

Synthetic Ionophores. Part 8.^{1,2} Amide–Ether–Amine-Containing Macrocycles: Synthesis, Transport and Binding of Metal Cations

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1,2-Bis(ethoxycarbonylmethoxy)benzene undergoes 1:1 stoichiometric condensation with 1,2-diaminoethane, 1,3-diaminopropane, diethylenetriamine and 3,3'-diaminodipropylamine to form the macrocycles **2a**, **2b**, **3a** and **4a** respectively. Methyl iodide, ethyl bromoacetate and chloro-*N,N*-diethylacetamide react with triamines **3a** and **4a** to give the respective *N*-substituted macrocycles **3b–d** and **4b–d**. Among these macrocycles, compounds **3a** and **4a** selectively extract lead picrate over silver, alkali metal and alkaline earth metal picrates and the former shows a higher order of specificity. IR and ¹³C NMR studies depict a preferential co-ordination of the amide oxygen of these macrocycles with metal ions.

The role of various inbuilt and appended functional groups in macrocycles on their selective recognition characteristics towards metal cations has led to the design of macrocycles suitable as specific ionophores.^{3–5} The 'hard' ether-oxygen-containing macrocycles show binding preference towards 'hard' alkali and alkaline earth cations, but the incorporation of 'soft' sulfide or amine linkages for ether linkages shifts their preference towards 'soft' heavy metal ions.^{6–9} The ionophores containing ether and amide moieties exhibit selectivities towards alkaline earth metal cations.^{10–15} For inducing selectivity of recognition amongst alkaline earth metal cations and 'soft' lead cation, we have designed and synthesized ether–amide–amine macrocycles **3a** and **4a** suitable for further modifications by requisitioning appropriate ester/amide appendages at amine nitrogen (**3b–d**, **4b–e**) in order to show co-operative binding effects.^{16–18} It has been found that the

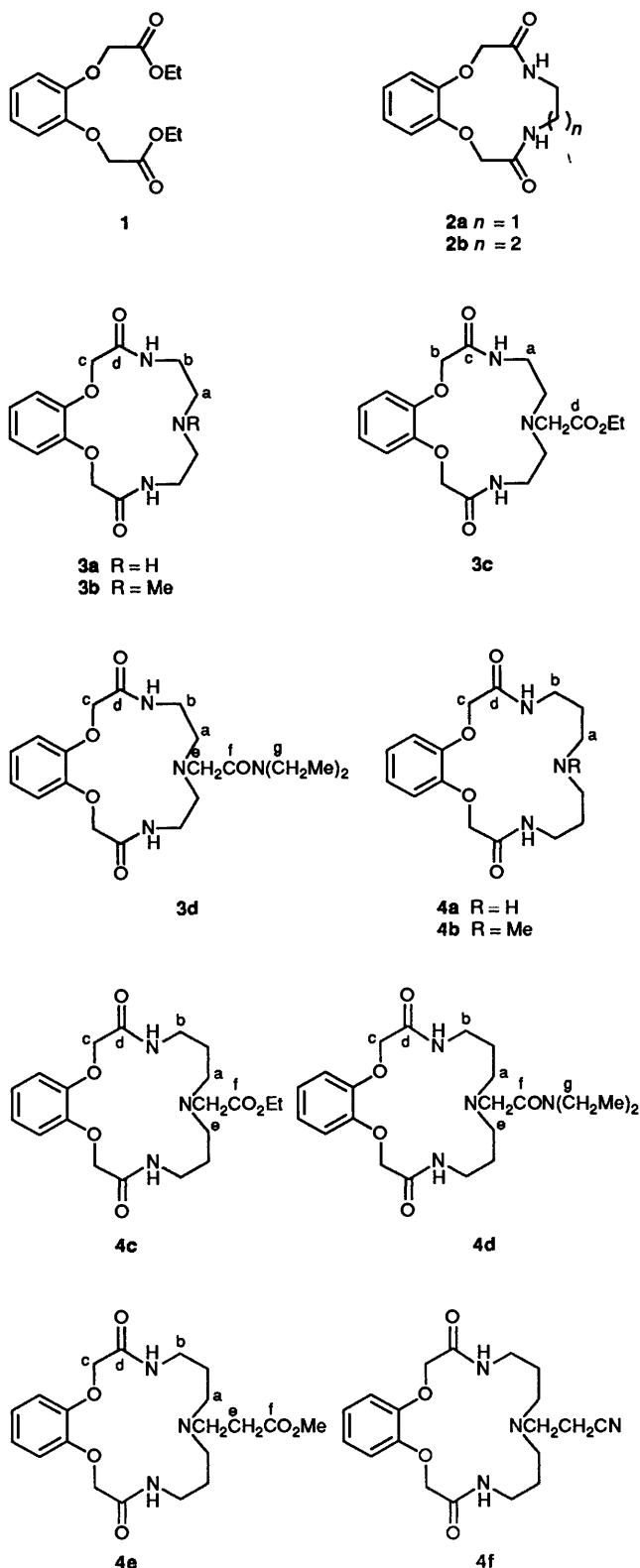
macrocycles **3a** and **4a** bind Pb²⁺ ions with remarkable selectivity. However, the effect of co-operative binding in macrocycles **3b–d**, **4b–e** on selectivity is not significant.

Synthesis of Macrocycles.—1,2-Bis(ethoxycarbonylmethoxy)benzene **1** was prepared by the solid–liquid phase-transfer-catalysed reaction of catechol with ethyl bromoacetate in improved yield 95%.¹⁹ Compound **1**, on being refluxed with 1,2-diaminoethane and 1,3-diaminopropane in ethanol for 4–5 days provided macrocycles **2a** (5%) and **2b** (10%), respectively. In these reactions, the corresponding 2:2 stoichiometric condensation products were not isolated. The macrocycles **2a** and **2b** possess 12- and 13-membered rings and their CPK molecular models show that they possess very small cavities which are not suitable for incapsulation of metal cations. Therefore to increase the cavity size and the number of heteroatoms in the

Table 1 Cation transport and extraction profiles of macrocycles **3a–d** and **4a–f**

Macrocycle	Li ⁺	Na ⁺	K ⁺	Tl ⁺	Mg ²⁺	Ca ²⁺	Ba ²⁺	Sr ²⁺	Pb ²⁺	Ag ⁺
Transport rates (10 ⁸ mol/24 h) ^a										
3a	21.9	23.9	26.6	61.0	34.4	37.7	43.0	<i>c</i>	<i>c</i>	43.0
3b	256.7	209.5	195.9	172.4	54.0	143.6	46.5	<i>c</i>	<i>c</i>	164.5
3c	206.0	20.7	19.1	62.8	36.1	78.7	66.3	<i>c</i>	<i>c</i>	108.0
3d	164.0	45.6	41.0	76.9	38.8	17.1	30.2	<i>c</i>	<i>c</i>	71.9
4a	550.0	665.0	510.0	600.0	493.0	530.0	400.0	<i>c</i>	<i>c</i>	615.0
4b	478.4	628.1	409.9	459.4	193.5	484.3	214.2	<i>c</i>	<i>c</i>	440.6
4c	37.2	92.9	53.4	130.8	66.2	42.6	63.1	<i>c</i>	<i>c</i>	95.2
4d	172.2	244.5	167.6	398.1	197.2	370.8	346.6	<i>c</i>	<i>c</i>	914.9
4e	14.4	48.9	56.8	98.7	43.7	39.3	32.5	<i>c</i>	<i>c</i>	72.2
4f	5.1	21.9	27.2	75.9	24.9	17.7	14.9	<i>c</i>	<i>c</i>	33.7
Extraction constants (<i>R</i> /10 ³) ^b										
3a	1.0	3.8	2.0	2.2	1.8	1.4		9.7	139.0	4.9
3b	60.5	74.3	75.9	62.5	45.0	46.2		11.7	47.7	67.6
3c	9.2	7.2	7.4	5.2	4.7	5.3		21.2	21.3	5.8
3d	12.3	10.3	9.9	8.8	6.9	6.1		19.4	53.3	16.8
4a	4.3	37.0	37.0	40.0	11.7	23.7		21.4	254.0	34.5
4b	35.8	33.0	31.7	27.6	24.8	22.2		58.5	133.3	98.8
4c	54.0	47.8	47.2	48.3	27.8	22.2		89.9	119.9	59.1
4d	31.7	31.8	34.3	39.4	21.6	42.4		80.0	131.6	180.9
4e	12.4	6.9	6.8	11.9	8.5	9.0		74.4	132.2	25.7
4f	9.9	13.0	13.1	10.3	11.1	6.1		16.2	12.3	18.7

^a Transport conditions: Aq. I; metal picrate (0.01 mol dm⁻³) (3 cm³); membrane: macrocycle 0.001 mol/CHCl₃ (15 cm³); Aq. II: water (10 cm³). Stirred for 8 h at 27 ± 1 °C. Each value is the mean of three experiments which are within ± 15% error. ^b Extraction conditions: metal picrate (0.02 mol dm⁻³); thallium picrate (0.01 mol dm⁻³); Pb²⁺ picrate (0.001 mol dm⁻³) (2 cm³); macrocycle solution in chloroform (0.001 mol dm⁻³) (2 cm³). The *R*-values are the mean of three independent measurements which are consistent within ± 2% error. *R* = ratio of the concentration of metal picrate extracted in the organic layer and the concentration of ligand present in the organic layer. ^c Ligand-induced transport rates of Sr²⁺ and Pb²⁺ could not be calculated due to their significant leakage and also the low extraction of Ba²⁺ due to the lack of solubility of barium picrate in acetonitrile.



macrocycles, diester 1 was condensed with diethylenetriamine and with 3,3'-diaminodipropylamine to form the macrocycles 3a (45%) and 4a (35%), respectively.

The IR carbonyl group absorption of compound 3a (1650 cm^{-1}) shows the presence of strong intramolecular hydrogen bonding between amine NH and amide C=O groups, which is not observed in macrocycle 4a (1690 cm^{-1}). In order to determine the effect of hydrogen bonding on the binding

properties of these macrocycles, compounds 3b and 4b possessing NMe groups were prepared, by refluxing the parent heterocycles 3a and 4a with methyl iodide.

Furthermore, to develop the effect of co-operative binding in the macrocycles 3a and 4a, the macrocycles 3c and 3d and 4c and 4d, containing ethoxycarbonylmethyl and *N,N*-diethylcarbamoylmethyl chains, were prepared by the reaction of substrates 3a and 4a with ethyl bromoacetate and chloro-*N,N*-diethylacetamide, respectively. However, attempted reaction of methyl 3-bromopropionate or 3-bromopropionitrile with substrates 3a and 4a failed. Alternatively, compound 4a easily underwent Michael addition with methyl acrylate and acrylonitrile to give macrocycles 4e and 4f, respectively. However, a similar reaction did not occur with macrocycle 3a, probably because of the lower reactivity of its amine nitrogen due to hydrogen bonding.

Extraction and Transport Studies.—The role of the embedded amide group in directing the binding selectivity of macrocycles towards alkaline earth cations^{10–15} has emphasized the importance of ionophore studies on amide–ether-containing macrocycles. Also, as the process of ligand-facilitated transport of cations through a non-polar membrane involves extraction (complexation) and release (decomplexation) of the cation, extraction studies having direct relevance to the complexation are necessary to characterize the transport properties of an ionophore. In the present study, we have determined the extraction and transport rates of Li^+ , Na^+ , K^+ , Tl^+ , Mg^{2+} , Ca^{2+} , Pb^{2+} and Ag^+ picrates with ionophores 3a–d and 4a–f by using chloroform as apolar membrane.

It has been found that Ag^+ is selectively extracted and transported and in these respects alkaline earth cations are marginally preferred over alkali metal cations. The Pb^{2+} cation is extracted at the highest rate (Table 1). The appendages possessing terminal ester and amide groups also affect the binding characteristics. The 'hard' ester-containing side-chains prefer 'hard' alkali cations and the 'softer' amide chain increases selectivity towards Ag^+ and Pb^{2+} cations.

The macrocycle 3a transports alkaline earth cations with marginal preference over alkali cations (Table 1). It extracts Pb^{2+} picrate nearly 28- and 14-times more than the similarly sized Ag^+ and Sr^{2+} picrates, respectively. With an increase in size over that of macrocycle 3a by two methylene units, the macrocycle 4a extracts metal picrates with significantly higher efficiency, but with lowered selectivity towards Pb^{2+} over Ag^+ (7.4), Sr^{2+} (11.9) and other cations. In transport experiments, macrocycle 4a transports all the cations (Table 1) at remarkably higher rates than does the macrocycle 3a, but lacks selectivity towards any of these cations.

The macrocycle 3a, during complexation, has to make some compensation for removal of its hydrogen bonding and consequently makes relatively weaker complexes than does the macrocycle 4a. This is further supported by the fact that the NMe analogue of macrocycle 3a, *i.e.* macrocycle 3b which lacks intramolecular hydrogen bonding in comparison with the parent 3a, exhibits significantly higher extraction rates of metal picrates except for Pb^{2+} , and also transports metal picrates with higher efficiency. The macrocycle 4b, having a larger ring size by two methylene units, shows lower extraction but better transport rates as compared with compound 3b. Therefore, here the change in ring size in macrocycles 3b and 4b does not effect their ionophoric character much and, in macrocycle 3a, the presence of hydrogen bonding is the main cause of the lower extraction and transport rates compared with the macrocycle 4a.

The macrocycle 3c, possessing a $\text{CH}_2\text{CO}_2\text{Et}$ appendage for co-operative binding, shows lower extraction and transport of cations in comparison with macrocycle 3b. However, ester 3c

Table 2 IR ($\nu_{\max}/\text{cm}^{-1}$) data of the macrocycles **3** and **4** and their complexes with Na^+ , Ag^+ and Pb^{2+} picrates

Macrocyclic	Free ligand	Complexes with		
		Na^+	Ag^+	Pb^{2+}
3a	1650, 1600	1650, 1560	1605	1610
3c	1735, 1680	1735, 1640	1735, 1624	1735, 1628
3d	1690, 1660	1640, 1624	1660, 1620	1640, 1610
4a	1690, 1660	1640, 1620	1640, 1620	1640, 1612
4b	1670	1625	1624	1608
4c	1740, 1660	1740, 1636	1740, 1620	1740, 1612
4e	1740, 1660	1740, 1636	1740, 1612	1740, 1612

transports Li^+ picrate with some selectivity over other metal picrates. The macrocycle **4c** shows better extraction and poorer transport of cations than does macrocycle **4b**. The increase in side-chain length by one methylene unit in ester **4e** further lowers the extraction and transport rates. These results indicate that the ester side-arms do not contribute much towards co-operative binding but do influence to some extent the preference towards 'hard' alkali metal cations.

The amide group-containing side-arms are known to exhibit selective binding towards alkaline earth cations.³ The macrocycle **3d** shows marginally improved extraction over **3c**. However, **4d** conspicuously extracts Ag^+ three times more effectively than **4c**. However, significant selectivity towards 'soft' Ag^+ or Pb^{2+} is not observed.

Complexation Studies through IR and ^{13}C NMR spectroscopy.—The macrocycles **3** and **4** possess amine, ether and amide functionalities along with ester and amide functions in the side-chain. The extraction and transport studies reflect the overall effect of all the functionalities present in a macrocycle, but the role of different functional groups on complexation is not known. The comparison of IR and ^{13}C NMR spectral data of these ligands with the respective data of their complexes with metal picrates (Mg^{2+} , Ca^{2+} , Sr^{2+} , Ba^{2+} , Pb^{2+} , Ag^+) could provide a closer scrutiny of the mode of complexation of these macrocycles.

The IR spectra of macrocycles **3b–d** and **4a–e** show amide carbonyl absorption bands in the range 1660–1690 cm^{-1} , but the macrocycle **3a** shows a similar band at 1650 cm^{-1} (Table 2). The latter is attributed to the strong hydrogen bonding between amine NH and amide oxygen, which forms a seven-membered ring. Compound **4a**, owing to the necessity of forming an H-bonding eight-membered ring, and other macrocycles, owing to the absence of an NH group, do not show hydrogen bonding.

The IR spectra (KBr) of (a) pure complexes of macrocycles **3a** and **4a** with Pb^{2+} picrate prepared in ethanol and (b) their respective, thoroughly pulverized equimolar mixtures of the reactants gave identical IR spectra except for some additional, low-intensity peaks in the latter due to free ligands. So for all other cases of complexes of macrocycles **3** and **4** with Na^+ , Ag^+ and Pb^{2+} picrates the IR spectra (Table 2) have been taken using procedure b. The metal picrate complexes of ligands **3a** and **4a** show an amide C=O absorption band at $1615 \pm 5 \text{ cm}^{-1}$. The metal picrate complexes of macrocycles **3c**, **4c** and **4e** having a CO_2R group in the side-chain exhibit an ester C=O absorption band at 1735–1740 cm^{-1} as in the parent compound and the amide C=O band at $1625 \pm 15 \text{ cm}^{-1}$. Therefore, in all metal complexes, the amide C=O absorption bands shift to lower frequency, which indicates that the complexation occurs through the amide oxygen and not through the amide nitrogen. Furthermore, this complexation is stronger in the case of macrocycles **3a** and **4a** (1610 cm^{-1}) than for the macrocycles **3c**,

Table 3 ^{13}C NMR co-ordination shifts ($\Delta\delta$) for compounds **3** and **4**

Macrocyclic	Carbon	Induced chemical shifts ^a					
		Mg^{2+}	Ca^{2+}	Sr^{2+}	Ba^{2+}	Ag^+	Pb^{2+}
3a	a	+0.3	+0.6	+0.2	+0.5	+0.1	+0.1
	b	+0.2	+0.4	+0.1	+0.4	+1.6	+0.1
	c	-0.2	-0.4	-0.1	-0.4	+2.0	-0.1
	d	+0.1	+0.1	0	0	+1.9	+0.1
4a	a	-0.1	+0.1	-0.1	0	-0.9	-0.1
	b	+0.1	0	-1.0	-0.1	+1.6	-0.2
	c	0	0	-0.3	0	-0.4	-0.1
	d	+0.3	+0.2	+1.8	+0.3	+1.2	+0.4
3c	a	0	0	+0.1	0	0	0
	b	0	-0.1	+0.1	0	0	0
	c	+0.1	+0.4	+0.4	+0.4	+0.3	+0.3
	d	+0.1	+0.1	0	+0.1	0	-0.1
4c	a	-0.8	-0.7	-0.8	-0.8	0	-0.8
	b	0	0	+0.3	0	+1.1	+0.1
	c	0	0	0	0	+0.3	+0.1
	d	+0.3	+0.5	+0.6	+0.4	+0.3	+0.4
	e	+0.1	+0.2	+0.1	+0.1	+1.2	+0.1
	f	+0.1	+0.1	-0.2	+0.1	+0.4	-0.1
3d	a	+0.1	+0.1	0	-0.1	0	+0.1
	b	+0.1	+0.1	+0.2	+0.1	+0.1	+0.1
	c	0	0	+0.1	0	+0.2	0
	d	+0.3	+0.3	+0.4	+0.3	+0.7	+0.3
	e	0	0	-0.1	0	-0.3	0
	f	0	0	+0.1	0	+0.2	0
	g	+0.1	+0.1	+0.1	+0.1	+0.2	+0.1
	h	0	0	+0.4	0	0	0
4d	a	+0.1	+0.2	0	+0.1	+0.4	+0.5
	b	-0.1	0	-0.4	0	-0.6	-0.2
	c	+0.4	+0.5	+0.5	+0.5		
	d	0	+0.2	-0.4	0	+0.1	
	e	+0.2	+0.2	+0.1	+0.2	+0.3	+1.1
	f	+0.1	+0.2	+0.1	+0.1	+0.2	-1.5
	g	0	0	0	0	+1.4	0
4e	a	+0.1	+0.1	+0.1	+0.1	+0.2	+0.1
	b	+0.2	+0.3	+0.4	+0.3	+0.3	+0.5
	c	0	+0.1	+0.1	+0.1	+1.5	-0.1
	d	+0.2	+0.3	+0.4	+0.3	+0.3	+0.5
	e	0	+0.1	+0.1	+0.1	+1.5	-0.1
	f		+0.2	0	+0.2	-0.3	-0.1

^a Conditions: macrocycle (0.15 mmol); metal picrate (0.15 mmol in DMF-CDCl_3 (3:1) 0.5 cm^3). Positive is downfield shift.

4c and **4e** ($1630 \pm 6 \text{ cm}^{-1}$). The IR data of the liquid macrocycle **4d** could not be recorded for the solid state.

Comparison of ^{13}C NMR spectra of the macrocycles with the ^{13}C NMR spectra of their complexes gives significant information about the complexation character of these macrocycles. The magnitudes of changes in the chemical shifts show that these macrocycles complex with Ag picrate more strongly than with other metal picrates, which is contrary to the extraction results, where maximum complexation is observed with Pb^{2+} picrate. This difference could be attributed to the difference in medium [dimethylformamide (DMF)- CDCl_3 in ^{13}C NMR studies and CHCl_3 -water (biphasic) in extraction studies] in both cases. Furthermore, ^{13}C NMR spectra of macrocycles and their complexes with alkaline earth, Ag^+ and Pb^{2+} cations show significant changes, but only minor changes with alkali cations. Therefore the results with alkali cations have been omitted from Table 3.

Ligand **3a** shows maximum metal-induced changes in the ^{13}C NMR chemical shifts of its C=O, OCH_2 and amide NHCH_2 signals with silver picrate ($\Delta\delta$ 1.6–2.0). However, alkaline earth cations show most shift in the amine CH_2 signal. Similarly, in macrocycle **4a**, Ag picrate shifts amide NCH_2 and C=O signals downfield, but the amine CH_2 signal is shifted upfield. However, the maximum shift in the C=O signal is observed in the case of Sr^{2+} . Therefore, the amine nitrogen

Table 4 Spectral and other data of macrocycles 2-4

Compound	M.p. (T/°C)	Yield (%)	m/z (M ⁺)	¹ H NMR (CDCl ₃ except where shown) (δ)	¹³ C NMR (DMF-CDCl ₃) (δ _c)
2a	188	5	250	(CDCl ₃ + CF ₃ CO ₂ H) 3.53 (4 H, s, 2 × NCH ₂), 4.47 (4 H, s, 2 × OCH ₂), 6.67–7.06 (4 H, m, ArH), 7.3–7.9 (2 H, br, 2 × NH)	
2b	133	10	264	1.66–2.00 (2 H, m, CH ₂), 3.5 (4 H, q, J 6, 2 × CH ₂ N), 4.30 (4 H, s, 2 × OCH ₂), 6.67 (4 H, s, ArH), 7.00–7.45 (2 H, br, 2 × NH, exchanges with D ₂ O)	
3a	233	45	293	1.55–2.03 (1 H, br, exchanges with D ₂ O), 2.93 (4 H, t, J 6, NHCH ₂), 3.47 (4 H, q, J 6, 2 × CH ₂ , collapses to triplet on D ₂ O exchange), 4.47 (4 H, s, 2 × OCH ₂), 6.87 (4 H, s, ArH), 7.40–7.97 (2 H, br, 2 × amide H, exchanges with D ₂ O)	33.52 (t, CH ₂), 43.00 (t, CONHCH ₂), 67.4 (t, OCH ₂), 113.85 (d, ArCH), 120.82 (d, ArCH), 145.98 (s, ArC), 166.88 (s, C=O)
3b	180	70	307	2.13 (3 H, s, Me), 2.93 (4 H, t, J 6, 2 × NCH ₂), 3.43 (4 H, q, J 6, 2 × CONHCH ₂ , collapses to triplet on D ₂ O exchange), 4.40 (4 H, s, 2 × CH ₂), 6.67–7.00 (4 H, m, ArH), 7.50–7.83 (2 H, br, 2 × CONH, exchanges with D ₂ O)	
3c	103	61	379	1.16 (3 H, t, J 7, Me), 2.90 (4 H, t, J 6, 2 × NCH ₂), 3.10 (2 H, s, NCH ₂), 3.37 (4 H, q, J 6, 2 × CONHCH ₂ , collapses to triplet on D ₂ O exchange), 4.10 (2 H, q, J 7, OCH ₂), 4.43 (4 H, s, 2 × OCH ₂), 6.67–7.06 (4 H, m, ArH), 7.43–8.87 (2 H, br, 2 × CONH, exchanges with D ₂ O)	12.03 (q, Me), 33.99 (t, NCH ₂), 50.01 (t, NCH ₂), 52.25 (t, NCH ₂), 56.63 (t, OCH ₂), 65.65 (t, OCH ₂), 111.55 (d, ArCH), 120.14 (d, ArCH), 144.97 (s, ArC), 165.31 (s, CO ring), 169.75 (s, CO side-arm)
3d	165	70	406	1.06 (3 H, t, J 7, Me), 1.18 (3 H, t, J 7, Me), 2.95 (4 H, t, J 6, 2 × CH ₂), 3.20–3.54 (10 H, m, 3 × NCH ₂ and CONCH ₂ CH ₂), 4.48 (4 H, s, 2 × OCH ₂), 6.80–7.03 (4 H, m, ArH), 8.06–8.20 (2 H, br, 2 × CONH, exchanges with D ₂ O)	10.83 (q, Me), 12.14 (q, Me), 34.21 (t, NCH ₂ ring), 38.21 (t, NCH ₂), 39.15 (t, NCH ₂), 50.21 (t, NCH ₂ ring), 53.39 (t, NCH ₂ side-arm), 65.65 (t, OCH ₂), 111.31 (d, ArCH), 119.89 (d, ArCH), 145.11 (s, ArC), 165.10 (s, CO ring), 168.06 (s, CO side-arm)
4a	187	35	321	1.47–2.00 (5 H, m, 2 × CH ₂ and NH), 2.63 (4 H, t, J 6, 2 × NHCH ₂), 3.40 (4 H, q, J 6, 2 × CONHCH ₂ , collapses to triplet on D ₂ O exchange), 4.37 (4 H, s, 2 × OCH ₂), 6.83 (4 H, s, ArH), 7.10–7.50 (2 H, br, 2 × CONH, exchanges with D ₂ O)	26.13 (t, CH ₂), 33.46 (t, NCH ₂), 43.60 (t, CONHCH ₂), 62.62 (t, OCH ₂), 112.09 (d, ArCH), 120.19 (d, ArCH), 145.76 (s, ArC), 166.48 (s, CO)
4b	90	35	335	1.53–1.93 (4 H, m, 2 × CH ₂), 2.07 (3 H, s, Me), 2.23–2.57 (4 H, t, J 6, 2 × NCH ₂), 3.25–3.79 (4 H, q, J 6, 2 × CONHCH ₂ , collapses to triplet on D ₂ O exchange), 4.55 (4 H, s, 2 × OCH ₂), 6.70–7.13 (4 H, m, ArH), 7.15–7.65 (2 H, br, 2 × CONH, exchanges with D ₂ O)	23.86 (t, CH ₂), 33.69 (t, NCH ₂), 37.31 (q, NMe), 52.62 (t, CONHCH ₂), 66.04 (t, OCH ₂), 111.98 (d, ArCH), 120.14 (d, ArCH), 145.51 (s, ArC), 165.92 (s, CO)
4c	115	43	407	1.20 (3 H, t, J 7, Me), 1.63–2.00 (4 H, m, 2 × CH ₂), 2.73 (4 H, t, J 6, 2 × NCH ₂), 3.25 (2 H, s, NCH ₂), 3.56 (4 H, q, J 6, 2 × CONHCH ₂ , collapses to triplet on D ₂ O exchange), 4.03 (2 H, q, J 7, OCH ₂), 4.50 (4 H, s, 2 × OCH ₂), 6.87–7.10 (4 H, m, ArH), 7.33–7.67 (2 H, br, 2 × NH, exchanges with D ₂ O)	12.19 (q, Me), 24.48 (t, CH ₂), 34.65 (t, NCH ₂ ring), 49.51 (t, NHCH ₂), 50.11 (t, NCH ₂ side-arm), 66.25 (t, OCH ₂ ring), 112.18 (d, ArCH), 120.15 (d, ArCH), 145.73 (s, ArC), 166.04 (s, CO ring), 169.22 (s, CO side-arm)
4d	liquid	53	334	0.84 (3 H, t, J 7, Me), 1.11 (3 H, t, J 7, Me), 1.77 (4 H, m, 2 × CH ₂), 2.59 (4 H, t, J 7, 2 × NCH ₂), 3.0 (2 H, q, J 7, CH ₂), 3.16 (4 H, t, J 7, 2 × CH ₂), 3.54 (4 H, t, J 7, 2 × NHCH ₂), 4.46 (4 H, s, 2 × OCH ₂), 6.80–7.1 (4 H, m, ArH), 8.03–8.30 (2 H, br, 2 × CONH, exchanges with D ₂ O)	10.77 (q, Me), 12.09 (q, Me), 24.56 (t, CH ₂), 34.53 (t, NCH ₂), 37.78 (t, NCH ₂), 39.07 (t, NCH ₂), 50.53 (t, NCH ₂), 52.74 (t, NCH ₂), 66.72 (t, OCH ₂), 112.36 (d, ArCH), 120.14 (d, ArCH), 146.09 (s, ArC), 166.13 (s, CONH), 168.10 (s, CO)
4e	109	55	407	1.84 (4 H, quint, J 6, 2 × CH ₂), 2.39–2.52 (6 H, m, 3 × NCH ₂), 2.80 (2 H, t, J 7, CH ₂ CO), 3.30–3.63 (7 H, m, OMe and 2 × OCH ₂ ring), 6.88–7.04 (4 H, m, ArH), 7.37–7.44 (2 H, br, 2 × NH, exchanges with D ₂ O)	24.39 (t, CH ₂), 28.85 (t, NCH ₂), 34.15 (t, NCH ₂), 45.53 (t, NHCH ₂), 66.49 (t, OCH ₂), 112.49 (d, ArCH), 120.27 (d, ArCH), 145.79 (s, ArC), 165.98 (s, CO ring), 170.89 (s, CO side-arm)
4f	115	58	374	1.50–2.42 (4 H, m, 2 × CH ₂), 2.18–2.93 (8 H, m, 2 × NCH ₂ ring, NCH ₂ CH ₂), 3.30–3.67 (4 H, q, J 6, 2 × NHCH ₂ , collapses to triplet on D ₂ O exchange), 4.43 (4 H, s, 2 × OCH ₂), 6.6–6.93 (4 H, m, ArH), 7.00–7.23 (2 H, br, 2 × NH, exchanges with D ₂ O)	

^a Elemental analysis: **3a** (Found: C, 57.2; H, 6.7; N, 13.9. C₁₄H₁₉N₃O₄ requires C, 57.33; H, 6.48; N, 14.33%). **3b** (Found: C, 58.6; H, 6.6; N, 14.0. C₁₅H₂₁N₃O₄ requires C, 58.63; H, 6.84; N, 13.96%). **3c** (Found: C, 56.9; H, 6.3; N, 11.0. C₁₈H₂₅N₃O₆ requires C, 56.99; H, 6.59; N, 11.08%). **3d** (Found: C, 58.2; H, 7.0; N, 13.95. C₂₀H₃₀N₃O₅ requires C, 59.11; H, 7.3; N, 13.79%). **4a** (Found: C, 59.2; H, 6.8; N, 13.3. C₁₆H₂₃N₃O₄ requires C, 59.81; H, 7.16; N, 13.08%). **4b** (Found: C, 60.4; H, 7.1; N, 12.5. C₁₇H₂₅N₃O₄ requires C, 60.89; H, 7.46; N, 12.53%). **4c** (Found: C, 58.4; H, 6.8; N, 10.5. C₂₀H₂₉N₃O₄ requires C, 58.96; H, 7.12; N, 10.31%). **4e** (Found: C, 58.8; H, 6.85; N, 10.6. C₂₀H₂₉N₃O₆ requires C, 58.96; H, 7.12; N, 10.31%). **4f** (Found: C, 60.3; H, 6.9; N, 14.5. C₁₉H₂₆N₄O₄ requires C, 60.96; H, 6.95; N, 14.97%).

participates more effectively in complexation with alkaline earth cations, and the amide group complexes more actively with silver cation.

In parallel with the results of extraction and IR studies, the ligands bearing a functionality at the amine nitrogen show relatively poor complexation, *i.e.* small changes in chemical

shifts in ^{13}C NMR studies. All these ligands show downfield chemical shifts for the C=O signal. These results indicate a major role of the amide C=O in complexation with metal ions. In macrocycles **3d** and **4d** significant participation of the amide appendage in complexation with Ag^+ is also observed.

Therefore the results of extraction, transport, IR and ^{13}C NMR studies on the macrocycles **3** and **4** and their interaction with metal picrates show that the metal ions bind with these macrocycles through the amide oxygen and, owing to lower cavity size, metal ions reside above the plane of the macrocycles. The ether oxygens contribute only marginally to the complexation; the amine NH group shows significant complexation with metal ions but in the presence of an appendage its participation decreases.

Experimental

M.p.s were determined in capillaries and are uncorrected. ^1H NMR spectra were recorded on a JEOL-JNM (60 MHz) instrument for solutions in CDCl_3 – $(\text{CD}_3)_2\text{SO}$ with SiMe_4 as internal standard. ^{13}C NMR spectra were recorded on a Bruker AC 200 instrument for solutions in DMF – CDCl_3 (3:1) and chemical shifts are reported with respect to CDCl_3 (middle peak at δ_{C} 77.00). IR spectra were recorded for KBr pellets on a NICOLET 5DX FT-IR spectrophotometer. Mass spectra were run on a JEOL JMS-D 300 or a V G micromass 7070F machine operating at 70 eV at CDRI, Lucknow. TLC was performed on precoated plates of silica gel-G. Column chromatography was carried out using silica gel (60–120 mesh).

1,2-Bis(ethoxycarbonylmethoxy)benzene 1.—A solution of catechol (11.0 g, 0.1 mol) and ethyl bromoacetate (33.4 g, 0.2 mol) in acetonitrile (dry; 50 cm^3) containing K_2CO_3 (27.8 g, 0.4 mol) and triethylbenzylammonium chloride (TEBA) (100 mg) was refluxed in an oil-bath ($90 \pm 5^\circ\text{C}$). After completion of the reaction (TLC, 8 h), the solid suspension was filtered and the residue was washed with ethyl acetate (100 cm^3). The solvent was removed under reduced pressure and the residue was found to be diester **1** (95% yield) which was sufficiently pure for further reactions.

Synthesis of Macrocycles 2a, 2b, 3a and 4a.—A solution of diester **1** (2.8 g, 0.01 mol) and ethylenediamine (0.6 g, 0.01 mol) in ethanol (150 cm^3) was refluxed (40 h) on a water-bath. Ethanol was distilled off and the residue was chromatographed to isolate the pure macrocycle **2a**. Similarly, reaction of diester **1** with 1,3-diaminopropane, diethylenetriamine and 3,3'-diaminodipropylamine gave macrocycles **2b**, **3a** and **4a**, respectively (Table 4).

Synthesis of Macrocycles 3b, 3c, 4b and 4c.—Macrocycle **3a** (2.93 g, 0.01 mol) was dissolved in the minimum amount of chloroform, methyl iodide (0.01 mol) was added, and the reaction mixture was refluxed for 4.5 h. During this period a solid separated out. The reaction mixture was cooled, diluted with CHCl_3 , and treated with 10% aq. NaHCO_3 . The chloroform layer was separated, dried (Na_2SO_4), and distilled off. The residue was chromatographed to isolate the macrocycle **3b**. Similarly, reaction of compound **3a** with ethyl bromoacetate and of compound **4a** with methyl iodide and ethyl bromoacetate gave the macrocycles **3c**, **4b** and **4c**, respectively.

Synthesis of Macrocycles 3d and 4d.—A solution of macrocycle **3a** (1.0 g, 0.003 mol), chloro-*N,N*-diethylacetamide (0.6 g, 0.004 mol) and NaI (0.6 g, 0.004 mol) in dry ethanol (15 cm^3) was refluxed for 12 h. After completion of the reaction (TLC), ethanol was distilled off. The residue was dissolved in chloroform and was treated with 10% aq. NaHCO_3 . The chloroform layer was separated, dried (Na_2SO_4), and evaporated. The residue was chromatographed to isolate macrocycle **3d**. Similarly, compound **4a** gave macrocycle **4d**.

Synthesis of Macrocycles 4e and 4f.—A solution of macrocycle **4a** (1.0 g, 0.003 mol) in chloroform containing either methyl acrylate or acrylonitrile (0.004 mol) was refluxed on a water-bath. After completion of the reaction (5 h, TLC), the solvent was distilled off and the residue was chromatographed to isolate compound **4e** or **4f**, respectively.

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