Pergamon

Tetrahedron, Vol. 52, No. 42, pp. 13483-13492, 1996

0040-4020/96 $15.00 + 0.00

PII: S0040-4020(96)00803-4

Synthetic Ionophores Part 14 : Effect of Pyridine and Thioether Ligating Units on Ag^+ Selectivity in 18-Membered Diamide -Diester Macrocycles[1]

Subodh Kumar*, Navneet Kaur and Harjit Singh*
Department of Chemistry
Guru Nanak Dev University, Amritsar 143 005 INDIA
Telefax: +91 (0)183-258820

Abstract: The eight new diamide - diester macrocycles **8-15** possessing pyridine / thioether / ether as ligating units have been prepared by dehydrochlorination of appropriate diacid dichlorides and diols (**4 - 7**) obtained by aminolysis of diethyl pyridine-2,6-dicarboxylate / diethyl thiodiglycolate with aminoalcohols. Amongst these macrocycles, the substituted ones elaborate mixtures of three dimensional cisoid / transoid configurations and the unsubstituted ones are planar. Macrocycles **9**, **10**, **11**, **13** have high order of binding preference for Ag^+ and its highest extraction and transport selectivities are shown by **13** and **10**, respectively.

The amide group, so generously distributed in a variety of antibiotic ionophores[2], has acquired a special status in designing of synthetic ionophores due to its dual (O or N / NH) ligating character, higher negative charge on oxygen than ether and ester and incorporation of geometrical rigidity around carbon nitrogen bond, through partial double bond character induced steric control and hydrogen bonding (where possible)[2]. Thus its presence in macrocycles has shown paramount influence in the preorganisation and consequently the binding selectivity of cations[3-8] and organic molecules[9-12]. In Ag^+ selective 18-membered pyridine - amide macrocycles, the Npy ---HN amide hydrogen bonding is detrimental to cation binding[13]. Hence we envisaged that in such macrocycles, the presence of CH_2-S-CH_2 linkage in place of a pyridine unit, both due to its binding preference towards soft cations and lack of possibility of hydrogen bonding would enhance silver selectivity.Based on these features and optimal requirement of 2-4 coordination sites for Ag^+ binding[14-17], we have designed 18-membered diamide - diester receptors with one pyridine -one thioether (**8, 9, 10, 11**) and two thioether (**12 and 13**) units. In order to elaborate the role of thioether units in Ag^+ selectivity, two receptors **14** and **15** possessing ether units in place of the thioether in case of **8** and **9** have been synthesized. It has been found that the receptor **10** which lacks intramolecular hydrogen bonding and **9, 11** and **13** with three dimensional cavities show high order of binding selectivity towards Ag^+ which is lacking in **14** and **15**.

Synthesis:

For the synthesis of macrocycles **8-15**, the two step approach involving the aminolysis of diethyl pyridine-2,6-dicarboxylate / diethyl thiodiglycolate with amino alcohols to form diols **4-7** followed by their intermolecular cyclodehydrochlorination with appropriate diacid dichlorides was adopted. The compound **1** on heating with aminoethanol and N-methyl-2-aminoethanol gives respective diols **6** (92%), m.p. 68°C, MS m/z 236 and **7** (94%), liquid, MS m/z 264. The diols **4** and **5** have been prepared by method reported earlier[13]. The phase transfer catalysed (KF/K_2CO_3 - CH_2Cl_2 - $TBAHSO_4$) cyclodehydrochlorination of diols **4** and **5** with diacid dichlorides **2a** and **2c** gave respective macrocycles **8** (23%), mp 200°C, MS m/z 367; **9** (13%), mp 135°C, MS m/z 395; **14** (28%), mp 154°C, MS m/z 351 and **15** (15%), mp 109°C, MS m/z 379. Similarly diols **6** and **7** undergo cyclodehydrochlorination with diacid dichlorides **2b** and **2a** to give respective macrocycles **10** (13%), mp 155°C, MS m/z 367; **11** (10%), mp 185°C, MS m/z 395; **12** (18%), mp180oC, MS m/z 350 and **13** (15%), liquid, MS m/z 378 (Fig. 1).

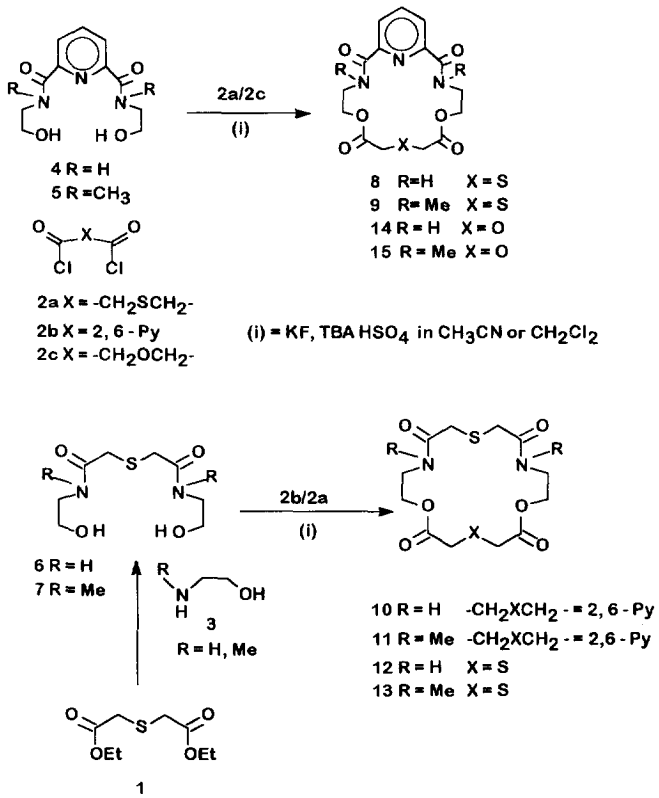


Fig. 1

Configurational analysis:

The CPK models of macrocycles **8, 10, 12 and 14** show more or less planar structures with both amide H occupying the cavity. The possibility of H-bonding induces rigidity in **8** and **14** but **10** and **12** constitute rather flexible structures with enhanced possibility of the availability of thioether unit for complexation. In macrocycles **9, 11, 13 and 15**, the steric restriction would place one or both methyl groups out of the cavity. In the later case the possibility of methyl groups being on the same or on the opposite sides of the macrocycles.

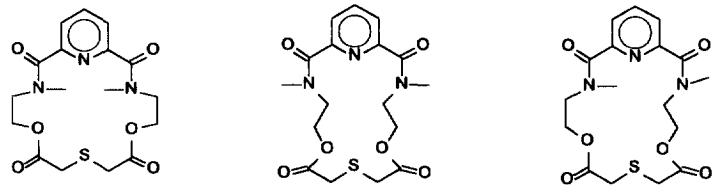


Fig. 2

The macrocycles **8- 15** have two amide units in the ring and would constitute three configurational isomers: cisoid - cisoid, transoid - transoid and cisoid - transoid (Fig 2). The macrocycles **8**, **10**, **12** and **14** have two amide NH units and in their ^{1}H nmr show expected multiplicity of signals for SCH_2, OCH_2 and NCH_2 and in their ^{13}C nmr show one signal for each chemically equivalent carbon and could be assigned symmetrical structures lacking any configurational isomerism. In the ^{1}H nmr of **8** and **14**, the appearance of downfield NH signal, in comparison with those in **10** and **12** shows the presence of N_{py}---HN_{amide} intramolecular hydrogen bonding and therefore cisoid - cisoid configurations.In case of macrocycles **10** and **12**, due to steric repulsions between two methylene units in the cavity, transoid - transoid configuration could again be ruled out.

The macrocycle **9**, in its ^{1}H nmr spectrum in $CDCl_3$ shows three N-Me (1.3 : 1 : 1) and SCH_2 (1.3:1:1) singlets each and spread out multiplets due to NCH_2 and OCH_2 units. Its ^{1}H nmr in d_6-DMSO shows only two singlets each due to NMe and SCH_2 (1:1). On addition of Ag^+ picrate to solution of **9** in DMSO, NMe and OCH_2 signals collapse to broad singlets (Fig. 3). The addition of alkali, alkaline earth or Pb^{2+} picrates do not affect the ^{1}H nmr pattern of **9**. Therefore, the presence of relatively bulky methyl substituents on amide N in **9** leads to restricted rotation around amide bond and generates three configurations. Since strong steric repulsions between Me -- Me, CH_2 -- CH_2 and CH_2 - Me are evident in CPK models, the two CONMe groups should be out of plane of the pyridine units. Moreover, once the PYCONRR unit loses its planarity, two CO units can be either on the same side or on the opposite sides of the pyridine unit. Therefore, **9** exists as a mixture of geometrical structures which on addition of Ag^+ picrate converge to one configuration.

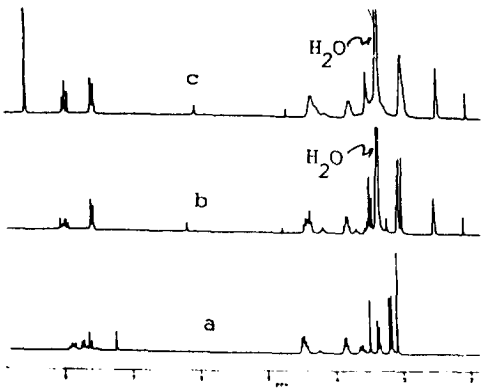


Fig 3. Comparison of the ^{1}H nmr spectra of (a) 9 in $CDCl_3$ (b) 9 in $CDCl_3$ - d_6-DMSO (1:1) (c) 9 + Ag^+ picrate (1:1) in $CDCl_3$ - d_6-DMSO (1:1)

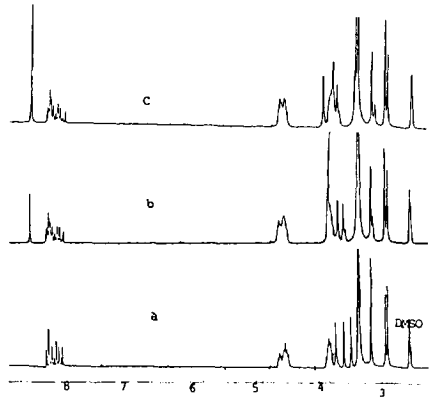


Fig 4. Comparison of the ^{1}H nmr spectra of (a) 11 (b) 11 + Ag^+ pic (1:1) (c) 11 + Ag^+ pic (1:2) in d_6-DMSO + $CDCl_3$ (1:1).

The macrocycle **11**, in its ^{1}H nmr spectrum in $CDCl_3$ shows four signals each due to NMe [δ 3.00, 3.03, 3.17, 3.22 (1:0.3:1:0.3)] and SCH_2 [δ 3.49, 3.54, 3.70, 3.75] and NCH_2 and OCH_2 appear as multiplets, which are much less spread out than in **9**. The addition of Ag^+ picrate (1 equiv.) to this solution leads to two singlets due to NMe [3.00, 3.19 (1:1)] and three singlets due to SCH_2 [δ 3.57, 3.69, 3.80 (1:1:1)] alongwith two triplets for OCH_2 at δ 4.57 and 4.59. As one SCH_2 singlet is embedded into the NCH_2 signal, the multiplicity of NCH_2 could not be ascertained. Its ^{1}H nmr in d_6-DMSO - $CDCl_3$ (1:1 v/v) shows three singlets each due to NMe (δ 2.90, 2.94, 3.17) and SCH_2 (δ 3.50, 3.61, 3.74) (1:1:1.4) alongwith multiplets for NCH_2 and OCH_2. On addition of Ag^+ picrate (1 equiv.) NMe, NCH_2 and OCH_2 signals are not affected but SCH_2 signals are shifted downfield to δ 3.62, 3.71 and 3.86. Further addition of 1 mol of Ag^+ picrate shifts the SCH_2 signals to δ 3.74, 3.81 and 3.96 (Fig. 4). However, unlike **9**, the addition of Ag^+ picrate does not lead to formation of one configuration. Similarly macrocycles **13** and **15** also exist as different configurational isomers but these on addition of Ag^+ picrate do not converge to one configuration.

Extraction and Transport studies:

As the process of ligand facilitated transport of cations across a non-polar membrane has relevance to development of separation techniques for cations, the extraction (complexation) (table 1, Fig. 5) and transport (complexation/decomplexation) (table 2, Fig. 6) profiles of macrocycles **8-15** 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 apolar membrane have been determined. On the basis of nmr based structural studies, the macrocycles **8-15** could be classified into (a) macrocycles possessing amide NH units and having more or less planar structures i.e **8**, **10**, **12** and **14** and (b) the macrocycles possessing amide NMe units and having cisoid , transoid configurations i.e. **9**, **11**, **13** and **15**.

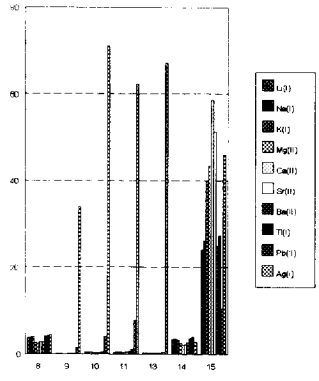


Fig. 5. Extraction profiles of macrocycles 8-12, 14, 15 towards metal picrates.

The macrocycles **8** and **14** which have N_{py}---HN_{amide} intramolecular hydrogen bonding, show only 2-5% extraction for all the cation picrates leading to poor selectivity towards any cation. The macrocycle **10**, which is isomeric with **8** but lacks any intramolecular hydrogen bonding, shows remarkable increase in extraction of Ag^+ (71%) and therefore leads to higher selectivity for (> 17) for even Ag^+ / Pb^{2+}. Hence, the lack of intramolecular hydrogen bonding in **10** makes the py N available for binding with cations and results in higher Ag^+ extraction and selectivity. The extraction and transport profiles for **12** could not be determined due to its poor solubility.The macrocycle **9**, which lacks intramolecular H-bonding of **8** extracts Ag^+ (33.9%), Pb^{2+}

Table-1: Metal ion Extraction Profile (% Extraction) of Macrocycles **8-15**

Sr. No.	Macrocycle No.	Li^+	Na^+	K^+	Mg^{2+}	Ca^{2+}	Sr^{2+}	Ba^{2+}	Tl^+	Pb^{2+}	Ag^+	$\frac{Ag^+}{Pb^{2+}}$
1.	**8**	3.66	3.82	3.89	2.45	2.29	2.67	2.75	4.00	4.10	4.40	1.1
2.	**9**	0.03	0.03	0.04	0.01	0.05	0.04	0.06	0.06	1.39	33.9	24.4
3.	**10**	0.46	0.50	0.50	0.28	0.31	0.31	0.36	0.57	4.03	71.0	17.6
4.	**11**	0.44	0.49	0.47	0.28	0.38	0.41	0.58	1.10	7.65	62.2	8.13
5.	**13**	0.24	0.23	0.24	0.19	0.18	0.18	0.19	0.23	0.42	67.0	159
6.	**14**	3.40	3.48	3.30	2.35	2.04	2.14	2.59	3.62	3.94	2.75	0.7
7.	**15**	24.0	26.0	39.9	43.4	58.6	51.2	24.9	27.2	10.5	45.9	4.37

(1.39%) and other cations (< 0.06%). Consequently Ag^+ / Pb^{2+} selectivity is significantly enhanced to >24. Also, in the ^{13}C nmr titrations, the multiple signals of each chemically equivalent CH_2 or CH_3 units in ^1H and ^{13}C nmr spectra of **9** on addition of silver picrate, spectacularly merge to one signal each for every chemically equivalent proton and carbon, respectively. This phenomenon is not observed with other cations. Therefore, **9** has such a high propensity of binding with Ag^+ that it undergoes configurational change during complexation. Macrocycle **11**, which is isomeric with **9**, shows increased extraction for all the cations relative to **9** and its Ag^+ binding selectivity is of the order of 8. The macrocycle **13**, which bears two thioether units in contrast to one thioether and one pyridine unit in **9** and **11**, shows increased extraction of Ag^+ but remarkably lower extraction of Pb^{2+} resulting in enhancement of Ag^+ / Pb^{2+} selectivity to 159 (Fig. 6, table 1). In **14**, the presence of ether unit in place of thioether of **9**, considerably increases the extraction of all the hard cations and somewhat lowers the extraction of soft Ag^+ cation.

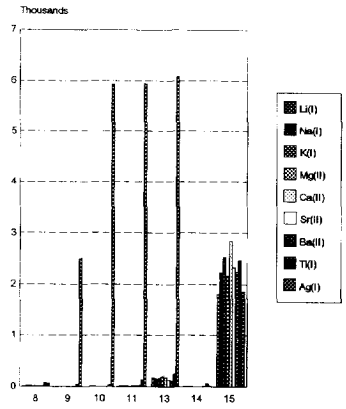


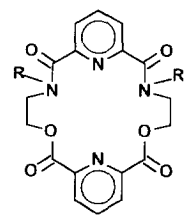
Fig. 6. Transport profile of macrocycles 8-12, 14, 15 towards metal picrates.

The transport rates of Pb^{2+} picrate could not be determined because of its significant leakage. But the transport results are in general parallel with the extraction results. The macrocycles **9**, **10**, **11**, **13** and **15** which lack intramolecular hydrogen bonding show high fluxes of Ag^+ across $CHCl_3$ membrane and macrocycles **8** and **14** possessing intramolecular H-bonding show poor transport of Ag^+ and other cations (Fig. 6, table 2). The macrocycle **15** due to the presence of ether linkage transports alkali and alkaline earth cations with similar or better efficiency relative to Ag^+ and leads to poor Ag^+ selectivity. The macrocycles **10**, **11** and **13**, which show higher extraction of Ag^+ also show the highest fluxes of Ag^+. The macrocycle 10 transports

Table -2: Metal ion Transport Rates Profiles (x 10^8 moles/24h) of Macrocycles **8-15**

Sr. No	Macro-cycle No.	Li^+	Na^+	K^+	Mg^{2+}	Ca^{2+}	Sr^{2+}	Ba^{2+}	Tl^+	Ag^+	$\frac{Ag^+}{Tl^+}$
1.	**8**	18.4	19.8	23.4	14.7	16.9	18.1	19.0	81.4	75.9	0.93
2.	**9**	2.5	7.5	7.2	6.4	4.6	2.1	3.8	45.1	2508	55.6
3.	**10**	1.72	3.95	6.94	2.00	2.69	1.85	2.67	34.7	5935	171
4.	**11**	14.5	17.5	20.2	6.85	16.8	15.4	23.0	124.6	5943	47.7
5.	**13**	175.7	161.1	156.6	195.0	177.6	127.5	121.5	250.0	6088	24.4
6.	**14**	5.8	10.0	10.1	1.5	3.2	2.8	4.0	66.9	14.8	0.22
7.	**15**	1800	2221	2537	2158	2848	2322	2242	2467	1855	0.75

Ag^+ over Tl^+ by 171 times and other cations are transported by much lower efficiencies. In case of **11** and **13**, though Ag^+ is transported at similar rate but the increased transport of alkali and alkaline earth and Tl^+ cations lowers the selectivity towards Ag^+.



16
R= CH_3, CH_2Ph

Earlier, in similar 18-membered diamide - diester macrocycles (**16**) possessing two pyridine units as soft ligating sites, the highest Ag^+ / Pb^{2+} selectivity of the order of 63 and 133 has been reported[13]. The analysis of the extraction results on the diamide - diester macrocycles possessing either 2 x py or 2 x -S- or one py and one -S- units as soft ligating sites shows that the macrocycles possessing same type of ligating sites i.e. **13** and **16** show much higher Ag^+ / Pb^{2+} selectivities than the macrocycles possessing mixed ligating sites[9,11]. As the py N and -S- have very different sizes, the lack of symmetrical overlaping in case of thioether pyridine combination may be leading to lower Ag^+ selectivities. But as transport of cations depends on both complexation (extraction) and

decomplexation phenomenon, such a rational could not be developed for results of transport studies, but a balance of the two phenomena seems to be optimum in case of macrocycle **10**.

Experimental :

^1H and ^{13}C NMR spectra were recorded on Bruker AC 200 MHz instrument using TMS as internal standard. Mass (70 ev) and IR spectra were taken on Shimadzu QP 2000A and PYE UNICAM SP 3 - 300 instruments, respectively. The multiplicities and phase of the signals in 13C nmr correspond to proton decoupled off resonance and DEPT spectra, respectively. C, H and N analysis were carried out on Perkin Elmer 2400 CHN elemental analyser at RSIC Chandigarh. UV measurements were made on Shimadzu Graphicord 240 instrument. M.p.s are uncorrected. Silica gel - G or Silica gel HF254 coated plates and columns of silica gel (60 - 120 mesh) were used for monitoring the reactions and purification of the products, respectively.

Synthesis of Diols 6 and 7 : Condensation of Diethyl Thiodiglycolate (2b) with 2-amino ethanol and N-methyl-2-aminoethanol.

General Procedure:

Diethyl thiodiglycolate **2a** (1g., 4.8 mmol) was mixed with 2 equivalents of 2-aminoethanol (0.59g., 9.6 mmol) and heated at 80-90°C for 4-5 hours. The ethanol formed during the reaction was stripped off under vacuum. A white solid product obtained was washed with chloroform ($10cm^3$) and was recrystallised from ethanol to get pure **6** (92%). Similarly diol **7** (94%) was obtained by heating **2a** with N-methyl-2-aminoethanol (**3**).

N, N' - Bis(hydroxyethyl)thiodiglycolamide (6) : (92%); mp 68°C (EtOH); IR ν_{max}(KBr) cm^{-1} 3400(NH, OH), 1660(CONH); (Found : C, 40.59 ; H, 6.82 ; N, 11.32. $C_8H_{16}N_2O_4S$ requires C, 40.68; H, 6.78; N, 11.86%); ^1H NMR [$CDCl_3$ + $(CD_3)_2SO$] δ (ppm): 3.26(4 H, m, 2 x SCH_2), 3.39(4 H, m, 2 x NCH_2), 3.73 - 3.93(6 H, bm, 2 x OCH_2 and 2 x OH); ^{13}C NMR [$CDCl_3$ + $(CD_3)_2SO$] δ (ppm): 34.12(-ve, SCH_2), 40.82(-ve, NCH_2), 58.87(-ve, OCH_2), 167.86(C = O); MS m/z 236.

N, N'-Dimethyl - N, N' - Bis(hydroxyethyl)thiodiglycolamide (7) : (94%); liquid; IR ν_{max}(KBr) cm^{-1} 3380 (OH), 1665(CONH); ^1H NMR [$CDCl_3$] δ (ppm): 2.98(3 H, s, NCH_3), 3.16(3 H, s, NCH_3), 3.38(4 H, s, SCH_2), 3.54(4 H, s, SCH_2), 3.75 - 3.82(4 H, m, 2 x NCH_2), 4.14 - 4.21(4 H, m, 2 x OCH_2), 4.65(2 H, b, 2 x OH, exchanges with D_2O); ^{13}C NMR [$CDCl_3$] δ (ppm): 32.61, 33.27(t, SCH_2), 34.28, 34.93(q, NCH_3), 41.69, 42.12(t, NCH_2), 62.73, 63.04(t, OCH_2), 167.56, 167.82(s, C = O); MS m/z 264.

Synthesis of Macrocycles 8 - 15 :

General Procedure : To a stirred mixture of KF (anhy.) and tetrabutylammonium hydrogen sulphate (10 mg.) in dry acetonitrile or dichloromethane (600 - 700 cm^3), a solution of diol **4** (1.0g, 3.9 mmol) in dry acetonitrile or dichloromethane (60 - 70 cm^3) and a solution of thiodiglycolyl dichloride (0.89 g., 4.7 mmol) in dry acetonitrile or dichloromethane (60 - 70°C) were simultaneously added dropwise during a period of 2hrs. and

stirring was continued at room temperature. After completion of reaction (TLC, 7hrs.), the suspension was filtered off and residue was washed with ethyl acetate. The combined filtrate and washings were distilled off and crude reaction product was chromatographed over silica gel column using chloroform - ethyl acetate as eluents to isolate pure macrocycle **8**. Similarly, diols **5 - 7** with their respective acid chlorides gave macrocycles **9 - 15**. In case of reactions of diols with **2b** , K_2CO_3 was used as base.

Macrocycle 8 : (23%); mp 200°C (CH_2Cl_2 - ether); IR ν_{max}(KBr) cm^{-1} 3430(NH), 1730(COO), 1675(CONH), 1655; (Found : C, 49.18 ; H, 4.56 ; N, 11.46. $C_{15}H_{17}N_3O_6S$ requires C, 49.05; H, 4.63; N, 11.43%); ^1H NMR [$CDCl_3$] δ (ppm): 3.41(4 H, s, 2 x SCH_2), 3.85(4 H, q, J 5, 2 x $NHCH_2$, collapses to triplet on D_2O exchange), 4.50(4 H. t, J 5, 2 x OCH_2), 8.05 - 8.09(1 H, m, PyH), 8.33 - 8.37(2 H, m, PyH), 8.62(2 H, t, J 5, 2 x CONH, exchanges with D_2O); ^{13}C NMR [$CDCl_3$] δ (ppm): 33.82(t, SCH_2), 39.72(t, NCH_2), 64.82(t, OCH_2), 124.86(d, PyC - 4), 139.07(d, PyC - 3), 148.46(s, PyC - 2), 163.63(s, CONH), 170.55(s, COO); MS m/z 367 (M^+, 100).

Macrocycle 9 : (13%), mp 135°C (CH_2Cl_2 - ether), IR ν_{max}(KBr) cm^{-1} 1745(COO), 1730(COO), 1630(CONH), 1625(CONH); (Found : C, 51.86; H, 5.36; N, 10.58. $C_{17}H_{21}N_3O_6S$ requires C, 51.65; H, 5.32; N, 10.63%); ^1H NMR [$CDCl_3$] δ (ppm): 3.08, 3.16, 3.20 three singlets(6 H, s, 2 x NCH_3), 3.35, 3.38, 3.49 three singlets(4 H, s, 2 x SCH_2), 3.57 - 3.92(4 H, m, 2 x NCH_2), 4.21 - 4.30, 4.38 - 4.54(4 H, m, 2 x OCH_2), 7.62 - 7.92(3 H, m, PyH); ^1H NMR [$CDCl_3$ + $(CD_3)_2SO$] δ (ppm): 3.02, 3.07 two singlets(6 H, s, 2 x NCH_3), 3.45, 3.49 two singlets(4 H, s, 2 x SCH_2), 3.78 - 3.86(4 H, m, 2 x NCH_2), 4.34- 4.45(4 H, m, 2 x OCH_2), 7.58 - 7.62(2 H, m, PyH), 7.96 - 8.07(1 H, m, PyH) ; ^{13}C NMR [$CDCl_3$] δ (ppm): 32.96, 33.89, 33.96(t, SCH_2), 38.16, 39.18(q, NCH_3), 47.24, 49.15(t, NCH_2), 60.95, 62.34, 62.91(t, OCH_2), 123.70(d, PyCH), 124.47(d, PyCH), 137.99(d, PyCH), 137.99(d, PyCH), 152.05(s, PyC), 152.73(s, PyC), 168.15, 168.32, 168.50(s, CONH), 169.23, 169.39, 169.48(s, COO); MS m/z 395 (M^+, 100).

Macrocycle 10 : (13%), mp 155°C (CH_2Cl_2 - ether), IR ν_{max}(KBr) cm^{-1} 3420(NH), 1720(COO), 1670(CONH) ; (Found : C, 48.95; H, 4.67; N, 11.34. $C_{15}H_{17}O_6N_3S$ requires C,49.05; H, 4.63; N, 11.43%); ^1H NMR [$CDCl_3$] δ (ppm): 3.37(4 H, s, 2 x SCH_2), 3.77(4 H, q, J 5, 2 x $NHCH_2$), 4.52(4 H, t, J 5, 2 x OCH_2), 7.80 (2 H, bt, J 5, 2 x CONH), 8.01 - 8.09 (1 H, m, PyH), 8.28 - 8.37(2 H, m, PyH); ^{13}C NMR [$CDCl_3$+ $(CD_3)_2SO$] δ (ppm): 33.46(t, SCH_2), 36.70 (t, NCH_2), 63.32(t, OCH_2), 126.53(d, PyC - 4), 137.23(d, PyC - 3), 146.61(s, CONH), 168.0(s, COO); MS m/z 367 (M^+, 9.0).

Macrocycle 11 : (10%), mp 185°C (CH_2Cl_2 - ether), IR ν_{max}(KBr) cm^{-1} 1720(COO), 1625(CONH); (Found : C, 51.24; H, 5.50; N, 10.86. $C_{17}H_{21}N_3O_6S$ requires C, 51.65; H, 5.32; N, 10.63%); ^1H NMR [$CDCl_3$] δ (ppm): 3.01, 3.03, 3.17, 3.22 four singlets(6 H, s, 2 x NCH_3), 3.49, 3.54, 3.70, 3.75 four singlets(4 H, s, 2 x SCH_2), 3.80 - 4.00(4 H, m, 2 x NCH2), 4.58 - 4.72(4 H, m, 2 x OCH_2), 7.97 - 8.05, 8.28 - 8.35(3 H, m, PyH); ^1H NMR [$CDCl_3$ + $(CD_3)_2SO$] δ (ppm): 2.90, 2.94, 3.17 three singlets(6 H, s, 2 x NCH_3), 3.50, 3.61, 3.74 three singlets(4 H, s, 2 x SCH_2), 3.84 - 3.89(4 H, m, 2 x NCH_2), 4.51- 4.66(4 H, m, 2 x OCH_2), 8.09 - 8.36(3 H, m,

PyH) ; ^{13}C NMR [$CDCl_3$] δ (ppm): 31.63, 33.18, 33.55(q, NCH_3), 33.90, 35.79, 38.37(t, SCH_2), 46.21, 49.57(t, NCH_2), 61.69, 62.52(t, OCH_2), 127.77(d, PyCH); MS m/z 395(M^+, 81).

Macrocycle 12 : (18%); mp 180°C (EtOH); IR ν_{max}(KBr) cm^{-1} 1710(COO), 1650(CONH); (Found : C, 45.15; H, 5.37; N, 8.25. $C_{12}H_{18}N_2O_6S_2$ requires C, 45.28; H, 5.66; N, 8.81%); ^1H NMR [$CDCl_3$+ $(CD_3)_2SO$] δ (ppm): 3.25(4 H, s, 2 x SCH_2), 3.47(4 H, s, 2 x SCH_2), 3.53(4 H, q, J 4.2, 2 X NHCH2, collapses to triplet on D2O exchange), 4.24(4 H, t, J 4.2, 2 x OCH_2), 8.36(2 H, t, J 4.2, 2 x CONH, exchanges with D_2O); ^{13}C NMR [$CDCl_3$ + $(CD_3)_2SO$] δ (ppm): 31.71(-ve, SCH_2), 33.18(-ve, SCH_2), 36.54(-ve, NCH_2), 62.29(-ve, OCH_2), 167.59(CONH), 168.02(COO); MS m/z 350(M^+, 12), 250(M^+ -$NCH_2CH_2CO(O)CH_2$, 51).

Macrocycle 13 : (15%); liquid; IR ν_{max}(KBr) cm^{-1} 1720(COO), 1640(CONH); ^1H NMR [$CDCl_3$] δ (ppm): 3.19, 3.24(6 H, s, 2 x NCH_3), 3.35, 3.38(4 H, s, 2 x SCH_2), 3.55, 3.59(4 H, s, 2 x SCH_2), 3.73(4 H, m, 2 x NCH_2), 4.53(4 H, m, 2 x OCH_2); ^{13}C NMR [$CDCl_3$] δ (ppm): 33.19, 33.34, 33.87, 34.06(-ve, SCH_2), 35.89, 36.69(+ve, NCH_3), 46.60, 46.93(-ve, NCH_2), 61.58, 61.91(-ve, OCH_2), 168.78, 168.86, 169.70, 169.83(absent, CO); MS m/z 378(M^+, 32), 334(M^+ -OCO, 4), 202(M^+ - $CH_2N(CH_3)COCH_2$ $SCH_2CON(CH_3)CH_2$, 4).

Macrocycle 14 : (28%); mp 154°C(CH_2Cl_2 - ether); IR ν_{max}(KBr) cm^{-1} 3420(NH), 1725(COO), 1650(CONH); (Found : C, 51.30; H, 4.84; N, 11.97. $C_{15}H_{17}N_3O_7$ requires C, 51.49; H, 4.37; N, 11.37%); ^1H NMR [$CDCl_3$] δ (ppm): 3.86(4 H, q, J 4, 2 x NCH_2, changes to triplet on D_2O exchange), 4.29(4 H, s, OCH_2), 4.49(4 H, t, J 4, 2 x OCH_2), 8.01 - 8.09(1 H, m, PyH), 8.34 - 8.38(2 H, m, PyH), 8.63(2 H, t, J 4, 2 x CONH, exchanges with D_2O); ^{13}C NMR [$CDCl_3$] δ (ppm): 39.40(t, NCH_2), 64.46(t, OCH_2), 69.74(t, OCH_2), 124.96(d, PyC - 4), 139.04(d, PyC - 3), 148.36(s, PyC - 2), 163.46(s, CONH), 170.27(s, COO); MS m/z 351(M^+, 51).

Macrocycle 15 : (15%), mp 109°C(CH_2Cl_2 - ether), IR ν_{max}(KBr) cm^{-1} 1720(COO), 1665(CONH), (Found : C, 53.53; H, 5.69; N, 11.24. $C_{17}H_{21}N_3O_7$ requires C, 53.53; H, 5.54; N, 11.24%); ^1H NMR [$CDCl_3$] δ (ppm): 3.06, 3.17, 3.26, 3.29 (6 H, s, 2 x NCH_3), 3.74 - 3.89 (4 H, m, 2 x NCH_2), 4.18, 4.24, 4.29 (4 H, s, 2 x OCH_2), 4.38 - 4.51 (4 H, m, 2 x OCH_2), 7.97 - 8.07 (3 H, m, PyH); ^{13}C NMR [$CDCl_3$] δ (ppm): 36.81, 39.54(+ve, NCH_3), 46.27, 47.46(-ve, NCH_2), 60.64, 62.17(-ve, OCH_2), 67.91, 68.40(-ve, OCH_2), 121.51, 123.91(+ve, PyCH), 137.67, 138.20(+ve, PyCH), 152.72, 153.02(PyC), 167.14(C=O), 169.31(C=O);MS m/z 379(M^+ , 57).

Extraction Measurements[18] :

An aqueous solution (2 cm^3) of metal picrate (0.01 mol dm^{-3}) and a chloroform solution (2 cm^3) 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 cm^{-3}) was withdrawn with a syringe and diluted with acetonitrile to 10 cm^{-3}. The UV absorption of this solution was measured against $CHCl_3$ - CH_3CN(1:9) solution at 374 nm. Extraction of metal picrates has been calculated as the percentage of metal

picrate extracted in chloroform layer and the values are the mean of three independent measurements which were within ± 2% error (Table 1).

Transport Measurements[19] :

Transport experiments were carried out in a cylindrical glass cell consisting of outer and inner jackets by using (i) metal picrate (0.01 mol dm^{-3}) in water (3 cm^3) in the inner phase; (ii) water (10 cm^3) in the outer phase; (iii) ligand (10 mmol dm^{-3}) in the chloroform layer (15 cm^3) with stirring (150±5 r.p.m.) at 27 ± 0.05 °C. After stirring for 8h, the concentrations of the picrates transported in the aqueous receiving phase were determined from the UV absorptions at 355 nm. Each value is a mean of three experiments which are consistent within ±10% (Table 2). 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 the research grant (SP/SI/623/92).

References:

1. Preliminary Communication: S. Kumar, N. Kaur and H. Singh, *Tetrahedron Letters*, **1996**, 37, 2071.
2. (a) Hilgenfeld, R.; Saenger, W. in"*Topics in Current Chemistry*" Ed. F.L. Boschke, **1982**, 101, pp 1-82. (b) Burger, H.M.; Seeback, D.; *Angew. Chem. Int. Ed. Engl.*, **1994**,33, 442. (c) Wipf, P.; Venkataraman, S.; Miller, C.P., Geib, S.S.; *Angew. Chem. Int. Ed. Engl.*, **1994**, 33, 1516.
3. Constable, E.C. in *Metals and ligand Reactivity*, VCH publishers, **1996,** pp 66.
4. Kimura, E.; Kadama, Y.; Koike, T.; Shiro, M.; *J. Am. Chem. Soc.*, **1995,** 117, 8304.
5. Beer, P.D.; Drew, M.G.B.; Kan, M. ; Leeson, P.B.; Ogden, M.I.; Williams, G.; *Inorg. Chem.*, **1996,** 35, 2202.
6. Lu, S.L. ; Frenklin, S.J.; Raymond, K.N. ; Horrocks, W.W.; *Inorg. Chem.*, **1996**, 35, 162.
7. Pigot, T.; Duriez, M.C.; Cazaux, L.; Picard, C. ; Tisnes, P.; *J.Chem. Soc. Perkin Trans. 2*, **1993,** 221.
8. Steemers, F.J.; Verboom, V.; Reinhoudt, ; van der Tol, D.N. E.B.; Verhoeven, J.W.; *J. Am. Chem. Soc.* **1995,** 117, 9408.
9. Hamuro, Y.; Geib, S.J.; Hamilton, A.D. *Angew Chem. Int. Ed. Eng.*,**1994**, 33, 446.
10. Hunter, C.A. *Chem. Soc. Rev.*, **1994**, 23, 101.
11. Brooksby, P.A.; Hunter, C.A.; Mcquillan, A.T.; Purvis, D.H.; Rowan, A.F.; Shannan, R.J.; Walsh, R. *Angew. Chem. Int. Ed. Engl.*, **1994**, 33, 2489.
12. Mitchell, M.C.; Cawley, A.; Kee, T.P. *Tetrahedron Lett.*, **1995**, 36, 287.
13. (a) Kumar, S.; Hundal, M.S.; Kaur, N.; Singh, R.; Singh, H.; Hundal, G.; Ripoll, M. M.; Aparicio, J. S. *Tetrahedron Letters,* **1995,** 9543. (b)
14. Kumar, S.; Kaur, I.; Singh, H. *Indian J. Chem.*, **1994**, 33A, 412.
15. Butler, J.; Kellogg, R.M.; VanBolheis, F. *J.Chem.Soc. Chem. Commun.*, **1991**, 910.
16. Nabeshima, T.; Nishijima, K.; Tsukada, N.; Furusawa, H.; Hosoya, T.; Yano, Y. *J. Chem. Soc. Chem. Commun.*, **1992**, 1092.
17. Nabeshima, T.; Furusawa, H; Yano, Y. *Angew. Chem. Int. Ed. Engl.*, **1994**, 33, 1750.
18. (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.
19. (a) Maruyama, K.; Tsukube, H. ; Akai, T.; *J. Am. Chem. Soc.*, **1980,** 102, 3246.(b) Maruyama, K.; Tsukube, H.; Akai, T.; *J. Chem. Soc. Dalton Trans.* **1981,** 1486.

(*Received in UK* 1 *August* 1996; *revised* 3 *September* 1996; *accepted* 5 *September* 1996)