Pergamon

Tetrahedron 54 (1998) 5575–5586

TETRAHEDRON

Synthetic Ionophores Part 19:[1] Synthesis and Ionophore Character of 2-Aminothiophenol Based Silver Selective Acyclic and Cyclic Receptors[2].

Subodh Kumar*, Vandana Bhalla and Harjit Singh*
Department of Chemistry, Guru nanak Dev University, Amritsar - 1143005, India.

Received 31 December 1997; accepted 12 March 1998

Abstract: The phase transfer catalysed nucleophilic displacements of 1,5-dibromo-3-oxapentane, 1,8-dibromo-3,6-dioxaoctane and 1,11-dibromo-3,6,9-trioxaundecane with thiophenol and 2-aminothiophenol provide respective acyclic receptors α,ω-bis(phenylthio/2-aminophenylthio)oxaalkanes (**6-11**). 1,8-Bis(2-aminophenylthio)-3,6-dioxaoctane (**10**) reacts with acetic anhydride and isophthaloyl chloride to provide acyclic (**12**) and macrocyclic (**14**) receptors, respectively. α,ω-(2-Aminophenylthio) oxaalkanes (**9-11**) undergo intermolecular cyclodehydrochlorination with thiodiglycolyl dichloride and pyridine-2,6-dicarbonyl dichloride.HCl to provide respective macrocycles **16-18** and **20-22**. The acyclic receptors **6-11** show strong complexation with Ag^+ and Pb^{2+} with poor specificity towards Ag^+. The conversion of amine units to amides in **12** significantly lowers the complexation but increases Ag^+ / M^{z+} selectivities. The organisation of ligating sites by converting acyclic receptor **12** to its cyclic analogs and the presence of additional ligating sites in cyclic receptors **16-18** and **20-22** not only restores the extraction abilities but also leads to high Ag^+ /M^{z+} slectivities. The macrocycles **17** and **21** respectively exhibit the highest transport (425) and extraction (564) Ag^+ / Pb^{2+} selectivites.

Introduction

The development of fast estimation, removal and separation techniques for the silver, the use of silver complexes in photographic materials and their potential use in cancer radioimmunotherapy has drawn the attention of supramolecular chemists[3] towards the design, synthesis and evaluation of silver selective ionophores. For the design of Ag^+ selective ionophores, the structural parameters such as presence of appropriately placed -S-, minimal incorporation of hard ligating sites (ether/amine); availability of 2-4 ligating sites,[4-8] induction of conformational and stereochemical restrictions to avoid 2:1 (L : M) complexation to engineer cavity based complexation,[9-11] have been delineated. Recently, cavity based complexation of Ag^+ with macrocycles possessing -S- on non-flexible ethylene bridges have been observed.[12,13]

0040-4020/98/$19.00
PII: S0040-4020(98)00229-4

We argue that in 2-aminothiophenol unit, due to the possible interaction of -S- lone pair with adjacent ArH, the electrons will be directed towards the interior and would be more readily available for cavity based metal ion complexation in a receptor possessing such a unit and if an array of different types of ligating sites is built around these two heteroatoms, the resulting receptor will have at least partially preorganised ligating sites. So, in the present investigations, 2-aminothiophenol based acyclic (**9-12**) and cyclic receptors (**14, 16-18, 20-22**) possessing some additional structural feature such as amide, -O-, pyridine N etc. have been designed and synthesized. Also, to evaluate the role of NH_2, in acyclic receptors, in complexation with Ag^+, acyclic receptors **6-8** have been synthesized. The ionophore behaviour of these receptors towards alkali (Li^+, Na^+, K^+), alkaline earth (Mg^{2+}, Ca^{2+}, Sr^{2+}, Ba^{2+}), Ag^+, Tl^+ and Pb^{2+} cations has been studied through extraction and transport studies.

Synthesis: The phase transfer catalysed (K_2CO_3 -DMF - TEBA Cl) nucleophilic displacements of α,ω-dichlorooxaalkanes **3-5** with thiophenol (**1**) and 2-aminothiophenol (**2**) provide the respective acyclic receptors α,ω-bis(phenylthio)- and α,ω-bis(2-aminophenylthio)- oxaalkane **6-11** (54-85%) (fig. 1).

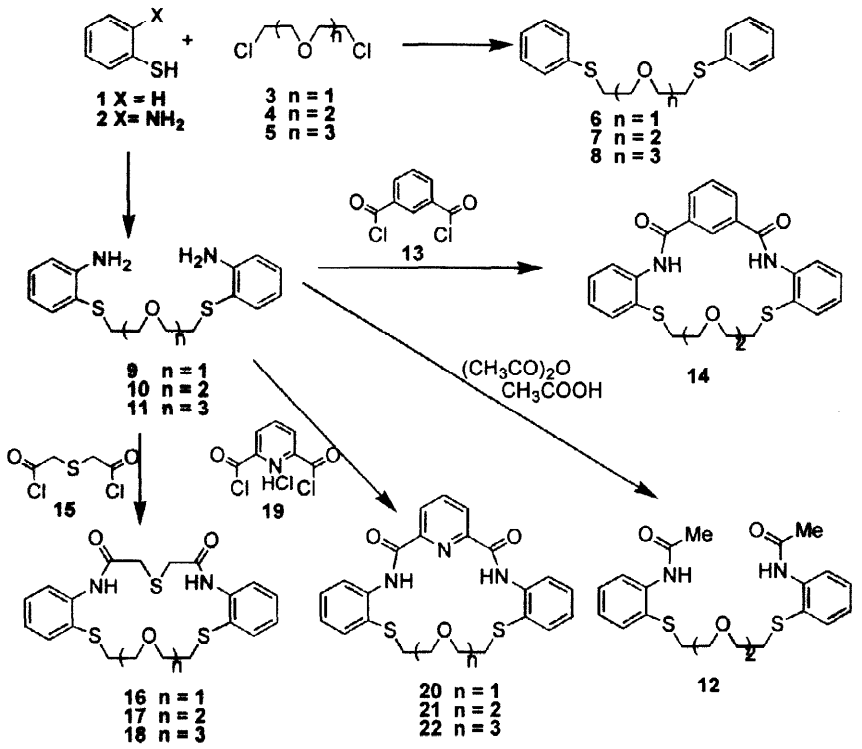

Fig. - 1

The podand **10** on refluxing in acetic anhydride - acetic acid mixture gives **12** (90%), MS m/z 448 (M^+). In its ^{1}Hnmr spectrum, the appearance of $COCH_3$ as two singlets in 1:4 ratio and SCH_2 as three sets of triplets and in its ^{13}C nmr (normal / DEPT-135) spectrum the appearance of two signals each due to CH_3 (δ

24.75, 26.37) and SCH_2 (δ 31.61, 35.93) and OCH_2 (δ 68.85. 69.45; 70.03, 70.34) carbons and more signals in aromatic region than the number of chemically equivalent carbons shows that due to restricted rotation around amide bond, this compound exists as a mixture of cisoid, transoid configurations around an amide bond (fig. 2).

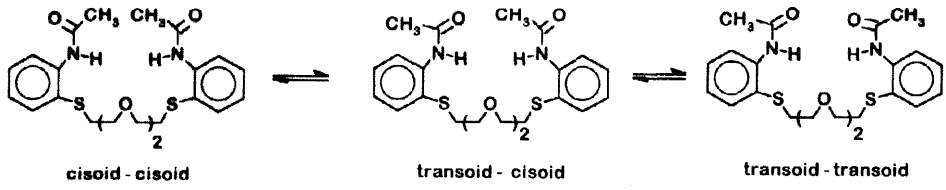

Fig 2

The slow addition of isophthaloyl dichloride (**13**) to a solution of diamine **10** in dichloromethane containing a suspension of K_2CO_3 (anhyd.) and TBA HSO_4 (catalyst) gives macrocycle **14** (78%), m.p. 174-178°C ($CHCl_3$); MS m/z 494 (M^+). Unlike, **12**, the cyclic diamide compound **14** attains only one configuration around the amide bond. The addition of thiodiglycolyl dichloride (**15**) to a solution of **9** in dichloromethane containing KF (anhyd.) as base and TBA HSO_4 as catalyst provides macrocycle **16** (80%), m.p. 210 °C, MS m/z 434 (M^+). On using K_2CO_3 as base, **15** decomposes and **16** is not formed. The diamines **10** and **11** react with thiodiglycolyl dichloride (**15**) under PTC conditions (KF-CH_2Cl_2-TBA HSO_4) to give the respective macrocycles **17** (75%), m.p. 205°C; MS m/z 478 (M^+) and **18** (68%) m.p. 180°C, MS m/z 522 (M^+) (fig.1). The addition of pyridine-2,6-dicarbonyl dichloride . hydrochloride (**19**) to a solution of **9** in dichloromethane containing K_2CO_3 (anhyd.) as base and TBA HSO_4 as catalyst provides macrocycle **20** (85%), m.p. 160-162°C, MS m/z 451 (M^+). Similar cyclocondensations of diamines **10** and **11** with **19** give **21** (80%), m.p. 195°C, MS m/z 495 (M^+) and **22** (75%), m.p. 148-152°C, MS m/z 539 (M^+), respectively. In the case of **22**, the appearance of two triplets at δ 3.09 and 3.65 and a singlet at δ 3.52 along with aromatic protons in ^1H nmr and the presence of more than one signal for each carbon shows that **22** exists as a mixture of two isomeric structures. Such isomeric structures could not be observed in the case of other cyclic diamide derivatives (**14**, **16-18**, **19** and **20**). Probably, due to increased ring size and rigidity of the pyridine ring, in **22** a mixture of cisoid, transoid configurations around amide bond could be stabilised.

Extraction[14] and transport[15] Studies

As the process of ligand facilitated transport of cations across a nonpolar membrane has relevance to the development of separation techniques for cations, the extraction (complexation) (Table **1**) and transport (complexation- decomplexation) (Table **2, 3**) profiles of ionophores **6-12**, **14**, **16-18** and **20-22** towards Ag^+, Pb^{2+}, Tl^+, alkali metal cations (Li^+, Na^+, K^+) and alkaline earth cations (Mg^{2+}, Ca^{2+}, Sr^{2+}, Ba^{2+}) by using chloroform as the apolar membrane have been determined.

All these ionophores possess two alkyl aryl thioether units and one ether units as common binding sites along with a combination of additional one or more of ether, thioether, amine or pyridine unit(s) and show some selectivity towards Ag^+. The acyclic ionophores **6-11**, due to their enhanced dynamic structural adaptability and possibility of formation of 2:1 ionophore-metal complexes, show high extractions but relatively low Ag^+/Pb^{2+} selectivity. The organisation of these ligating sites in the cyclic systems **14**, **16-18** and **20-22**, in general, leads to remarkably high Ag^+/Pb^{2+} selectivity. The effect of nature and organization of ligating sites in these receptors on Ag^+/Pb^{2+} , selectivity, is discussed.

The acyclic ionophore **6** possessing three ligating sites (O, 2S) extracts Ag^+ picrate nearly 21 and 7 times more than similar sized $Sr^{2+}$and Pb^{2+} and nearly 480 times more than Tl^+ picrate (table-1). **6** transports Ag^+ nearly 143, 36 and 95 times faster as compared with Sr^{2+}, Pb^{2+} and Tl^+ picrates (table -2). Therefore, in comparison with extraction results, **6** transports Ag^+ more selectively than Sr^{2+} and Pb^{2+}. The increase in number of ether binding species by one and two in acyclic ionophores **7** and **8**, leads to an increase in extraction of all the metal picrates and Ag^+/M^{z+} selectivities are marginally lowered. In transport experiments, as compared with ionophore **6** the ionophores **7** and **8** show higher order of flux for all metal picrates except Ag^+. This decrease in Ag^+ transport could be attributed to the poor decomplexation of **7**.Ag^+ and **8**.Ag^+ complexes first formed in the transport phenomenon.

As expected, the presence of an additional two NH_2 units in **9** as compared with **6** increases marginally the extraction of Ag^+ and also of other cations and hence the selectivities are not affected. In transport experiments, the increase in extraction is coupled with lower selectivities which could be due to poor decomplexation of **9**.Ag^+ complex. In analogy with receptors **7** and **8**, the increase in number of ether units in the receptors **10** and **11** also results in lower Ag^+ binding selectivity, in both extraction and transport experiments, as compared with the results with receptor **9**. The comparison of extraction results of receptors **6-8** with diamine based receptors **9-11** shows that the presence of additional NH_2 ligating sites does not result in any significant increase in extraction of Ag^+ picrate. The ^{13}C nmr titration studies[4] showed that in receptors **9-11**, Ag^+ binds preferably with the NH_2 groups over thioether units. Probably the binding of NH_2 units with Ag^+ leads to the formation of pseudocavity and it shifts the two thioether units out of the cavity and thus decreases their participation.

The conversion of amine units of **10** to amides in ionophore **12** results in a sharp decrease in extraction of Ag^+ picrate to 26.32% as compared with 77.58% in **7** and 70.00% in **9**. If it was only due to the absence of ligation of NH_2 groups, then the extraction ability of **12** should be of the order of receptor **7** lacking NH_2 . Evidently, the amide group induced topology of 12 is responsible for the lowering of cation extraction order which is more drastic in the case of Pb^{2+} and thus **12** extracts Ag^+ nearly 61 times more than Pb^{2+}. Hence, it was visualised that organisation of ligating sites by cyclization of acyclic receptors **9-11** through amide units and the presence of additional binding sites (S, N) could enhance Ag^+ / M^{z+} selectivities. Therefore, **14** extracts Ag^+ picrate (51.49%) more than the corresponding acyclic receptor **12** (26.32%). Also

Ag^+/Pb^{2+} binding selectivity of **14** is increased to 129 as compared to 61 in case of **12** (table-1). In transport experiments also, **14** shows relatively enhanced fluxes for Ag^+ and Ag^+/Pb^{2+} selectivity.

We further envisaged that the presence of additional ligating sites in the cyclic analog **14** would further increase the extraction and probably the selectivities also. Macrocycle **16** exhibits nearly a 20% increase in Ag^+ extraction relative to **14** (51.49%) though it is still less than its acyclic analog **9** (79.65%) but the organisation of ligating sites in the cyclic system increases Ag^+/Pb^{2+} selectivity to 281. Therefore, **16** which possesses three thioether units and one ethereal unit and appropriate organisation of the cavity shows high order of binding towards Ag^+ but negligible complexation with alkali, alkaline earth metal ions, Tl^+, Ba^{2+} and Pb^{2+}. The macrocycle **17**, extracts Ag^+ nearly 148 times more than Pb^{2+} and transports Ag^+ nearly 425 times faster than Pb^{2+}. The macrocycle **18** which possesses two ethereal units along with three thioether units shows a lowering in extraction of Ag^+ and an increase in extraction of Pb^{2+}, and results in lower Ag^+/Pb^{2+} selectivity. Similarly, in transport experiments, the higher flux of Pb^{2+} lowers the Ag^+/Pb^{2+} selectivity. Therefore macrocycles **16-18** exhibit a slightly lower extraction and transport rates for Ag^+ as compared with their acyclic analogs **9-11**, but they show significantly higher Ag^+/M^{z+} selectivities in extraction experiments.

Table 1: Extraction (%) profile for receptors 6-12, 14, 16-18 and 20-22

Ligand	Li^+	Na^+	K^+	Mg^{2+}	Ca^{2+}	Sr^{2+}	Pb^{2+}	Tl^+	Ag^+	$\frac{Ag^+}{Pb^{2+}}$
6	---	---	---	---	---	3.15	8.97	0.14	66.80	7.4
7	0.10	0.07	0.11	1.08	---	12.56	12.57	0.10	77.58	6.2
8	0.18	0.16	0.15	0.19	0.11	4.74	10.80	0.44	89.11	8.3
9	0.34	0.55	0.40	0.17	0.39	3.80	10.11	0.54	79.65	7.8
10	1.79	1.83	1.93	0.30	0.15	15.00	14.00	0.32	70.00	5.0
11	0.25	0.28	0.27	0.27	0.24	5.50	14.22	0.57	88.47	6.2
12	0.17	0.20	0.17	0.12	0.14	0.17	0.43	0.26	26.32	61
14	0.47	0.50	0.50	0.29	0.32	0.27	0.40	0.58	51.49	129
16	0.15	0.29	0.23	0.12	0.39	0.17	0.25	0.21	70.37	281
17	0.01	0.01	0.02	0.08	0.01	0.02	0.43	0.03	63.65	148
18	0.02	0.02	0.01	0.03	0.01	0.01	1.10	0.04	59.22	54
20	0.19	0.24	0.22	0.15	0.07	0.19	0.17	0.16	58.85	346
21	0.07	0.15	0.12	0.08	0.06	0.09	0.12	0.15	67.74	564
22	0.50	0.50	0.36	0.22	0.32	0.20	0.38	0.28	68.77	180

Macrocycle **20**, possessing one pyridine unit in place of thioether in **16**, extracts Ag^+ 346 times more than Pb^{2+}. Macrocycle **21** extracts Ag^+ nearly 564 times more than Pb^{2+} which is the highest amongst all the receptors studied here. **21** transports Ag^+ nearly 80 times more than Pb^{2+}. Macrocycle **22** extracts Ag^+ 180 times as compared with Pb^{2+}. Receptor **22** transports Ag^+ nearly 70 times more than Pb^{2+} . In all these ligands (**20-22**) two thioether units and one pyridine unit with one / two / three ethereal oxygens respectively are available for binding with Ag^+.

Table 2: Transport rates (x10^8moles/24h) for receptors 2-8, 10, 12-15 and 16-18 at Ligand 0.001M, Metal picrate 0.001M concentrations

Ligand	Li^+	Na^+	K^+	Mg^{2+}	Ca^{2+}	Sr^{2+}	Ba^{2+}	Tl^+	Pb^{2+}	Ag^+
6				9	4	4		16	6	572
7				15	8	19		10	13	246
8				12	9	6		19	10	494
9				6	4	14		20	7	498
10				8	6	6		34	24	665
11				11	9	34		35	16	513
12	1	2	5	3	3	3	1	5	3	28
14	1	2	3	1	4	5	2	11	7	85
16	3	5	4	4	1	1	2	25	7	355
17	1	2	3	2	2	1	1	1	1	425
18	10	16	15	5	5	4	5	46	47	406
20	5	6	3	2	2	1	2	7	4	331
21	1	1	2	2	2	2	1	8	5	398
22	4	3	1	1	3	3	1	2	5	348

Therefore, both amongst tristhioether macrocycles **16-18** and bisthioether, monoamine macrocycles **20-22**, the macrocycles **17** and **21** possessing 21-membered rings show highest extraction and transport selectivities for Ag^+. Further, the observation that the increase in concentration of metal picrates (table 3) by ten times in source phase of transport experiments, increases the transport rates by nearly ten times points towards the formation of 1:1 homogeneous cavity based complexes. The transport rates for Pb^{2+} picrate could not be determined under its higher concentration conditions because of its significant leakage.

Thus, acyclic receptors **6-11** show strong complexation with Ag^+ and Pb^{2+} but poor specificity towards Ag^+. The conversion of amine units to amides in **12** significantly lowers the complexation but increases Ag^+ / M^{z+} selectivities. The organisation of ligating sites by conversion to cyclic systems and the

presence of additional ligating sites (-S-, PyN) in cyclic receptors **16-18** and **20-22** not only restores the extraction abilities but also leads to high Ag^+ / Pb^{2+} selectivities.

Table 3: Transport rates (x10^8moles/24h) for receptors 12,14, 16-18 and 20-22 at Ligand 0.001M, Metal picrate 0.01M concentrations

Ligand	Li^+	Na^+	K^+	Mg^{2+}	Ca^{2+}	Sr^{2+}	Ba^{2+}	Tl^+	Ag^+
12	4	4	6	4	4	3	2	32	517
14	3	7	4	1	4	7	2	25	1222
16	3	18	6	12	5	5	6	52	2995
17	24	33	28	20	54	46	35	18	2856
18	14	35	18	6	5	8	9	81	5708
20	7	7	7	8	3	5	7	50	3609
21	3	9	6	2	3	6	2	50	2944
22	10	13	2	9	5	5	3	51	3472

Experimental:

Melting points were determined in capillaries and are uncorrected. ^{1}H nmr spectra were run on JNMPMX 60 MHz and Bruker AC200 MHz instruments using TMS as an internal standard. ^{13}C nmr spectra were run on Bruker AC 200 MHz instrument. Mass spectra were recorded on JEOL JMSD-300, VG micromass 7070 F mass spectrometers, at Central Drug Research Institute Lucknow and Shimadzu GCMS-QP-2000 mass spectrometer at Amritsar. Infrared spectra were recorded on PYE UNICAM SP3-300 infrared spectrophotometer by using $CHCl_3$ or KBr (solid) as medium. UV spectra were recorded on Shimadzu UV-240 spectrophotometer. Elemental analyses of solid samples were performed at the microanalytical laboratory RSIC, Chandigarh.

Synthesis of α ,ω -Bis(phenylthio- /2-aminophenylthio-)oxaalkanes 6-11: General Procedure

A solution of 1,5-dichloro-3-oxapentane (**3**) (1.0g, 0.007 mol) in dimethylformamide (20ml) containing thiophenol (2.17g, 0.019 mol), potassium carbonate (anhyd.) (2.9g, 0.02 mol) as base and TEBA Cl as catalyst was stirred at room temperature. After completion of the reaction (4h, tlc), the solid was filtered and the filtrate was distilled off under vacuum. The residue was chromatographed over silica gel to isolate **6**. Similarly, reaction of **3** with 2-aminothiophenol (**2**) gave **9**. The reactions of 1,8-dichloro-3,6-dioxaoctane (**4**) and 1,11-dichloro-3,6,9-trioxaundecane (**5**) with thiophenol and 2-aminothiophenol gave receptors **7, 8** and **10, 11,** respectively.

1,5 -Bis(phenylthio)-3-oxapentane (6) (77%), liquid; MS m/z 290 (M^+); ^{1}Hnmr ($CDCl_3$): δ 2.95 (4H, t, J = 6 Hz, 2 x SCH_2), 3.53 (4H, t , J = 6Hz, 2 x OCH_2) , 6.76-7.40 (10H, m, ArH) ; ^{13}Cnmr ($CDCl_3$-DMF, 1:3): δ

30.86 (t, SCH_2), 67.50 (t, OCH_2), 124.03 (d, ArCH), 126.90 (d, ArCH), 127.12 (d, ArCH), 134.60 (s, ArC) ; ν_{max} ($CHCl_3$): 1100 (C-O) cm^{-1}.

1,8-Bis(phenylthio)-3, 6-dioxaoctane (7) (54%), liquid; MS m/z 334 (M^+); ^{1}Hnmr ($CDCl_3$): δ 2.92 (4H, t, J = 7 Hz, 2 x SCH_2), 3.40-3.90 (8H, m, 4 x OCH_2) , 6.79-7.46 (10H, m, ArH) ; ^{13}Cnmr ($CDCl_3$-DMF, 1:3): δ 30.81(t, SCH_2), 67.77 (t, OCH_2), 68.30 (t, OCH_2), 123.96 (d, ArCH), 126.80 (d, ArCH), 127.14 (d, ArCH), 134.69 (s, ArC) ; ν_{max} ($CHCl_3$): 1110 (C-O) cm^{-1}.

1,11 -Bis(phenylthio)-3, 6, 9-trioxaundecane(8) (84%), liquid; MS m/z 378 (M^+); ^{1}Hnmr ($CDCl_3$): δ 3.00 (4H, t, J = 6 Hz, 2 x SCH_2), 3.30-3.72 (12H, m, 6 x OCH_2) , 7.00-7.45 (10H, m, ArH) ; ^{13}Cnmr ($CDCl_3$-DMF, 1:3): δ 30.85 (t, SCH_2), 67.88 (t, OCH_2), 68.35 (t, OCH_2), 68.54 (t, OCH_2), 123.94 (d, ArCH), 126.82 (d, ArCH), 127.15 (d, ArCH), 134.69 (s, ArC) ; ν_{max} ($CHCl_3$): 1100 (C-O) cm^{-1}.

1,5 -Bis(2-aminophenylthio)-3-oxapentane (9) (85%), liquid; MS m/z 320 (M^+); ^{1}Hnmr ($CDCl_3$): δ 2.73 (4H, t, J=7Hz, 2 x SCH_2), 3.30 (4H, t, J = 7Hz, 2 x OCH_2) , 4.00 (4H, s, 2 x NH_2, exchanges with D_2O) , 6.18-7.12 (8H, m, ArH) ; ^{13}Cnmr ($CDCl_3$-DMF, 3:1): δ 32.15 (t, SCH_2), 67.32 (t, OCH_2), 112.71 (d, ArCH). 114.06 (s, ArC), 114.97 (d, ArCH), 127.81 (d, ArCH), 133.97 (d, ArCH), 148.19 (s, ArC); ν_{max} ($CHCl_3$): 3480 , 3360 (NH_2), 1105 (C-O)cm^{-1}.

1,8 -Bis(2-aminophenylthio)-3, 6-dioxaoctane (10) (58%), liquid; MS m/z 364 (M^+); ^{1}Hnmr ($CDCl_3$): δ 2.92 (4H, t, J = 6 Hz, 2 x SCH_2), 3.27-3.69 (8H, m, 4 x OCH_2), 3.95 (4H, s, 2 x NH_2, exchanges with D_2O), 6.40-7.43 (8H, m, ArH); ^{13}Cnmr ($CDCl_3$-DMF, 1:3): δ 32.22 (SCH_2), 67.64 (OCH_2), 68.14 (OCH_2), 112.72 (ArCH), 114.14 (ArC), 114.98 (ArCH), 127.79 (ArCH), 133.99 (ArCH), 148.19 (ArC); ν_{max} ($CHCl_3$): 3460 , 3320 (NH_2), 1120 (C-O)cm^{-1}.

1,11 -Bis(2-aminophenylthio)-3, 6, 9-trioxaundecane (11) (80%), liquid ; MS m/z 408 (M^+); ^{1}Hnmr ($CDCl_3$): δ 2.90 (4H, t, J = 6 Hz, 2 x SCH_2), 3.27-3.70 (12H, m , 6 x OCH_2) , 4.3 (4H, s, 2 x NH_2, exchanges with D_2O) , 6.36-7.36 (8H, m, ArH) ; ^{13}Cnmr ($CDCl_3$-DMF, 1:3): δ 32.25 (t, SCH_2), 67.57 (t, OCH_2), 68.18 (t, OCH_2), 68.42 (t, OCH_2), 112.88 (d, ArCH). 114.32 (s, ArC), 115.18 (d, ArCH), 127.80 (d, ArCH), 134.00 (d, ArCH), 147.95 (s, ArC) ; ν_{max} ($CHCl_3$): 3480, 3360 (NH_2) , 1110 (C-O)cm^{-1}.

Synthesis of receptor 12:

A solution of **10** (1.00g, 2.8 mmol), acetic anhydride (4ml) and acetic acid (2ml) was refluxed. After completion of the reaction (2h, tlc), acetic acid was distilled off under vacuum and the residue was chromatographed over silica gel to isolate compound **12** (85%), liquid; MS m/z 448 (M^+); ^{1}Hnmr ($CDCl_3$): δ 2.22 (3H , s, CH_3), 2.27 (3H, s, CH_3), 2.91 (1H, t, J = 6.2 Hz, SCH_2), 3.08, 3.10 (3H, t, J = 6.2 Hz, SCH_2), 3.50-3.67 (8H, m, 4xOCH_2) , 7.03-7.23 (7H , m, ArH), 8.33 (0.5H, d, J = 8.4 Hz, ArH), 8.62 (0.5H, b, ArH) ; ^{13}Cnmr ($CDCl_3$) (normal / DEPT-135): δ 24.75 (+ve, CH_3), 26.37 (+ve, CH_3), 31.61 (-ve, SCH_2), 35.93 (-ve, SCH_2), 68.85 (-ve, OCH_2), 69.45 (-ve, OCH_2), 70.03 (-ve, OCH_2), 70.34 (-ve, OCH_2), 120.30 (+ve, ArCH), 123.89 (+ve, ArCH), 126.68 (+ve, ArCH), 128.25 (+ve, ArCH), 129.41 (+ve, ArCH), 129.74

(+ve, ArCH), 135.65 (absent, ArC), 136.30 (absent, ArC-N), 172.25 (absent, C=O); ν_{max} ($CHCl_3$): 1716 (C=O)cm^{-1}.

Synthesis of macrocycle 14 :

The diamine **10** (1.00g, 2.7 mmol), K_2CO_3 (anhd., 5.00g) and TBA HSO_4 (10 mg, catalyst) were taken in dry dichloromethane (100 ml). Isophthaloyl dichloride (**13**) (0.557g, 2.7 mmol) dissolved in dichloromethane (dry, 50 ml) was added dropwise over half an hour and the reaction mixture was stirred at room temperature. After completion of the reaction (tlc, 7h), the suspension was filtered off and the solid residue was washed with ethyl acetate (2 x 10 ml) and was recrystallised from chloroform to isolate **14** (78%), m.p. 174-178°C ($CHCl_3$); MS m/z 494 (M^+); ^{1}Hnmr ($CDCl_3$): δ 2.90 (4H, t, J = 6.0 Hz, 2 x SCH_2) , 3.00 (4H, s, 2 x OCH_2) , 3.38 (4H, t, J = 6.0 Hz , 2 x OCH_2) , 7.11 (2H, t, J = 6.0Hz, ArH) , 7.45 (2H, t, J = 8.4 Hz, ArH) , 7.64 (2H, d, J = 8.4 Hz, ArH) , 7.71 (1H, d, J = 6.0 Hz, ArH), 8.17 (2H , d, J = 8.4 Hz, ArH) , 8.42 (1H, s, ArH), 8.55 (2H, d, J = 8.4 Hz), 9.75 (2H, s, 2 x NH, exchanges with D_2O); ^{13}Cnmr ($CDCl_3$) (normal / DEPT-135): δ 37.77 (-ve , SCH_2), 67.78 (-ve , OCH_2), 68.68 (-ve , OCH_2), 120.57 (+ve , ArCH), 122.65 (absent), 124.53 (+ve , ArCH), 125.00 (+ve , ArCH), 129.58 (+ve , ArCH), 130.59 (+ve , ArCH), 131.21 (+ve , ArCH), 136.46 (+ve , ArCH), 136.66 (absent, ArC), 141.17 (absent, ArC), 165.31 (absent, C=O); ν_{max} (KBr): 1595 (C=O)cm^{-1}; Found (C, 62.97, H, 5.1 5, N, 5.83, $C_{26}H_{26}N_2O_4S_2$ requires C, 63.15, H, 5.26 and N 5.66%)

Synthesis of macrocycles 16-18: General Procedure

The compound **9** (1.00g, 3.12 mmol), KF (anhd., 5g) and TBA HSO_4 (10 mg, catalyst) were taken in dry dichloromethane (100 ml). Thiodiglycolyl dichloride (**15**) (0.58g, 3.12 mmol) dissolved in dichloromethane (50 ml) was added dropwise to this solution over half an hour and the reaction mixture was stirred at room temperature. After completion of the reaction (tlc, 7h), the suspended solid was filtered off and washed with ethyl acetate (2 x 10 ml). The combined filtrate was distilled off. The compound **16** was crystallized from chloroform. Similar cyclocondensations of **10** and **11** with **15** gave macrocycles **17** and **18**, respectively.

Macrocycle 16 (80%), m.p. 210°C ($CHCl_3$); MS m/z 434 (M^+); ^{1}H nmr ($CDCl_3$): δ 2.94 (4H, t, J = 6.0 Hz , 2 x SCH_2), 3.47 (4H, t, J = 6.0 Hz, 2 x OCH_2) , 3.68 (4H, s, 2 x SCH_2), 7.08 (2H, t, J = 7.6 Hz, ArH), 7.34 (2H, t, J = 7.6 Hz, ArH), 7.53 (2H, d, J = 7.6 Hz, ArH), 8.30 (2H, d, J = 7.6 Hz, ArH), 9.43 (2H, s, 2 x NH, exchanges with D_2O); ^{13}Cnmr ($CDCl_3$) (normal / DEPT-135): δ 36.19 (-ve, SCH_2), 37.93 (-ve, SCH_2), 67.71 (-ve, OCH_2), 121.00 (+ve, ArCH), 123.34 (absent, ArC), 124.74 (+ve, ArCH), 129.47 (+ve, ArCH), 135.16 (+ve, ArCH), 146.12 (absent, ArC) 161.72 (absent, C=O); ν_{max} (KBr): 1672 (C=O)cm^{-1}; Found (C, 55.10, H, 4.91, N, 6.80%, $C_{20}H_{22}N_2O_3S_3$ requires C, 55.29, H, 5.06 and N, 6.45%).

Macrocycle 17 (75%), m.p. 205°C ($CHCl_3$); MS m/z 478 (M^+); ^{1}H nmr ($CDCl_3$): δ 2.97 (4H, t, J = 6.0 Hz, 2 x SCH_2), 3.58 (4H, t, J = 6.0 Hz, 2 x OCH_2), 3.45 (4H, s, OCH_2), 3.69 (4H, s, 2 x SCH_2), 7.07 (2H, t, J = 7.6Hz, ArH), 7.37 (2H, t, J = 7.6 Hz, ArH), 7.58 (2H, d, J = 7.6 Hz, ArH), 8.44 (2H, d, J = 7.6 Hz, ArH), 9.73 (2H , s , 2 x NH , exchanges with D_2O) ; ^{13}Cnmr ($CDCl_3$) (normal / DEPT-135): δ 36.73 (-ve , SCH_2),

37.37 (-ve, SCH_2), 67.75 (-ve , OCH_2), 69.73 (-ve, OCH_2),120.15 (+ve, ArCH), 122.45 (absent, ArC), 124.37 (+ve, ArCH), 129.58 (+ve, ArCH), 136.33 (+ve, ArCH), 140.42 (absent, ArC), 166.60 (absent, C=O); ν_{max} (KBr): 1685 (C=O)cm^{-1}; Found (C, 55.31, H, 5.17, N, 5.61%, $C_{22}H_{26}N_2O_4S_3$ requires C, 55.23, H, 5.43 and N, 5.85%).

Macrocycle 18 (68%), m.p.180°C ($CHCl_3$); ;MS m/z 522 (M^+); ^{1}H nmr ($CDCl_3$): δ 3.00 (4H, t, J = 6.0 Hz, 2 x SCH_2), 3.58-3.70 (12H, m, 6 x OCH_2), 3.70 (4H, s, 2 x SCH_2), 7.08 (2H, t, J = 7.6 Hz, ArH), 7.30 (2H, t, J = 7.6Hz, ArH), 7.56 (2H, d, J = 7.6 Hz, ArH), 8.42 (2H, d, J = 7.6 Hz, ArH), 9.79 (2H, s, 2 x NH, exchanges with D_2O); ^{13}Cnmr ($CDCl_3$), normal (DEPT-135): δ 37.05 (-ve, SCH_2), 68.73 (-ve, OCH_2), 70.06 (-ve, OCH_2), 70.67 (-ve, OCH_2), 120.45 (+ve, ArCH), 122.73 (absent, ArC), 124.44 (+ve, ArCH), 130.08 (+ve, ArCH), 136.11 (+ve, ArCH), 140.44 (absent, ArC), 166.74 (absent, C=O); ν_{max} (KBr): 1690 (C=O)cm^{-1}; Found (C, 55.22, H, 5.53, N, 5.40, $C_{24}H_{30}N_2O_5S_3$ requires C, 55.17, H, 5.74 and N, 5.36%).

Synthesis of macrocycles 20, 21 and 22: General Procedure

The diamine **9** (1.00g, 3.12 mmol), K_2CO_3 (anhd., 5.00g) and TBA HSO_4 (10 mg, catalyst) were taken in dry dichloromethane (100 ml). Pyridine-2,6-dicarbonyl dichloride.hydrochloride(**19**) (0.659g, 3.12 mmol) dissolved in dichloromethane (dry, 50 ml) was added dropwise over half an hour and the reaction mixture was stirred at room temperature. After completion of the reaction (tlc, 7h), the suspension was filtered off and the solid residue was washed with ethyl acetate (2 x 10 ml) and crystallized from chloroform to give **20**. Similarly, diamines **10** and **11** underwent cyclocondensation with **19** to give macrocycles **21** and **22**, respectively.

Macrocycle 20 (85%), m.p.160-162°C ($CHCl_3$); MS m/z 451 (M^+); ^{1}H nmr ($CDCl_3$): δ 3.01 (4H, t, J = 6.0 Hz, 2 x SCH_2), 3.50 (4H, t, J = 6.0 Hz, 2 x OCH_2), 7.17 (2H, t, J = 7.8 Hz, ArH), 7.36 (2H, t, J = 7.8 Hz, ArH), 7.52 (2H, d, J = 7.8 Hz, ArH), 8.15 (1H, t, J = 7.8 Hz, PyH), 8.22 (2H, d, J = 7.8 Hz, ArH), 8.52 (2H, d, J = 7.8 Hz , PyH), 10.54 (2H, s, 2 x NH, does not exchange with D_2O) ; ^{13}Cnmr ($CDCl_3$) (normal / DEPT-135): δ 36.20 (-ve, SCH_2), 67.48 (-ve, OCH_2), 123.34 (+ve, ArCH), 125.65 (+ve , PyCH), 125.74 (+ve, ArCH), 127.08 (absent, ArC), 133.75 (+ve, PyCH), 138.42 (absent, ArC), 139.21 (+ve, ArCH), 149.43 (absent, PyC-N), 161.72 (absent, C=O);. ν_{max} (KBr): 1682 (C=O)cm^{-1}; Found (C, 61.30, H, 4.27, N, 9.00%, $C_{23}H_{21}N_3O_3S_2$ requires C, 61.19, H, 4.65 and N 9.31%)

Macrocycle 21 (80 %), m.p. 195°C ($CHCl_3$); MS m/z 495 (M^+); ^{1}H nmr ($CDCl_3$): δ3.07 (4H, t, J = 5.8 Hz, 2 x SCH_2), 3.46 (4H, s, 2 x OCH_2), 3.62 (4H, t, J = 5.8 Hz, 2 x OCH_2), 7.20 (2H, t, J = 7.6 Hz, ArH), 7.39 (2H, t, J = 7.6Hz, ArH), 7.58 (2H, d, J = 7.6 Hz, ArH), 8.16-8.21 (3H, m, ArH + PyH), 8.54 (2H, d, J = 7.6 Hz, PyH), 10.65 (2H, s, 2 x NH, does not exchange with D_2O) ; ^{13}Cnmr($CDCl_3$) (normal / DEPT-135): δ 36.39 (-ve, SCH_2), 69.41 (-ve, OCH_2), 70.65 (-ve, OCH_2), 123.05 (+ve, ArCH), 125.82 (+ve, PyCH), 127.46 (+ve, ArCH), 128.85 (+ve, ArCH), 133.89 (+ve, PyCH), 138.41 (absent, ArC), 139.38 (absent, ArC),

149.19 (absent, PyC-N) , 161.78 (absent, C=O); ν_{max} (KBr): 1684 (C=O)cm^{-1}; (Found C, 61.00, H, 4.97, N, 8.38, $C_{25}H_{25}N_3O_4S_2$ requires C, 60.60, H, 5.05 and N 8.48%)

Macrocycle 22 (75 %) , m.p. 148-152°C ($CHCl_3$); MS m/z 539 (M^+); ^{1}H nmr ($CDCl_3$): δ 3.09 (4H, t, J = 6.6 Hz, 2 x SCH_2), 3.52 (8H, s, 4 x OCH_2), 3.65 (4H, t, J = 6.6 Hz, 2 x OCH_2), 7.19 (2H, t, J = 7.6 Hz, ArH), 7.38 (2H, t, J = 7.6 Hz, ArH), 7.57 (2H, d, J = 7.6 Hz, ArH), 8.18 (1H, t, J = 7.6 Hz, PyH), 8.26 (2H, t, J = 7.6 Hz, ArH), 8.55 (2H, d, J = 7.6 Hz , PyH), 10.57 (2H, s, 2 x NH, does not exchange with D_2O); ^{13}Cnmr ($CDCl_3$) (normal / DEPT-135): δ 34.36 (-ve, SCH_2), 36.36 (-ve, SCH_2), 69.35 (-ve, OCH_2), 70.36 (-ve, OCH_2), 70.59 (-ve, OCH_2), 122.72 (+ve, ArCH), 123.00 (+ve, ArCH), 125.55 (+ve, PyCH), 125.82 (+ve, PyCH), 127.43 (ArC, absent), 128.53 (+ve , ArCH), 128.85 (+ve, ArCH), 132.80 (+ve, ArCH), 133.91 (+ve , ArCH), 137.61 (absent, ArC), 138.39 (absent, ArC), 139.40 (+ve, ArCH), 149.14 (absent, PyC-N), 161.60 (absent, C=O), 161.75 (absent, C=O); ν_{max} (KBr): 1684 (C=O)cm^{-1}; (Found C, 60.20, H, 5.20, N, 8.00, $C_{27}H_{29}N_3O_5S_2$ requires C, 60.11, H, 5.38 and N 7.79%)

Extraction Measurements:[14]

For the extraction experiments, metal picrate solutions (0.01M) were prepared in deionised distilled water. The solutions of macrocycles (0.01 M) were prepared in chloroform (A.R. grade). An aqueous solution (2 ml) of metal picrate (0.01 M) and a chloroform solution (2ml) of the macrocycle (0.01 mol dm^{-3}) were shaken in a cylindrical tube closed with a septum for 5 minutes and kept at 27±1°C for 3-4 h.An aliquot of chloroform layer (1 ml) was withdrawn with a syringe and diluted with acetonitrile to 10 ml. The UV absorption was measured against $CHCl_3$-CH_3CN (1:9) solution at 374 nm. Extraction of metal picrate was calculated as the percentage of metal picrate extracted in chloroform layer and the values reported here are the mean of three independent measurements which were within ± 2% error (Table 2).

Transport Measurements:[15]

The transport experiments were carried out at constant temperature (27±1^{0}C) in a cylindrical glass cell consisting of outer and inner jackets by using (i) metal picrate (0.01 M) in water (3 ml) in the inner phase; (ii) water (10 ml) in the outer phase; (iii) ligand (10 M) in chloroform layer (15 ml) with stirring (150±5 r.p.m.) at 27±0.05°C. After stirring for 6h the picrates transported in the aqueous receiving phase were determined from the U.V. absorptions at 355 nm. Each value is a mean of three experiments which are consistent ±10% (Table 3,4). Before determining the transport rates, blank experiments were performed in the absence of the carrier macrocycle in the chloroform layer to check the leakage of metal picrates. Only a significant leakage was observed in case of Pb^{2+} and so, transport of Pb^{2+} was not determined.

Acknowledgement: We thank DST, New Delhi for a research grant (SP/SI/623/92).

References.

1 Part 18. Kumar, S.; Bhalla, V.; Hundal, G.; Hundal, M. and Singh, H. *J. Chem. Soc. Perkin Trans. 2*, (in press)

2 Preliminary Communication: Kumar, S.; Bhalla, V. and Singh, H., *Bioorg. Med. Chem. Letters*, 1995, **5**, 1917.

3. (a) Parker, D., *Chem. Soc. Rev.*, **1990**, 19, 271. (b)Siswanta, D.; Nagatsuka, K.; Yamada, H.; Kumakura, K.; Hisamoto, H.; Shichi, Y.; Toshima, K. and Suzuki, K., *Anal. Chem.*, **1996**, 68, 4166. (c) Nabeshima, T.; Tsukada, N.; Nishijima, K.; Ohshiro, H. and Yano, Y., *J. Org. Chem.*, **1996**, 61, 4342 and references therein. (d) Lerchi, M. and Pretsch, E., *Anal. Chem.*, **1996**, 68, 3210.

4 Kumar, S.; Hundal, M.S.; Kaur, N.; Singh, R.; Singh, H.; Hundal, G.; Ripoll, M. M. and Aparicio, J.S., *J. Org. Chem.*, **1996**, 61, 7819.

5 Kumar, S.; Kaur, I. and Singh, H., *Indian J. Chem.*, **1994**, 33A, 412.

6 Kumar, S.; Kaur, N. and Singh, H., *Tetrahedron*, **1996**, 52, 13483

7 Kumar, S.; Kaur, N. and Singh, H., *Tetrahedron*, **1997**, 53, 10841

8 Tsukube, H.; Venishi, J.; Kojima, N. and Yanemitsu, O., *Tetrahedron Letters*, **1995**, 36, 2257.

9 Nabeshima, T.; Nishijima, K.; Tsukada, N.; Furusawa, H.; Hosoya, T. and Yano, Y., *J.Chem.Soc. Chem. Commun.*, **1992**, 1092.

10 Casabo, J.; Flor, T.; Stuart, M.N.; Jenkins, H.A.; Lockhart, J.C.; Loeb, S.J.; Romero, I. and Texidor, F., *Inorg. Chem.*, **1995**, 34, 5410.

11 Texidor, F.; Flores, M.A.; Eschriche, L.; Vinas, G. and Cassabo, J.; *J. Chem. Soc. Chem. Commun.*, **1994**, 963.

12 Sibert, J. W.; Lange, S. L.; Williams, D. J.; Barrett G. M. and Hoffman, B. M., *Inorg. Chem.* **1995**, 34, 2300.

13 Dieing, R.; Morrisson, V., Moore, A. J.; Goldenberg, L. M.; Bryce, M. R.; Raoul, J. M.; Petty, M. C.; Grin, J.; Saviron, M.; Lednew, I. K.; Herter, R. E. and Moore, J. M., *J. Chem. Soc., Perkin Trans 2*, **1996**, 1587.

14 (a) Moore, S. S.; Tarnowski, T. L.; Newcomb, M.; Cram, D. J.; *J. Am. Chem. Soc.*, **1977**, 99, 6398. (b) Koeing, K. E.; Lehn, G. M.; Stuckler, P.; Kaneda, T.; Cram, D. J.; *J. Am. Chem. Soc.*, **1979**, 101, 3553.

15 (a) Maruyama, K.; Tsukube, H. and Akai, T., *J. Am. Chem. Soc.*, **1980**, 102, 3246. (b) Maruyama, K.; Tsukube, H. and Akai, T., *J. Chem. Soc., Dalton Trans.*, **1981**, 1486.