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Synthetic Ionophores. Part 20: Synthesis and Ionophore Character of 2-Aminothiophenol and 1,3-/1,4-Phenylene Based Silver Selective Receptors *

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Abstract

Nucleophilic displacements of 1,3- and 1,4-bis(bromomethyl)benzenes with 2-aminothiophenol provide 1,3- and 1,4- bis(2-aminophenylthiomethyl)benzenes **3** and **11** which undergo intermolecular cyclodehydrochlorination with thiodiglycolyl dichloride and isophthaloyl dichloride to give respectively **6**, **8** and **12**, **13**. The diamine **3** and its *N*,*N*′-dibenzyl derivative **4** with pyridine-2,6-dicarbonyl dichloride give **7** and **5**, respectively. The extraction and transport behaviour of these receptors have been determined towards alkali (Li^+, Na^+, K^+), alkaline earth (Mg^{2+}, Ca^{2+}, Sr^{2+}, Ba^{2+}), Tl^+, Ag^+ and Pb^{2+} picrates. The participation of various ligating sites in binding have been evaluated through ^{13}C NMR studies. The acyclic receptors **3**, **4** and **11** show higher Ag^+ selectivity than the cyclic analogs **6** and **12**. In the case of acyclic receptor **3** the organisation induced by the 1,3-phenylene spacer and 2-aminophenylthio units and its flexibility generates optimal binding and selectivity towards Ag^+. However, in cyclic receptors **3** and **12** though the three thioether units are better organised, the inward placement of the NH_{amide} units restricts the entry of Ag^+ into the cavity and lowers both the order of binding and selectivity. The lack of binding ability in **7** due to an intramolecular NH_{amide}—N_{py} H-bond is restored in the *N*-benzyl derivative **5**.

Introduction

The development of fast estimation, removal and separation techniques for Ag^+, the use of Ag^+ complexes in photographic materials and their potential use in cancer radioimmunotherapy have drawn the attention of supramolecular chemists towards Ag^+ selective receptors [2]. For their design, structural parameters such as the presence of appropriately placed 2–4 soft ligating sites, the minimal incorporation of hard ligating sites (ether, ester etc.) [3–8], the induction of conformational and stereochemical restrictions to avoid 2:1 complexation [9–11] towards Pb^{2+} and cavity engineered complexation [12–13], have been delineated. In our recently reported silver selective receptors [1, 4] (Figure 1, Model I and II) we observed that in receptors I, segment A induces selectivity of Ag^+ binding but segment B adversely affects the same due to its flexibility. In receptors II, the 2-aminophenylthio unit keeps the thioether lone pair towards the interior of the cavity for favoured Ag^+ binding but the preferred binding of the ether units with alkali and alkaline earth cations disfavour binding of Ag^+ selectively. So, we envisaged that if part B (—SCH_2CH_2O—) of model I is replaced by part B (2-aminophenylthio unit) of model II, the resulting receptors III would show higher complexation and selectivities towards Ag^+.

In the present investigations, based on model III, the receptors **5–9**, **12** and **13** possessing two thioether or three thioether or two thioether and amine unit as soft ligating sites and acyclic receptors **3**, **4** and **11** have been synthesized and their binding behaviours towards Ag^+, Pb^{2+}, Tl^+, alkali and alkaline earth cations (extraction and transport) and mode of participation of the various ligating sites in binding (^{13}C NMR) have been studied.

Experimental

Synthesis of receptors **3** *and* **11***: A general procedure*

A solution of 1,3-bis(bromomethylene)benzene (1) (2.00 g, 7.6 mmol) and 2-aminothiophenol (**2**) (2.3 g, 2.4 mmol) in DMF (dry, 50 mL) containing K_2CO_3 (anhyd) (5 g, 36.23 mmol) and tetrabutyl ammonium hydrogensulphate (TBA-HSO_4) (10mg) was stirred. After completion of the reaction (TLC, 10 h), the solid suspension was filtered off and washed with ethyl acetate (100 mL). The combined filtrate was distilled under vacuum. The residue was chromatographed over silica gel column using hexane and its mixtures with ethyl acetate as eluents to isolate diamine 3. A similar reaction for 1,4-bis(bromomethylene)benzene (**10**) with **2** gave **11**.

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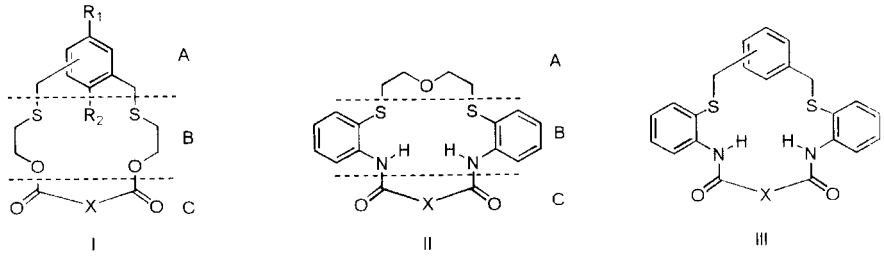


Figure 1. The structures of models I, II and III.

Receptor **3**: (82%), liquid, M^+ *m/z* 352 (M^+,100), 228 (M^+-$SC_6H_4NH_2$, 89.8); ^{1}H NMR ($CDCl_3$): δ 3.79 (s, 4H, 2 × CH_2), 6.52–6.69 (m, 4H, ArH), 6.90–7.19 (m, 8H, ArH); ^{13}C NMR (normal/DEPT-135): δ 39.39 (−ve, CH_2), 114.78 (+ve, CH), 117.24 (ab, ArC), 118.37 (+ve, CH), 127.45 (+ve , ArCH), 128.23 (+ve, ArCH), 129.31 (+ve , ArCH), 129.97(+ve, ArCH), 136.47 (+ve, ArCH), 138.29 (ab, ArC), 148.48 (ab, ArC); IR ν_{max} ($CHCl_3$) (cm^{-1}): 3980, 3482 (doublet, NH_2).

Receptor **11**: (60%), m.p. 104–106 °C ($CHCl_3$); M^+ *m/z* 352 (M^+, 11); ^{1}H NMR ($CDCl_3$): δ 3.63 (bs, 4H, 2 × NH_2), 3.82 (s, 4H, 2 × CH_2), 6.55–6.67 (m, 4H, ArH), 6.97 (s, 4H, ArH), 7.04–7.18 (m, 4H, ArH); ^{13}C NMRC (normal/DEPT-135) ($CDCl_3$): δ 39.26 (−ve, CH_2), 114.81 (+ve, ArCH), 117.19 (ab, ArC), 118.39 (+ve, ArCH), 128.78 (+ve, ArCH), 129.98 (+ve, ArCH), 136.48 (+ve, ArCH), 137.06 (ab, ArC), 148.58 (ab, ArC); IR ν_{max} (cm^{-1}): 3250 (NH). (*Found*: C 67.9; H 5.7; N 7.9; S 17.95. $C_{20}H_{20}N_2S_2$ requires C 68.18; H 5.68; N 7.95 and S 18.18%)

Synthesis of receptor **4**

Diamine **3** (2.00 g, 5.68 mmol), benzaldehyde (1.33 g, 12.5 mmol) and a catalytic amount of *p*-toluenesulphonic acid were dissolved in dry benzene (150 mL) and the mixture was refluxed on a water bath. After completion of the reaction (7 h), benzene (100 mL) was removed by distillation. Ethanol (75 mL) was added to the cooled reaction mixture. $NaBH_4$ was added and stirring was continued for 6 h. The reaction mixture was diluted with water (500 mL) and extracted with chloroform. Solvent was removed and the residue was chromatographed over a silica gel column using hexane and its mixtures with ethyl acetate as eluents to isolate **4**, liquid, (65%), M^+ *m/z* 532 (M^+, 6), 441 (M^+-CH_2Ar, 19), 319 (M^+-$SC_6H_4NHCH_2C_6H_5$, 20), 105 ($CH_2C_6H_4CH_2^+$, 100); ^{1}H NMR ($CDCl_3$): δ 3.74 (s, 4H, 2 × SCH_2), 4.25 (s, 4H, 2 × N CH_2), 6.47–6.57 (m, 4H, ArH), 6.81–6.93 (m, 3H, ArH), 7.02–7.34 (m, 15H, ArH); ^{13}C NMR normal/DEPT-135) ($CDCl_3$): δ 39.77 (−ve, CH_2), 47.91 (−ve, CH_2), 110.41 (+ve, ArCH), 116.95 (+ve, ArCH), 117.11 (ab, ArC), 127.17 (+ve, ArCH), 127.51 (+ve, ArCH), 128.32 (ab, ArC), 128.62 (+ve, ArCH), 129.33 (+ve, ArCH), 130.39 (+ve, ArCH), 136.62 (+ve, ArCH), 138.35 (ab, ArC), 139.16 (ab, ArC), 149.21 (ab, ArC); IR ν_{max} (KBr) (cm^{-1}): 1655 (C=O), 3490 (NH).

Synthesis of receptors **5–8**, **12** *and* **13***: A General procedure*

Diamine **3** (2.00 g, 5.68 mmol), K_2CO_3 (anhyd.) and a catalytic amount of TBA-HSO_4 (10 mg) were taken in dry dichloromethane (400 mL) and the reaction was stirred at room temperature. Thiodiglycolyl dichloride (2.33 g, 12.5 mmol) dissolved in dichloromethane (75 mL) was added dropwise, over 3-4 hrs. After completion of the reaction (TLC, 10 h), the suspended solid was filtered off and washed with chloroform (2 × 10 mL). The combined filtrate was distilled off. The crude reaction product was crystallized from $CHCl_3$—CH_3OH mixture to isolate **6**.

Similarly, cyclocondensation of diamine **3** with pyridine-2,6-dicarbonyl dichloride and isophthaloyl dichloride gave receptors **7** and **8**, and diamine **11** with thiodiglycolyl dichloride and isophthaloyl dichloride gave receptors **12** and **13**, respectively. The cyclocondensation of receptor **4** with pyridine-2,6-dicarbonyl dichloride gave receptor **5**.

Receptor **5**: (55%), m.p. 101 °C; FAB mass M^+ *m/z* 664 (M^+ + 1); ^{1}H NMR ($CDCl_3$): 3.66–4.45 (m, 4H, SCH_2), 5.44–5.65 (m, 2H, CH_2), 5.44–5.65 (m, 2H, CH_2), 6.31–6.59(m, 4H, ArCH), 6.82–7.44 (m, 8H, ArH), 7.56–8.38 (m, 3H, PyH). IR ν_{max} (KBr) (cm^{-1}): 1660 (C=O). (*Found*: C, 74.1; H 5.0; N 6.6. $C_{41}H_{33}N_3O_2S_2$ requires C, 74.21; H 4.97; N 6.33%).

Receptor **6**: (45%), m.p. 238 °C ($CHCl_3$—MeOH); M^+ *m/z* 466 (M^+, 15); ^{1}H NMR ($CDCl_3$): δ 3.42 (s, 4H, 2 × SCH_2), 3.91 (s, 4H, 2 × CH_2), 6.87–7.04 (m, 3H, ArH), 7.16 (t, J = 7.6 Hz, 2H, ArH), 7.33(t, J = 7.6 Hz, 2H, ArH), 7.65 (d, J = 7.6 Hz, 2H, ArH), 8.26 (d, J = 7.6 Hz, 2H, ArH), 8.91 (bs, 2H, NH); ^{13}C NMR (normal/DEPT-135) ($CDCl_3$): δ 37.55 (−ve, CH_2), 39.84 (−ve, CH_2), 120.97 (+ve, ArCH), 123.79 (ab, ArC), 125.09 (+ve, ArCH), 127.65 (+ve, ArCH), 128.03 (+ve, ArCH), 129.12 (+ve, ArCH), 130.15 (+ve, ArCH), 135.52 (+ve, ArCH), 138.89 (ab, ArC), 139.50 (ab, ArC), 165.66 (ab, C=O); IR ν_{max} (KBr) (cm^{-1}): 1655 (C=O), 3450 (NH). (*Found*: C 61.4; H 4.8; N 5.8; S, 20.3. $C_{24}H_{22}N_2O_2S_3$ requires C 61.80; H 4.72; N 6.01; S 20.6%).

Receptor **7**: (60%), m.p. 188 °C ($CHCl_3$-*n*-hexane); M^+ *m/z* 483 (M^+, 30), 349 (M^+-$HCOC_3H_4CO$, 5), 226 ($H_2CC_6H_4CH_2SC_6H_4N$, 100); ^{1}H NMR ($CDCl_3$): δ 3.95 (s, 4H, 2 × SCH_2), 6.92 (bs, 3H, ArH), 7.22 (dt, J_1 = 7.8 Hz, J_2 = 1.2 Hz, 2H, ArH), 7.37 (dt, J_1 = 7.6 Hz, J_2 = 1.5 Hz, 2H, ArH), 7.74 (dd, J_1 = 7.6 Hz, J_2 = 1.5 Hz, 2H, ArH), 8.01 (dd, J_1 = 7.8 Hz, J_2 = 1.2 Hz, 2H, ArH), 8.17 (t, J = 7.6

Table 1. Extraction (%) profile of receptors **3–9** and **11–13**

M^{n+}	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**11**	**12**	**13**
Li^+	0.62	0.24	0.08	0.04	0.04	0.24	–	0.01	0.51	0.02
Na^+	0.61	0.28	0.07	0.02	0.04	0.58	–	0.00	0.40	0.49
K^+	0.60	0.28	0.11	0.6	0.04	0.88	–	0.03	0.39	0.18
Tl^+	0.62	0.26	2.15	0.04	0.11	0.72	–	0.05	0.53	0.29
Mg^{2+}	0.35	0.18	0.05	0.12	0.02	0.14	–	0.01	0.42	0.20
Ca^{2+}	0.34	0.15	0.80	0.04	0.04	0.86	–	0.05	0.38	0.16
Sr^{2+}	0.36	0.18	0.87	0.02	0.05	0.38	–	0.01	0.40	0.00
Ba^{2+}	0.40	0.20	0.72	0.00	0.05	0.80	–	0.01	0.42	0.26
Pb^{2+}	0.09	0.27	53.5	1.24	0.46	1.92	0.11	0.28	0.34	0.87
Ag^+	97.67	36.5	56.1	78.0	6.90	2.88	16.0	59.4	47.8	1.8
Ag^+/Pb^{2+}	1085	135	1.04	63	15	1.5	145	212	141	2

Hz, 1H, PyH), 8.51 (d, J = 7.6 Hz, 2H, PyH), 10.51 (bs, 2H, 2 × NH); ^{13}C NMR (normal/DEPT-135) ($CDCl_3$): δ 41.72 (−ve, CH_2), 122.88 (+ve, ArCH), 125.58 (+ve, ArCH), 126.21 (+ve, ArCH), 128.07 (+ve, ArCH), 128.38 (ab, ArC), 129.72 (+ve, ArCH), 135.40 (+ve, ArCH), 137.74 (ab, ArC), 138.84 (ab, ArC), 139.59 (+ve, ArCH), 148.65 (ab, ArC), 161.33 (ab, C=O); IR ν_{max} (KBr) (cm^{-1}): 1655 (C=O), 3450 (NH). (*Found*: C 66.9; H 4.4; N 8.7, S 13.0. $C_{27}H_{21}N_3O_2S_2$ requires C 67.08; H, 4.35; N 8.69; S 13.25%).

Receptor **8**: (75%), m.p. 185 °C; M^+ *m/z* 482 (M^+, 29); ^{1}H NMR ($CDCl_3$): δ 4.02 (s, 4H, 2 × SCH_2), 6.88–7.25 (m, 5H, ArH), 7.38–7.46 (m, 3H, ArH), 7.67–7.75 (m, 4H, ArH), 8.19 (d, J = 7.6 Hz, 2H, ArH), 8.34 (d, J = 7.6 Hz, 2H, ArH), 8.91 (bs, 2H, 2 × NH); ^{13}C NMR (normal/DEPT-135) ($CDCl_3$): δ 41.65 (−ve, CH_2), 121.50 (+ve, ArCH), 121.72 (+ve, ArCH), 124.62 (ab, ArC), 125.18 (+ve, ArCH), 127.62 (+ve, ArCH), 128.36 (+ve, ArCH), 128.60 (+ve, ArCH) 129.61 (+ve, ArCH), 130.15 (+ve, ArCH), 132.49 (+ve, ArCH), 134.50 (+ve, ArCH), 135.57 (ab, ArC), 138.27 (ab, ArC), 139.01 (ab, ArC), 165.02 (ab, C=O); IR ν_{max} (KBr) (cm^{-1}); 1682 (C=O), 3450 (NH). (*Found*: C 69.8; H 4.3; N 5.7; S 13.7. $C_{28}H_{22}N_2O_2S_2$ requires C 69.71; H 4.56; N 5.81; S 13.28%).

Receptor **12**: (45%); m.p. 169 °C ($CHCl_3$—MeOH); M^+ *m/z* 466 (M^+, 16); ^{1}H NMR ($CDCl_3$): δ 3.30 (s, 4H, 2 × CH_2), 3.89 (s, 4H, 2 × CH_2), 6.84 (s, 4H, ArH), 7.13 (dt, J_1 = 7.6 Hz, J_2 = 1.4 Hz, 2H, ArH), 7.31 (dt, J_1 = 7.6 Hz, J_2 = 1.4 Hz, 2H, ArH), 7.64 (dd, J_1 = 7.6 Hz, J_2 = 1.4 Hz, 2H, ArH), 8.20 (d, J = 8 Hz, 2H, ArH), 8.72 (bs, 2H, 2 × NH); ^{13}C NMR (normal/DEPT-135) ($CDCl_3$): δ 37.00 (−ve, CH_2), 42.03 (−ve, CH_2), 120.95 (+ve, ArCH), 123.89 (ab, ArC), 125.05 (+ve, ArCH), 128.45 (+ve, ArCH), 129.94 (+ve, ArCH), 135.46 (+ve, ArCH), 138.08 (ab, ArC), 139.70 (ab, ArC), 166.10 (ab, C=O); IR ν_{max} (KBr) (cm^{-1}): 1698 (C=O), 3500 (NH). (*Found*: C 61.7; H 5.0; N 5.8, S 20.2. $C_{24}H_{22}N_2O_2S_3$ requires C 61.80, H 4.72; N 6.01; S 20.6%).

Receptor **13**: (80%), m.p. 193 °C ($CHCl_3$); M^+ *m/z* 482 (M^+, 7); ^{1}H NMR ($CDCl_3$): δ 3.88 (s, 4H, 2 × CH_2), 6.74 (s, 4H, ArH), 7.04 (s, 1H, ArH), 7.23 (dt, J_1 = 7.6 Hz, J_2 = 1.5 Hz, 2H, ArH), 7.48 (dt, J_1 = 7.6 Hz, J_2 = 1.5 Hz, 2H, ArH), 7.62 (t, J = 8.0 Hz, 1H, ArH), 7.76 (dd, J_1 = 7.6 Hz, J_2 = 1.5 Hz, 2H, ArH), 8.07 (dd, 2H, J_1 = 7.9 Hz, J_2 = 1.6 Hz, ArH), 8.52 (dd, J_1 = 8.8 Hz, J_2 = 1.5Hz, 2H, ArH), 8.84 (s, 2H, NH); ^{13}C NMR (normal/DEPT-135) ($CDCl_3$): δ 42.90 (−ve, CH_2), 120.26 (+ve, ArCH), 121.55 (+ve, ArCH), 124.00 (ab, ArC), 125.05 (+ve, ArCH), 127.85 (+ve, ArCH), 129.71 (ab, ArC), 130.13 (+ve, ArCH), 131.70 (+ve, ArCH), 135.83 (ab, ArC), 135.07 (+ve, ArCH), 138.94 (ab, ArC), 140.30 (ab, ArC), 165.02 (ab, C=O); IR ν_{max} (KBr) (cm^{-1}): 1682 (C=O), 3500 (NH). (*Found*: C 69.3; H 4.6; N 5.7; S 13.0. $C_{28}H_{22}N_2O_2S_2$ requires C 69.71; H 4.56; N 5.81; S 13.28%).

Synthesis of receptor **9**

A 250 mL two neck round bottom flask was fitted with a magnetic stirbar, a reflux condenser , and an addition funnel. The flask was charged with $NaBH_4$ (0.79 g, 20.8 mmol) and THF (50 mL, pre-dried over sodium). Receptor **8** (2.00 g, 4.14 mmol) was added in one portion and the flask was cooled to 0 °C in an ice bath. A solution of iodine (2.11 g, 8.3 mmol) in THF (20 mL) was added dropwise over 30 min resulting in vigorous evolution of hydrogen. After addition was complete and gas evolution had ceased, the reaction mixture was refluxed for 30 h, cooled to room temperature and methanol was added cautiously until the mixture became clear. After stirring (30 min), the solvent was removed leaving a white paste, which was dissolved in 20% aqueous KOH (30 mL). The solution was stirred for 4 h and extracted with chloroform (3 × 30 mL). The solvent was evaporated and the crude product was chromatographed over a silica gel column using hexane and its mixtures with ethyl acetate as eluents to isolate **9** (20%); m.p 161 °C ($CHCl_3$); M^+ *m/z* 454 (M^+, 47) ; ^{1}H NMR ($CDCl_3$): δ 3.64 (s, 4H, 2 × SCH_2), 4.43 (d, J = 5.2 Hz, 4H, 2 × NCH_2), 5.47 (t, 2H, J = 5.2 Hz, 2 × NH), 6.09 (s, 1H, ArH), 6.36 (t, J = 8.1 Hz, 2H, ArH), 6.51 (d, J = 8.1 Hz, 2H, ArH), 6.89–7.23 (m, 10H, ArH), 7.44 (s, 1H, ArH); ^{13}C NMR (normal/DEPT-135) ($CDCl_3$): δ 36.11 (−ve, CH_2), 48.52 (−ve, CH2), 110.27 (+ve, ArCH), 116.57 (+ve, ArCH), 116.95 (ab, ArC), 125.32 (+ve, ArCH), 126.70 (+ve, ArCH), 127.06 (+ve, ArCH), 128.26 (+ve, ArCH),

Table 2. Transport profile* of receptors **3–6** and **11–12**

M^{n+}	**3**	**4**	**5**	**6**	**11**	**12**
Li^+	2.93	1.80	10.6	20.39	80.34	5.03
Na^+	2.02	1.67	10.3	17.98	95.96	6.71
K^+	2.04	1.87	10.4	16.09	52.89	6.53
Tl^+	3.21	4.68	23.7	16.70	65.11	8.03
Mg^{2+}	1.45	1.45	10.3	11.33	119.15	3.55
Ca^{2+}	1.89	1.83	12.4	11.11	118.57	4.47
Sr^{2+}	1.37	2.10	8.2	7.32	86.10	2.93
Ba^{2+}	1.23	1.19	12.1	10.51	70.37	1.85
Pb^{2+}	6.31	8.86	361	122.50	99.53	158.59
Ag^+	245	85.95	524	209.48	206.99	96.22

* $\times 10^{-8}$ mol 24 h^{-1}.

128.78 (+ve, ArCH), 130.17 (+ve, ArCH), 130.40 (+ve, ArCH), 136.98 (+ve, ArCH), 137.10 (ab, ArC), 140.22 (ab, ArC), 149.32 (ab, ArC). (*Found*: C 74.3; H 5.78; N 6.0; S 13.7. $C_{28}H_{26}N_2S_2$ requires C 74.01; H 5.73; N 6.01; S 14.1%)

Extraction measurements [14]

For the extraction experiments, metal picrate solutions (0.01 mol dm^{-3}) were prepared in deionised distilled water. The solutions of receptors (0.01 mol dm^{-3}) were prepared in chloroform (A.R. grade). An aqueous solution (2 mL) of a metal picrate (0.01 mol dm^{-3}) and a chloroform solution (2 mL) of a receptor (0.01 mol dm^{-3}) in a cylindrical tube closed with a septum was shaken for 5 min and kept at 27 ± 1 °C for 3–4 h. An aliquot of the 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 the metal picrate has been calculated as the percentage of metal picrate extracted in the chloroform layer and the values are the mean of three independent measurements which were within ±0.02% error. (Table 1).

Transport measurements [15]

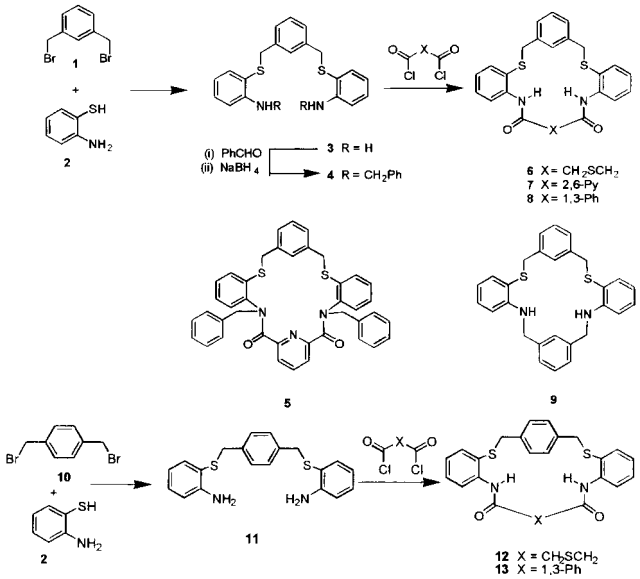
The transport experiments were carried out at constant temperature (27 ± 1 °C) in a cylindrical glass cell consisting of outer and inner jackets by using (i) metal picrate (0.01 moles dm^{-3}) in water (3 mL) in the inner jacket; (ii) water (10 mL) in the outer jacket; (iii) ligand (10 mmol dm-3) in the chloroform layer (15 mL) with stirring (150 ± 5 r.p.m.) at 27 ± 0.05 °C. After stirring for 6 h the picrate transported into the receiving phase was determined from UV absorption at 355 nm. Each value is a mean of three experiments which were consistent ±10% (Table 2). Before determining the transport rates, blank experiments were performed in the absence of carrier receptor in the chloroform layer to check the leakage of metal picrates. A significant leakage (50 mol 24 h^{-1}) was observed only in the case of Pb^{2+}.

Results and discussion

Synthesis

The phase transfer catalysed (K_2CO_3-DMF-TBA HSO_4) nucleophilic displacement of 1,3-bis(bromomethyl)benzene (**1**) with 2-aminothiophenol (**2**) gives compound **3** (82%), liquid, MS *m/z* 352 (M^+), which on reaction with benzaldehyde followed by $NaBH_4$ reduction gives **4** (65%), liquid, MS *m/z* 532 (M^+). The slow addition of thiodiglycolyl dichloride to a stirred solution of **3** in dichloromethane containing a suspension of K_2CO_3 (anhyd. base), TBA HSO_4 (catalyst) at 35 °C provides white solid **6** (45%), m.p. 238 °C, MS *m/z* 466 (M^+). Similarly, diamines **3** and **4** with pyridine-2,6-dicarbonyl dichloride and **3** with isophthaloyl dichloride under PTC conditions give **7** (60%), m.p. 188 °C , MS *m/z* 483 (M^+), 5 (20%), m.p. 161°C , MS m/z 454 (M^+) and **8** (75%), m.p. 185 °C, MS *m/z* 482(M^+), respectively. Receptor **8** on reduction with $NaBH_4/I_2$ in THF provides receptor **9** – a cyclic analog of **3/4**.

The reaction of **10** with 2-aminothiophenol under PTC conditions provides **11** (90%), m.p. 104-106 °C, MS *m/z* 352 (M^+) which on macrocyclization with thiodiglycolyl dichloride and isophthaloyl dichloride gives **12** (45%), m.p. 169 °C, MS *m/z* 466(M^+) and **13** (80%), m.p. 193 °C, MS *m/z* 482 (M^+), respectively.



The SCH_2CO and NH_{amide} proton singlets in the 1,4-phenylene based receptor **12** are shifted upfield by $\Delta\delta$ 0.12 and 0.19 ppm in comparison with those in the 1,3-phenylene based receptor **6**. Similarly, the isophthaloyl 2′-H singlet in receptor **13** is shifted upfield by $\Delta\delta$ 0.64 ppm than in receptor **8**, indicating that this proton is directed towards the receptor cavity and the region is shielded by the magnetically anisotopic 1,4-phenylene ring. Therefore, in **12** and **13**, the 1,4-phenylene ring is oriented perpendicular to the plane of the macrocycle, whereas the 1,3-phenylene ring of **6-8** is in the plane of the macrocycle. Further, the downfield shift ($\Delta\delta > 1.50$ ppm) of the NH_{amide} singlet in receptor **7** in comparison with the other cyclic receptors **6**, **8**, **12** and **13**

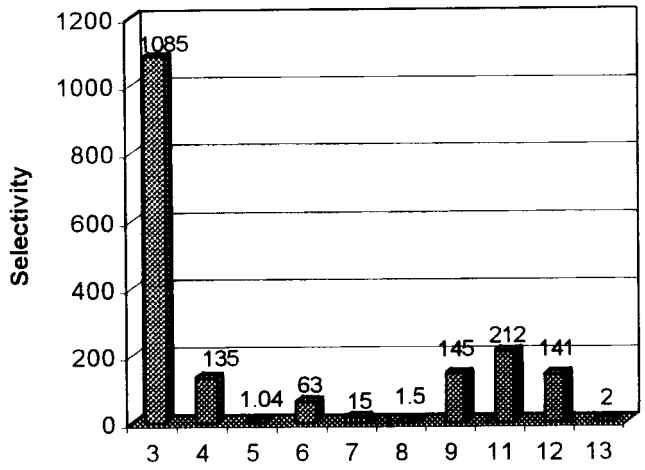


Figure 2. Ag^+/Pb^+ extraction selectivities for receptors **3–9** and **11–13**.

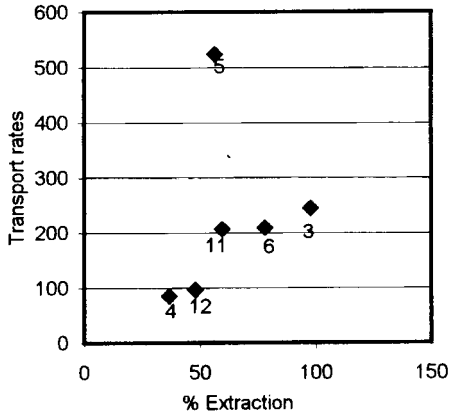
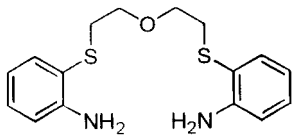


Figure 3. Plot of extraction (%) vs. transport rates ($\times 10^{-8}$ 24 h^{-1}) of Ag picrate by receptors **3–6** and **11–12**.

shows that in **7** the pyridine N is involved in H-bonding with NH_{amide} and may not be available for complexation with metal ions.

Extraction [14] and transport studies [15]

As the process of ligand facilitated transport of cations across apolar membrane has relevance to the development of separation techniques for the cations, the extraction (complexation) and transport (complexation - decomplexation) properties of receptors **3–9** and **11–13** towards Ag^+, Pb^{2+}, Tl^+, alkali (Li^+, Na^+, K^+) and alkaline earth (Mg^{2+}, Ca^{2+}, Sr^{2+} and Ba^{2+}) cations have been determined (Tables 1 and 2). These receptors (**3–9**, **11–13**) possess two alkyl aryl thioether units as common binding sites alongwith the combination of additional thioether, amine (NH_2)/amide or pyridine unit(s) and show some selectivity towards Ag^+ over other cations. The acyclic receptors **3**, **4** and **11**, due to their dynamic structural adaptability, show a higher extraction order as well as Ag^+/Pb^{2+} selectivity. In the cyclic systems **6–8**, **12** and **13**, the soft ligating sites are appropriately placed for complexation with Ag^+ but amide protons filling the cavity have to be displaced before complexation takes place. So, both the order of extraction and the selectivity towards Ag^+ is lowered (Figure 2). Comparison of the extraction and transport results (Figure 3) of Ag^+ shows that the increased extraction is by and large coupled with increased transport rates, which in the case of receptors **3** and **11** could be attributed to their more dynamic nature. The receptors **3**, **4**, **6**, **11** and **12** which have a similar geometry show a nearly linear increase in transport rates with an increase in extraction but **5**, which has a different geometry from the other receptors, shows a higher order of transport efficiency.



14

ext. Ag pic 79.65%
Ag^+/Pb^{2+} Sel. = 78

Amongst the acyclic receptors, **3** possessing four ligating sites (2 × NH_2, 2 × S) extracts 97.67% of the silver picrate from its aqueous solution whereas other cations are extracted by <0.6%. So, **3** extracts Ag^+ nearly 257 and 1085 times greater than similar sized Sr^{2+} and Pb^{2+}. Receptor **3** transports Ag^+ nearly 179 and 39 times more efficiently than the similar sized Pb^{2+} and Sr^{2+}. Therefore, the organisation of ligating sites on replacement of the CH_2OCH_2 unit of **14** [1] with the 1,3-phenylene spacer increases both the extraction and selectivity towards Ag^+. The 1,4-phenylene based receptor **11** extracts Ag^+ 59.4% and nearly 212 times more than Pb^{2+} in transport, but selectivity is not observed. **4** extracts Ag^+ 37% nearly one third of the extraction by **3**. In extraction experiments, **4** shows Ag^+/Pb^{2+} selectivity of the order of 135 which is lowered to only 10 in transport.

The cyclization of diamines **3** and **11** to receptors **6** and **12** decreases the number of participating ligating sites from four to three. The receptors **6** and **12** extract 78 and 48% Ag^+ picrate and exhibit a Ag^+/Pb^{2+} selectivity of the order of 63 and 140 , significantly lower than their acyclic precursors **3** (1085) and **11** (212). The energy minimizations of macrocycles **6** and **12** show that for complexation of the three thioether units with Ag^+ picrate, the amide NH units have to move out. So, in macrocycles **6** and **12** a considerable change in conformation occurs during complexation which decreases both the extraction and selectivity.

The poor extraction of Ag^+ (6.9%) and other metal ions (<2%) by **7** could be attributed to the non-availability of the pyridine N for complexation due to the presence of the PyN—HN_{amide} H-bond. Similar poor extraction of metal ions by macrocycles **8** and **13** points to the detrimental role of amide NH in complexation with metal ions.The replacement of the amide NH with N_{benzyl} in receptor **5** makes the

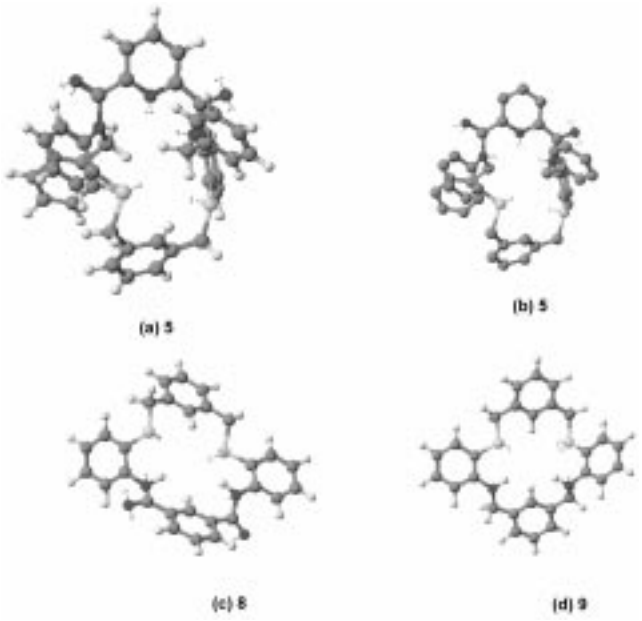


Figure 4. The energy minimized structures of receptors (a) **5**, (b) **5** shown without hydrogens (c) receptor **8** and (d) receptor **9**.

pyridine N available for complexation and restores its extraction capability for Ag^+. However **5** extracts Pb^{2+} with nearly similar effficiency as for Ag^+ and Ag^+/Pb^{2+} selectivity is lost. The reduction of **8** to diamine derivative **9** also results in an increase in the extraction of Ag^+ and a decrease in the extraction of Pb^{2+}. The extraction of Ag^+ by **9** is less than for the acyclic diamines **3/4**.

In order to rationalise the loss of Ag^+ selectivity in **5** and the poor extraction ability of **9**, the energy minimized conformations of receptors **5**, **8** and **9** have been computed by using PM3 calculations available in the CAChe 3.1 software (Figure 4). The conformation of **8** shows that the amide NH fills the cavity and due to the amide C—N partial double bond character and rigidity of the isophthaloyl group, the NH groups cannot be moved out of the cavity. Receptor **9** in its conformation shows that the amine NH groups also lie in the cavity and to make the nitrogen lone pair to participate in binding with Ag^+, amine hydrogens have to be moved out. But due to the C—N single bond, this rotation is easier than in the case of **8** and so the complexation order in **9** is increased, but it is still lower than that found in the acyclic analogs **3** and **4**. In the case of receptor **5**, during synthesis, the bulk of the benzyl groups on the amide N pushes the benzyl groups out of the cavity. The energy minimised conformations **5A** and **5B** (H not shown) (Figure 4) show that the cavity is quite open and the lone pairs of two thioether, two amide and one PyN unit all point inwards to the cavity and so induce complexation. However, due to the lack of any restriction and availability of five ligating sites, the binding selectivity towards Ag^+ over Pb^{2+} is lost.

Therefore, as receptors with two ligating sites are poor ionophores, three or four ligating sites are essential for optimal binding of Ag^+. As visualized in design III, 2-aminothiophenol and 1,3- and 1,4-phenylene units, due to a combination of steric and conformational control, induce Ag^+/Pb^{2+} selectivity in both acyclic and cyclic receptors. The presence of amide NH in the cavity also constitutes a major deterimental factor for Ag^+ complexation of cyclic receptors.

Complexation studies through ^{13}C NMR spectroscopy

In ^{13}C NMR titrations, the addition of Ag picrate to $CDCl_3$-DMF solutions of these receptors cause significant changes in chemical shifts but addition of other metal picrates does not cause any change. These results signify the higher binding orders of receptors with Ag^+ in comparison with other metal picrates which is in consonance with the extraction and transport results. ^{13}C NMR titration (Ag pic. vs. $\Delta\delta$) coordination shifts of various carbon signals of receptors **3**, **6**, **11** and **12** show that these receptors form 1 : 1 complexes with Ag picrate. On addition of Ag picrate in acyclic receptors **3** and **11**, the SCH_2 and 2-aminothiophenol unit carbons undergo significant changes in chemical shifts but the *m*- or *p*-phenylene carbons remain more or less unaffected (not included in Table 3). Therefore, the 2-aminophenylthio unit coordinates with Ag^+. In cyclic receptors **6** and **12**, the 2-aminophenylthio ring carbons and the SCH_2CO unit of the thiodiglycolyl unit are affected and the 1,3- and 1,4-phenylene ring carbons again remain unaffected. Therefore, all three —S— units seem to coordinate with Ag^+. In these receptors, the addition of Ag picrate shifts the SCH_2 and ArCH signals downfield but the Ar carbons attached to —S— or NH_2 are shifted upfield. The latter observation again points to the formation of $ArC^-—S^+$ and $ArC^-—N^+$ ylids through π-electron shift on complexation of S or NH_2 with Ag^+.

In consonance with the observations of computer modelled structures of cyclic receptors **6** and **12** that the presence of amide NH units in the cavity is detrimental to the entry of Ag^+ due to their electropositive character and during complexation with Ag^+, the $NHCOCH_2SCH_2CONH$ unit has to undergo considerable conformational changes. Therefore, only thioether units participate in complexation with Ag^+, which is quite evident from the marginal coordination shifts observed for the N—ArC and S—ArC carbon signals. The SCH_2 carbon signals show smaller changes in chemical shifts in cyclic receptors (**6**, **12**) than in acyclic receptors (**3**, **11**) which is in parallel with the extraction and transport results.

In conclusion the receptors **3**, **6**, **11** and **12** show binding selectivity towards Ag^+. In the case of receptor **3** the organisation achieved through the combination of a 1,3-phenylene spacer and 2-aminophenyl thio units increase both the order of binding and the selectivty towards Ag^+. In cyclic receptors though, the organisation of three thioether units takes place, the placement of NH_{amide} units restricts the entry of Ag^+ into the cavity and lowers both the order of binding and selectivity. The replacement of amide NH with N benzyl however causes drastic change in the geometry of the receptor which does not augur well for selective binding.

Table 3. Ag picrate (1 eqiv.) induced ^{13}C NMR coordination shifts ($\Delta\delta_c$ ppm) of receptors **3**, **6**, **11** and **12**

Receptor	SCH_2	SCH_2	ArCH	ArCH	ArCH	S—Car	N—Car	C=O
3	1.131	–	2.806	2.461	0.763	−0.512	−1.826	–
11	1.391	–	1.756	1.235	0.341	−0.151	−1.078	–
6	0.506	−0.055	1.784	1.096	0.287	−1.219	−0.152	0.32
12	0.643	0.691	2.303	0.314	−0.51	−1.264	−0.46	0.515

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