends on extraction constants but other factors, *e.g.* rate of decomplexation *etc.*, also affect the overall transport rates. The macrocycles (**3a**) and (**5b**) transport barium and thallium picrates respectively with significant selectivity over other cations.

Experimental

IR and ^{1}H NMR spectra were recorded on Spectromom 2000 and JEOL–JNM 60 MHz instruments respectively. Mass spectra (70 eV) were recorded at CDRI, Lucknow. M.p.s are uncorrected. Silica gel-coated plates and columns were used for monitoring the reactions and purification of products respectively. UV measurements were made on a Shimadzu Graphicord 240 instrument. The metal picrates were prepared by the reported methods.[15,16]

Synthesis of the Macrocycles (**2**)–(**4**).—A suspension of potassium fluoride (0.07 mol) in dichloromethane containing the oligo(ethylene glycol) (0.01 mol) and triethylbenzyl-ammonium chloride (TEBA) catalyst was stirred at ambient temperature. A solution of pyridine-2,6-dicarboxylic acid dichloride (0.01 mol) was added dropwise during 30 min, and the mixture was stirred for an additional 3 h. After completion of the reaction (TLC), the solid was filtered off and washed with dichloromethane, and the combined filtrate and washings were evaporated. The product mixture was purified by silica gel column chromatography (Table 1).

Synthesis of the Macrocycles (**5**)–(**8**).—A suspension of potassium carbonate (0.02 mol) in xylene containing the oligo(ethylene glycol) (0.01 mol) and TEBA (catalyst) was heated under reflux. A solution of 2,6-dichloropyridine in xylene was added dropwise during 30 min, and the mixture heated under reflux for an additional 3–4 h. After completion of the reaction (TLC), the solid was filtered off. The filtrate was evaporated; chromatography of the residue on a silica gel column gave the pure macrocycles (Table 1).

Extraction Constants.—An aqueous solution (2 ml) of the metal picrate (0.02M; thallium picrate 0.01M) and a chloroform solution (2 ml) of the macrocycle (0.01M) in a cylindrical tube were stirred for 5 min and kept at $25 \pm 0.1\,^{\circ}C$ for 2–3 h. A sample of the chloroform layer (1 ml) was diluted with acetonitrile to 10 ml. The UV absorption of this solution was

picrate and its decreased tendency for decomplexation results in a slower transport rate. Similarly, in the case of Ca^{2+} and Mg^{2+}, the extraction constants show a Ca^{2+}/Mg^{2+} selectivity of 40 but the transport selectivity is 6.5.

In a macrocycle, the replacement of a two-carbon unit with a one-carbon unit increases the number of heteroatoms per carbon atom and should increase its ligating ability towards metal ions. However, (**5a**), with five heteroatoms (4 O and 1 N) in a 13-membered ring, shows poor complexation and transportation of metal picrates with marginal selectivity. For its benzo derivative (**7**), the decreased electron density on the aryl ether oxygen atoms[10] further decreases its extraction and transport character for all cations except for Mg^{2+}, which is

Table 1. Spectral and other data of macrocycles (2)–(8).[a]

Compd.	M.p., $t/°C$	% Yield	m/z (M^+)	^1H NMR, δ(CDCl$_3$)
(3a)	168	72	265	2.0 (quint., J 9, 4 H, CH$_2$), 3.50 (t, J 9, 4 H, OCH$_2$), 4.30 (t, J 9, 4 H, CO$_2$CH$_2$), 7.53–8.13 (m, 3 H, PyH)
(4a)	182	12	530	2.10 (quint., J 9, 8 H, CH$_2$), 3.50 (t, J 9, 8 H, OCH$_2$), 4.30 (t, J 9, 8 H, CO$_2$CH$_2$), 7.53–8.13 (m, 6 H, PyH)
(3b)	97	35	323	1.67–2.10 (m, 6 H, CH$_2$), 3.10–3.67 (m, 8 H, OCH$_2$), 4.30 (t, J 6, 4 H, CO$_2$CH$_2$), 7.63–8.10 (m, 3 H, PyH)
(4b)	110	10	646	1.63–2.30 (m, 12 H, CH$_2$), 3.27–3.90 (m, 16 H, OCH$_2$), 4.40 (t, J 6, 8 H, OCH$_2$), 7.67–8.33 (m, 6 H, PyH)
(7)	145	15	273	4.20 (t, J 6, 4 H, ArOCH$_2$), 4.90 (t, J 6, 4 H, PyOCH$_2$), 6.10 (d, J 8, 2 H, PyH), 6.90 (s, 4 H, ArH), 7.50 (t, J 8, 1 H, PyH)
(8)	158	9	546	4.10–4.60 (m, 16 H, OCH$_2$), 6.70–7.50 (m, 14 H, 8 × ArH, 6 × PyH

[a] The ^1H NMR data for known compounds are comparable with literature data; other data (literature data in parentheses): (2a),[6] m.p. 78–80 (85) °C, yield 90% (77); (2b),[7] m.p. 136–138 (139) °C, yield 74% (25); (5a),[9] m.p. 79 (83–84) °C, yield 52% (16); (6a),[9] m.p. 122 (120) °C, yield 19% (2); (5b),[11] m.p. 74–76 (76–78) °C, yield 67% (4); (6b),[11] m.p. 82–83 (83–84) °C, yield 5% (3). [b] Py = pyridine.

**Table 2.** Transport rates ($\times 10^8$ mol/24 h) and extraction constants.

Macro-cycle	Li$^+$	Na$^+$	K$^+$	Mg^{2+}	Ca^{2+}	Ba^{2+}	Tl$^+$
Transport rate							
(3a)	21.8	50.9	139	75.6	200	39.3	2 142
(5a)	22.8	11.0	35	31.6	17.0	40.3	86.4
(7)	19.2	12.8	13.3	248	14.4	20.7	72
(3b)	4.9	104.6	106	45	14.4	33.6	181
(2b)	78.0	8 664	11 280	123	794	1 682	10 488
(5b)	14.4	64.8	38.4	31.2	10.8	23.5	238
(6a)	16.3	10.8	32.6	32.6	38	832	612
Extraction constant							
(3a)	3.32	7.89	90.55	395	4 890	—	700
(5a)	3.27	6.16	6.53	740	641.7	—	25.50
(7)	4.58	5.29	4.74	660	678	—	25.21
(3b)	1.23	25.26	8.79	98.8	1 057	—	39.81
(2b)	27.97	523.0	31 978	1 720	748	—	176 633
(5b)	2.55	31.14	9.77	307.6	228.9	—	101.15

Table 3. Selectivity ratios in transport and extraction experiments.

Macro-cycle	$\dfrac{Mg^{2+}}{Li^+}$	$\dfrac{Na^+}{Ca^{2+}}$	$\dfrac{Mg^{2+}}{Ca^{2+}}$	$\dfrac{Ba^{2+}}{K^+}$	$\dfrac{K^+}{Na^+}$	$\dfrac{Li^+}{Na^+}$	$\dfrac{Tl^+}{K^+}$
Transport rate							
(3a)	3.0	0.25	0.38	28.2	2.73	0.41	15.4
(5a)	1.4	0.64	1.86	1.15	3.18	2.07	2.47
(7)	12.9	0.89	17.1	15.4	1.04	1.5	5.41
(3b)	9.17	7.26	3.1	0.32	1.01	0.047	1.71
(2b)	1.7	10.9	0.15	0.15	1.30	0.009	0.93
(5b)	2.1	6.0	2.89	0.61	0.59	0.22	6.20
(6a)	2.0	0.28	0.86	2.33	33.1	1.5	1.71
Extraction constant							
(3a)			0.08	11.5	0.4		7.7
(5a)			1.15		1.05	0.5	3.9
(7)			0.97		0.9	0.86	5.3
(3b)			0.09		0.35	0.048	4.5
(2b)			0.023	61.1	0.053	5.5	
(5b)			1.34		0.31	0.082	10.3

measured against a blank solution at 374 nm (ε values: Li$^+$, 1.86 × 10^4; Na$^+$, 1.75 × 10^4; K$^+$, 1.74 × 10^4; Tl$^+$, 1.85 × 10^4; Mg^{2+}, 3.1 × 10^4; Ca^{2+}, 3.2 × 10^4 mol^{-1} cm^{-1}). The extraction constants (K_{ex}) are the mean of three independent measurements which are consistent within ±2%, and were

determined for the extraction equilibrium (1) (CE = crown ether).[15]

$$M^{m+}_{aq} + mA^-_{aq} + nCE_{org} \underset{}{\overset{K_{ex}}{\rightleftharpoons}} [M(CE)_nAm]_{org} \quad (1)$$
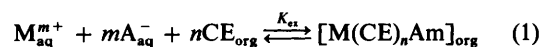
Transport Measurements.—Transport rates were determined by the method of Tsukube[17] using: (*i*) metal picrate (0.01M) in water (5 ml) in the inner phase; (*ii*) water (10 ml) in the outer phase; (*iii*) ligand (10^{-3}M) in the chloroform layer (15 ml), with stirring at 28 ± 1 °C. The concentrations of the picrates were determined from the UV absorption at 355 nm (ε values: Li$^+$, 1.55 × 10^4; Na$^+$, 1.52 × 10^4; K$^+$, 1.50 × 10^4; Tl$^+$, 1.59 × 10^4; Mg^{2+}, 2.2 × 10^4; Ca^{2+}, 2.33 × 10^4; and Ba^{2+}, 2.70 × 10^4 mol^{-1} cm^{-1}). Each value is a mean of three experiments which are consistent with ±15%.

Acknowledgements

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