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New Macrocyclic Ligands. XIV*
Synthesis and X-Ray Structures of Potentially Pentadentate Ligands Incorporating Non-Symmetrically Arranged N_4S-, N_3OS-, N_2O_2S- and N_2S_2O-Heteroatoms

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The synthesis and characterization of new mixed-donor macrocyclic ligands incorporating nitrogen, sulfur and/or oxygen heteroatoms are described. The new 17- or 18-membered macrocyclic rings contain unsymmetrical arrangements of their heteroatoms in contrast to related, previously reported rings in which the donor sets are arranged symmetrically. The X-ray structures of the 17-membered rings incorporating N_4O- and N_4S-donor sets are presented.

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Introduction

In previous studies an extended series of macrocyclic rings of type (1) (see Diagram 1), incorporating oxygen, nitrogen and/or sulfur heteroatoms, and *symmetrical* arrangements of their donor atom sets, has been synthesized.[1] These rings were employed to investigate structure–function relationships underlying discrimination behaviour within the metal ion series: cobalt(II), nickel(II), copper(II), zinc(II), cadmium(II), silver(I) and lead(II). Several examples of such discrimination have been observed and investigated; for example, by means of stepwise 'tuning' of the donor set present within the above ligand category, it has been possible to achieve greater than 10^9 discrimination for silver(I) over lead(II)[2] (two metals that occur together in nature). The mixed-donor ligands of this type tend to yield 1:1 (metal to ligand) complexes with the above metal ions, with the complexes not showing the sluggish kinetic behaviour that is often characteristic of all-nitrogen donor macrocyclic systems.[3,4] Both these properties tend to simplify the experimental determination of reliable log *K* values.[5]

As part of an overall strategy designed to understand more fully the nature of discrimination behaviour of the above type, the new macrocyclic systems (2)–(8), closely related to those of type (1), but incorporating a *non-symmetrical* arrangement of their donor atom sets, are now reported. Apart from the general desire to extend the previous metal-ion discrimination studies, log *K* values for the new

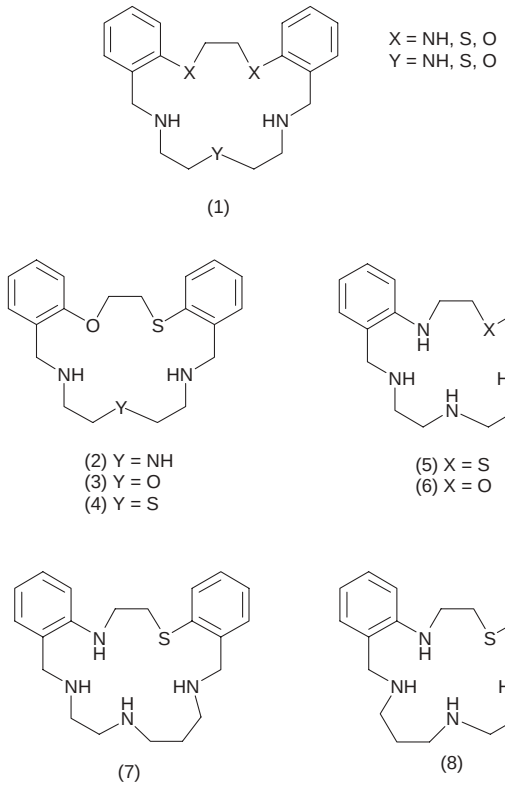

Diagram 1

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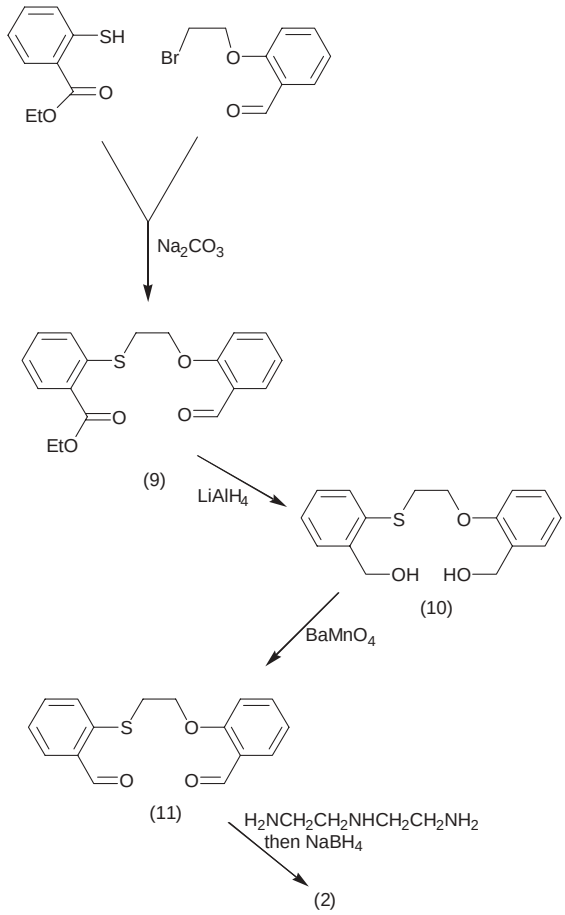
ligands would serve as additional data for use in an ongoing project concerned with the computation of free energies of metal complexation for systems of the present type. The results of this latter study will be reported in due course.



Scheme 1

Results and Discussion

The synthesis of the unsymmetrical *S*,*O*-dialdehyde (11) (see Scheme 1) was based on the earlier published syntheses of the corresponding S_2-dialdehyde.[6] Lower symmetry in the molecule was introduced by means of a Williamson ether condensation of the ethyl ester derivative of thiosalicylic acid and 2-(2-bromoethoxy)benzaldehyde.[7] The resulting intermediate (9) was easily reduced with lithium aluminium hydride to the corresponding diol (10), which was subsequently oxidized to the dialdehyde (11) with barium manganate.[8]

Related procedures were employed to obtain the amine-containing dialdehydes (16) and (17) (see Diagram 2). For the first of these, the ethyl ester of thiosalicylic acid was again employed (Scheme 2). This was condensed with the mesylate (13) in the presence of potassium carbonate to yield (14); (13) was obtained by reaction of ethylene oxide with methylanthranilate in glacial acetic acid to yield the corresponding alcohol (12), which was then converted into (13) by reaction with methanesulfonyl chloride in the presence of triethylamine. Subsequent reduction of (14) with lithium aluminium hydride yielded the diol (15), and selective oxidation of this product with barium manganate gave (16).

The dialdehyde (17), incorporating a secondary amine and an ether functionality in its backbone, was obtained via intermediates (18) and (19) using a parallel procedure to the above, but starting from (13) and salicylaldehyde.

All macrocycles were obtained by condensation of the appropriate linear di- or tri-amine and the required dialdehyde, followed by in situ reduction using sodium borohydride—by way of illustration the sequence for (2) is shown in Scheme 1. In this context it needs to be noted that

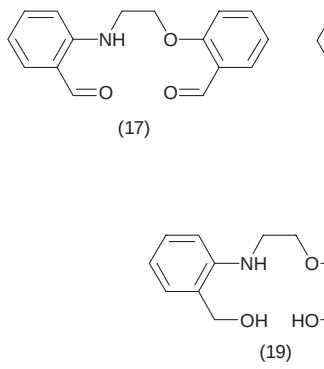
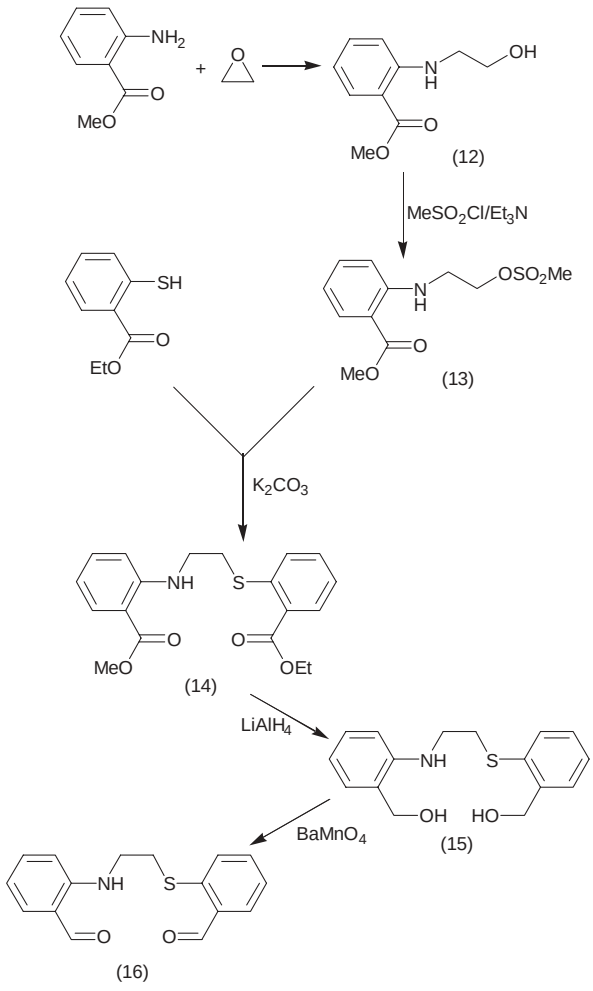


Diagram 2



Scheme 2

attempts to employ linear polyamines for Schiff base condensations have been shown in some cases to result in a secondary amine reacting in concert with one primary amine and an aldehyde group to yield a 1,3-diazapentane or a 1,3-diazacyclohexane derivative.[9] Nevertheless, reduction of such products leads to the generation of the required linear amine backbone incorporating only secondary amine groups.[10]

The infrared spectra of the respective macrocyclic products confirmed the absence of imine stretches, but all contained bands in the region 3300–3150 cm^{-1} that are attributable to the N–H stretching modes of secondary amines. The ^{1}H and ^{13}C nuclear magnetic resonance (NMR) spectra of the purified ligands also confirmed the absence of imine functions, and were as expected for the assigned structures. Similarly, where obtained, the mass spectra of the macrocyclic products did not contain peaks at *m/z* values greater than those expected for monomeric formulation of the respective rings.

Reaction of *N*-(2-aminoethyl)propane-1,3-diamine with the unsymmetrical dialdehyde (16) followed by reduction yielded a mixture of two isomeric macrocyclic products (7) and (8). The mixture was chromatographed on silica gel with (7) being eluted first. While pure (7) was readily obtained, (8) was obtained in approximately 80% purity. These isomers differ in the orientation in the macrocyclic ring on the fragment derived from *N*-(2-aminoethyl)propane-1,3-diamine. Isomer (7) has the propyl group orientated closest to the thioether group.

Table 1. ^{13}C NMR assignments and correlations for (7)[A]

^{13}C No.	δ ^{13}C	δ ^{1}H, mult.; *J* in Hz	^{1}H COLOC correlations
1	139.57	—	—
2	136.18	—	C3, C4
3	129.32	7.44, dd; 7.8, 1.0	—
4	127.30[B]	7.19, m	—
5	125.49[B]	7.10, m	C1
6	129.46	7.20, m	—
1′	123.63	—	—
2′	129.21	6.98, dd; 7.3, 1.3	—
3′	115.82	6.60, t; 7.4	—
4′	127.90	7.10, m	—
5′	109.47	6.56, br d; 7.9	—
6′	147.19	—	—
7	42.10	3.40, m	C6
8	34.20	3.25, m	C6
9	52.45	3.80, s	C1, C2, C6, C10
10	46.44	2.65, m	—
10′	27.52	1.62, m	C10
11	46.94	2.65, m	—
12	48.78	2.65, m	—
13	48.46	2.65, m	—
14	53.45	3.71, s	C1′, C2′, C6′, C13

[A] Assignments were carried out using the XHCORR and COLOC programs.
[B] Entries bearing this superscript are interchangeable.

The orientation of the *N*-(2-aminoethyl)propane-1,3-diamine fragment in (7) was assigned on the basis of observed correlation spectroscopy via long-range coupling [COLOC (COrrelation spectroscopy for LOng-range Couplings)] NMR spectroscopy (see the Experimetal section for the numbering scheme used for the assignments, with the latter listed in Table 1). The benzylic protons at δ 3.71 (H14) correlated with the ethylenediamine carbon (C13) at δ 48.5, and also to the aromatic carbon atoms at δ 123.6, 129.2 and 147.2. These were assigned to carbons 1′, 2′ and 6′ of the *N*-substituted aromatic ring using the low-field position (147.2 ppm) of the C6′ signal as evidence for *N*-substitution. This assignment was further supported by the upfield chemical shifts of H5′ and H3′ (δ 6.56 and 6.60, respectively). The benzylic protons at δ 3.80 correlated with C10 (46.5 ppm). The assignment of C10 was made on the basis of a correlation from H10′ (δ 1.62), the central protons of the 1,3-diaminopropane unit. The benzylic protons (δ 3.80, H9) also showed correlations to the aromatic carbon signals at δ 129.5, 136.2 and 139.6, which were assigned to carbons 6, 2 and 1 respectively of the *S*-substituted ring. Furthermore, the methylene protons at δ 3.40 (H7) correlated with the signal at 147.2 ppm (C6′), while the ethylene protons at δ 3.25 (H8) correlated with the signal at 136.2 ppm (C2). The chemical shifts of C7 and C8 are also diagnostic of attachment to *N* and *S*, respectively.

X-Ray Structures

X-Ray diffraction studies of (5) (CCDC No. 189957; formula $C_{20}H_{28}N_4S$) and (6) (CCDC No. 189956; formula $C_{20}H_{28}N_4O$), crystallized from acetonitrile, confirm the structures (see Figs 1 and 2) assigned from physical measurements. Selected bond lengths and angles for each structure are listed in Tables 2 and 3. Both structures are similar, with close agreement between bond lengths and angles of chemically equivalent bonds and angles being apparent. In each case there is a lack of pseudo symmetry relating equivalent 'halves' of the respective molecules. The adoption of closely related geometries for these two

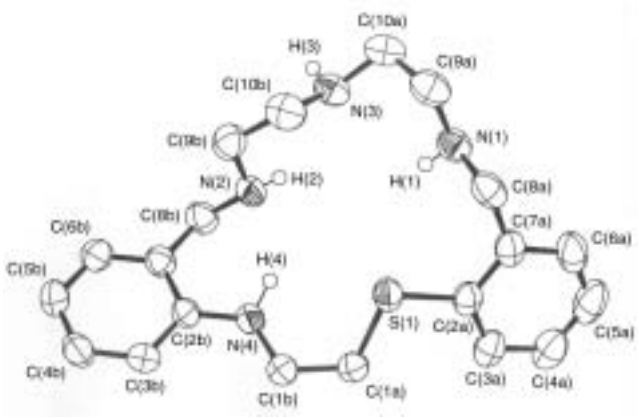


Fig. 1. The X-ray crystal structure of (5).

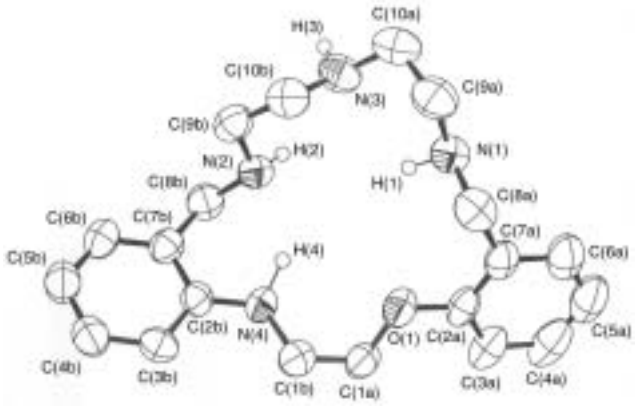


Fig. 2. The X-ray crystal structure of (6).

Table 2. Selected bond lengths (Å) for (5) and (6)

(5)		(6)	
Atoms	Distance	Atoms	Distance
S(1)–C(2a)	1.760(4)	O(1)–C(2a)	1.376(4)
S(1)–C(1a)	1.802(3)	O(1)–C(1a)	1.437(4)
N(1)–C(8a)	1.457(5)	N(1)–C(8a)	1.451(5)
N(1)–C(9a)	1.449(5)	N(1)–C(9a)	1.456(5)
N(2)–C(8b)	1.464(5)	N(2)–C(8b)	1.454(5)
N(2)–C(9b)	1.443(5)	N(2)–C(9b)	1.450(5)
N(3)–C(10a)	1.462(5)	N(3)–C(10a)	1.455(5)
N(3)–C(10b)	1.450(5)	N(3)–C(10b)	1.443(5)
N(4)–C(1b)	1.445(5)	N(4)–C(1b)	1.443(5)
N(4)–C(2b)	1.384(4)	N(4)–C(2b)	1.380(4)
C(1a)–C(1b)	1.515(5)	C(1a)–C(1b)	1.493(5)
C(7a)–C(8a)	1.493(5)	C(7a)–C(8a)	1.487(5)
C(9a)–C(10a)	1.502(6)	C(9a)–C(10a)	1.501(6)
C(7b)–C(8b)	1.506(5)	C(7b)–C(8b)	1.495(5)
C(9b)–C(10b)	1.513(6)	C(9b)–C(10b)	1.495(5)

macrocycles is somewhat surprising given the significant differences in bond lengths and angles that occur about the O(1) and S(1) heteroatoms in the respective structures.

Experimental

Unless otherwise specified, reagents used for the syntheses were of the highest grade obtainable commercially. 2,2′-Diaminoethyl thioether,[11] 2,2′-diaminoethyl ether[12] and 2-(2-bromoethoxy)benzaldehyde[7] were prepared by the literature methods. ^{1}H and ^{13}C NMR spectra were determined on a Bruker AM300 spectrometer at 300 and 75 MHz, respectively. ^{1}J correlations were determined using the standard Bruker heteronuclear correlation spectroscopy (XHCORR) pulse sequence optimized for J 140 Hz. ^{2}J and ^{3}J correlations were determined using the standard Bruker COLOC pulse sequence optimized for J 10 Hz.

Electrospray (ES) ionization mass spectra were obtained on a Bruker BioApex 47e ICR mass spectrometer; positive-ion fast atom bombardment mass spectra (FAB–MS) were determined using a JEOL JMS-DX300 spectrometer (samples in 3-nitrobenzyl alcohol). Chromatography on silica gel was performed as described previously.[13] Melting points are uncorrected.

X-Ray Studies

The data for (5) and (6) were collected on an Enraf Nonius CAD4 diffractometer and the structures were solved by direct methods using SHELXS-97[14] and refined with SHELXL-97[14] using WINGX as the graphical interface.[15] No absorption corrections were applied. All non-hydrogen atoms were refined anisotropically. Except for those on the amine nitrogen atoms, all hydrogen atoms were placed at calculated positions (riding model) and their parameters were not refined. The hydrogen atoms attached to the nitrogens were located with a Fourier difference map and were refined isotropically. Crystal data and details of the refinement are given in Table 4.

Table 3. Selected bond angles (deg) for (5) and (6)

(5)		(6)	
Atoms	Angle	Atoms	Angle
C(2a)–S(1)–C(1a)	103.31(17)	C(2a)–O(1)–C(1a)	117.1(3)
C(1b)–C(1a)–S(1)	109.7(2)	O(1)–C(1a)–C(1b)	109.3(3)
C(3a)–C(2a)–S(1)	122.8(3)	O(1)–C(2a)–C(3a)	123.0(4)
C(7a)–C(2a)–S(1)	117.7(3)	O(1)–C(2a)–C(7a)	115.6(3)
C(9a)–N(1)–C(8a)	111.6(3)	C(8a)–N(1)–C(9a)	111.6(3)
C(9b)–N(2)–C(8b)	113.7(3)	C(9b)–N(2)–C(8b)	113.1(3)
C(10b)–N(3)–C(10a)	115.0(3)	C(10a)–N(3)–C(10b)	115.4(4)
C(2b)–N(4)–C(1b)	120.5(3)	C(2b)–N(4)–C(1b)	120.4(3)
N(1)–C(8a)–C(7a)	112.3(3)	N(1)–C(8a)–C(7a)	112.0(3)
N(1)–C(9a)–C(10a)	112.3(3)	N(1)–C(9a)–C(10a)	111.9(4)
N(3)–C(10a)–C(9a)	112.1(3)	N(3)–C(10a)–C(9a)	111.5(4)
N(3)–C(10b)–C(9b)	110.6(3)	N(3)–C(10b)–C(9b)	111.5(3)
N(2)–C(8b)–C(7b)	112.7(3)	N(2)–C(8b)–C(7b)	112.4(3)
N(2)–C(9b)–C(10b)	111.0(3)	N(2)–C(9b)–C(10b)	111.3(3)
N(4)–C(1b)–C(1a)	110.6(3)	N(4)–C(1b)–C(1a)	111.6(3)
N(4)–C(2b)–C(3b)	123.6(3)	N(4)–C(2b)–C(3b)	123.3(3)
N(4)–C(2b)–C(7b)	117.8(3)	N(4)–C(2b)–C(7b)	118.3(3)
C(6a)–C(7a)–C(8a)	120.3(4)	C(6a)–C(7a)–C(8a)	119.5(4)
C(2a)–C(7a)–C(8a)	121.7(3)	C(2a)–C(7a)–C(8a)	122.5(3)
C(6b)–C(7b)–C(8b)	120.7(3)	C(6b)–C(7b)–C(8b)	121.8(3)
C(2b)–C(7b)–C(8b)	120.5(3)	C(2b)–C(7b)–C(8b)	119.3(3)

Synthesis of Intermediate (9)

Concentrated sulfuric acid (32 mL) was added dropwise to a stirred solution of thiosalicylic acid (100 g, 0.65 mol) in absolute ethanol (1 L). The mixture was refluxed for 16 h and cooled to room temperature. Following the addition of anhydrous sodium carbonate (96 g), the solution was heated and stirred for 1 h. 2-(2-Bromoethoxy)benzaldehyde (148.7 g, 0.70 mol) was then added dropwise and the mixture refluxed for a further 3 h. After cooling, the solution was poured into water (2 L) and then extracted with chloroform (2 × 500 mL). On slow evaporation of the chloroform, an orange-yellow solid separated which was isolated and recrystallized from acetonitrile (148.7 g, 73%). ^{1}H NMR ($CDCl_3$) δ 1.31, t, 3H, C**H**$_3$CH$_2$O; 3.43, t, 2H, ArSCH$_2$; 4.32–4.59, overlapping t and q, 5H, ArOCH$_2$, CH$_3$C**H**$_2$O; 6.9–8.1, m, 8H, Ar; 10.44, s, 1 H, CHO. ^{13}C NMR ($CDCl_3$) δ 14.3, 31.2, 61.3, 66.8, 112.5, 121.2, 124.8, 125.1, 128.3, 128.5, 129.1, 131.3, 132.3, 133.9, 135.8, 139.4, 160.6, 188.6. This intermediate was employed for the synthesis of the corresponding diol without further characterization.

Synthesis of Diol (10)

A suspension of (9) (25.0 g, 0.08 mol) in dry tetrahydrofuran (200 mL) was slowly added to a stirred suspension of lithium aluminium hydride (10.0 g, 0.26 mol) in dry (freshly distilled from sodium benzophenone) tetrahydrofuran (600 mL) under a nitrogen atmosphere. The mixture was stirred for 30 min after which excess lithium aluminium hydride was quenched by successive dropwise addition of water (10 mL), 12.5% sodium hydroxide (10 mL), and water (30 mL). The solution was filtered and the gelatinous white precipitate was washed with hot acetone. Slow evaporation of the combined filtrates yielded the product as a pale brown oil. A white solid was obtained on titration of the crude oil with a mixture (70:30) of light petroleum (b.p. 40–60°C) and diethyl ether. The *product* was recrystallized from dichloromethane to yield white fluffy crystals (16.2 g, 70%), m.p. 83°C (Found: C, 65.8; H, 6.2. $C_{16}H_{18}O_3S$ requires C, 66.2; H, 6.3%). ^{1}H NMR ($CDCl_3$) δ 3.33, t, ArSCH$_2$; 4.17, t, 2H, ArOCH$_2$; 4.64, s, 2H, C**H**$_2$OH; 4.77, s, 2H C**H**$_2$OH; 6.77–7.46, m, 8H, aromatics. ^{13}C NMR ($CDCl_3$) δ 34.3, 62.0,

Table 4. Crystal data and summary of data collection for (5) and (6)

Compound	(5)	(6)
Mol. formula	$C_{20}H_{28}N_4S$	$C_{20}H_{28}N_4O$
Mol. wt	356.52	340.46
T, K	296	296
Space group	$P\bar{1}$	$P\bar{1}$
a, Å	9.095(1)	8.807(1)
b, Å	11.124(2)	11.349(1)
c, Å	11.884(3)	11.840(2)
α, deg	117.427(11)	118.405(13)
β, deg	110.050(2)	109.825(10)
γ, deg	93.620(3)	90.588(10)
V, Å^3	966.6(3)	957.9(2)
Z	2	2
D_c, g cm^{-3}	1.225	1.180
μ, mm^{-1}	0.178	0.075
$T_{max,min}$	0.9645, 0.9570	0.9926, 0.9635
Dimensions, mm^3	0.25 × 0.20 × 0.20	0.5 × 0.2 × 0.1
F(000)	348	368
Radiation	Mo Kα	Mo Kα
θ range, deg	2.09–24.96	2.09–24.96
N_{coll}	3630	3607
N_{obs}	3395	3364
N_{var}	242	242
Sigma cutoff	$I > 2\sigma(I)$	$I > 2\sigma(I)$
R	0.064	0.056
R_w	0.181	0.129

63.5, 65.9, 111.3, 121.2, 127.6, 128.5, 128.9, 129.0, 129.3, 129.5, 131.4, 133.2, 141.7, 156.3. Mass spectrometric parent ion (FAB): *m/z* 290.

Synthesis of Dialdehyde (11)

Barium manganate (100.0 g, 0.39 mol) was added to a stirred solution of the above diol (11.5 g, 0.04 mol) in dichloromethane (1 L) under a dry nitrogen atmosphere. The solution was stirred for 18 h, filtered through a small amount of silica gel, and the black residue was washed with dichloromethane. Slow evaporation of the combined filtrates yielded the product as a white crystalline *solid*, which was recrystallized from ethanol (5.7 g, 50%), m.p. 79°C (Found: C, 67.2; H, 4.9. $C_{16}H_{14}O_3S$ requires C, 67.1; H, 4.9%). ^{1}H NMR ($CDC1_3$) δ 3.46, t, 2H, $ArSCH_2$; 4.34, t, 2H, $ArOCH_2$; 6.91–7.88, m, 8H, Ar; 10.36, s, 1H, ArCHO; 10.40, s, 1H, ArCHO. ^{13}C NMR ($CDCl_3$) δ 32.6, 66.8, 112.4, 121.3, 126.4, 128.6, 129.1, 132.2, 134.1, 135.8, 189.4, 191.4. Mass spectrometric parent ion (FAB): *m/z* 285.

Synthesis of Macrocycle (2)

2,2′-Diaminodiethylamine (0.55 g, 0.005 mol) in methanol (20 mL) was added slowly to a stirred boiling solution of 2,2′-(ethane-1,2-diyloxythio)bisbenzaldehyde (11) (1.50 g, 0.005 mol) in methanol (600 mL). The solution was boiled for a further 5 min, and then allowed to cool. Excess sodium borohydride (2.5 g) was added slowly to the mixture and the volume was reduced to 400 mL. Ice water (1.2 L) was slowly added and a white solid separated. The crude product was dissolved in chloroform, and acid-extracted by shaking with 3 M hydrochloric acid (300 mL). The aqueous phase was washed with chloroform (2 × 100 mL) and then the aqueous phase was separated and adjusted to pH 13. The white *solid* that separated was recrystallized from acetone (60%), m.p. 144°C (Found: C, 66.8; H, 7.7; N, 11.4. $C_{20}H_{27}N_3OS$ requires C, 67.2; H, 7.6; N, 11.4%). ^{1}H NMR ($CDCl_3$) δ 1.76, s, 3H, NH; 2.67–2.78, m, 8H, NCH_2CH_2N; 3.46, t, 2H, $ArSCH_2$; 3.80, s, 2H, $ArCH_2$; 3.86, s, 2H, $ArCH_2$; 4.32, t, 2H, $ArOCH_2$; 6.6–7.3, m, 8H, Ar. ^{13}C NMR ($CDCl_3$) δ 32.6, 48.7, 49.2, 49.7, 51.3, 53.6, 65.6, 110.4, 120.5, 125.4, 127.2, 128.09, 128.3, 130.3, 130.9, 137.1, 138.9, 156.8. Mass spectrometric parent ion (FAB): *m/z* 358.

Synthesis of Macrocycle (3)

In a similar manner, 2,2′-diaminoethyl ether (0.54 g) yielded a white crystalline *solid* (60%), m.p. 144.5°C (Found: C, 67.5; H, 7.5; N, 7.8. $C_{20}H_{26}N_2O_2S$ requires C, 67.0; H, 7.3; N, 7.8%). ^{1}H NMR ($CDCl_3$) δ 2.6–2.8, m, 4H, $NHCH_2CH_2$; 3.43, t, 2H, $ArSCH_2$; 3.55, centre of 2t, 4H, CH_2OCH_2; 3.81, s, 2H, $ArCH_2$; 3,88, s, 2H, $ArCH_2$; 4.30, t, 2H, $ArOCH_2$; 6.8–7.3, m, 8H, Ar. ^{13}C NMR ($CDCl_2$) δ 32.2, 48.9, 49.1, 51.0, 53.4, 65.2, 70.0, 70.6, 110.6, 120.7, 125.8, 127.2, 127.7, 128.0, 128.6, 130.9, 131.l, 135.8, 138.5, 156.7. Mass spectrometric parent ion (FAB): *m/z* 359.

Synthesis of Macrocycle (4)

In a similar manner, 2,2′-diaminoethyl thioether (0.65 g) yielded a pale yellow *solid* (40%), m.p. 94.5–95.5°C (Found: C, 64.1; H, 7.0; N, 7.3. $C_{20}H_{26}N_2OS_2$ requires C, 64.2; H, 7.2; N, 7.5%). ^{1}H NMR ($CHCl_3$) δ 2.2, s, 2H, NH; 2.27–2.86, m, 8H, NCH_2CH_2S; 3.45, t, 2H, $ArSCH_2$; 3.81, s, 2H, Ar**C**$\mathbf{H}_2$NH; 3.88, s, 2H, Ar**C**$\mathbf{H}_2$NH; 4.29, t, 2H, $ArOCH_2$; 6.81–7.41, m, 8H, Ar. ^{13}C NMR ($CDCl_3$) δ 32.9, 33.0, 34.2, 47.8, 47.9, 49.9, 52.5, 67.8, 110.8, 120.8, 126.3, 128.1, 128.3, 128.4, 129.0, 130.5, 130.6, 135.7, 139.6, 156.6. Mass spectrometric parent ion (FAB): *m/z* 375.

Synthesis of Intermediate (12)

Ethylene oxide (100 mL, 2.0 mol) was added to a solution of methylanthranilate (109 mL, 0.82 mol) in acetic acid (600 mL) at 0°C. The reaction mixture was stirred for 3 days (and monitored daily by ^{1}H NMR spectroscopy). The aqueous phase was then decanted and the residual oil washed quickly with 10% sodium hydroxide (200 mL) and then water (3 × 200 mL). The oil was then dissolved in dichloromethane and the solution was dried over anhydrous sodium sulfate. The product (12) crystallized as white *needles* upon the addition of cyclohexane (90 g, 56%) (Found (ES): $[M + H]^+$, 196.0958. $C_{10}H_{13}NO_3$ requires $[M + H]^+$, 196.0968). ^{1}H NMR ($CDCl_3$) δ 3.36, t, *J* 6.0 Hz, 2H, $NHCH_2$; 3.81, s, 3H, OCH_3; 3.84, t, *J* 6.0 Hz, 2H, C**H**$_2$OH; 6.59, ddd, *J* 8.0, 7.0, 0.9 Hz, 1H, Ar; 6.69, br d, *J* 8.5 Hz, 1H, Ar; 7.33, ddd, *J* 8.5, 7.1, 1.7 Hz, 1H, Ar; 7.88, dd, *J* 8.0, 1.7 Hz, 1H, Ar. ^{13}C NMR ($CDCl_3$) δ 44.9, 51.4, 60.9, 110.2, 111.3, 114.8, 131.6, 134.5, 150.9, 168.9.

Synthesis of Mesylate (13)

A solution of the alcohol (12) (65.7 g, 0.34 mol) and triethylamine (34.1 g) in dichloromethane (200 mL) was cooled in ice and methanesulfonyl chloride (44 g, 0.38 mol) was added dropwise with stirring. A white precipitate formed during the addition. The mixture was stirred for 1 h at room temperature and water (700 mL) was added. The organic layer was separated and washed with 1 M hydrochloric acid (200 mL), water (200 mL) and 5% sodium hydroxide (200 mL), and then dried over sodium sulfate. Removal of the dichloromethane yielded a solid, which was recrystallized from boiling ethanol to give the *mesylate* as white needles (56.2 g, 61%) (Found: C, 48.1; H, 5.7; N, 5.1. $C_{11}H_{15}NO_5S$ requires C, 48.3; H, 5.5; N, 5.1%). ^{1}H NMR ($CDCl_3$) δ 3.02, s, SO_2CH_3; 3.62, t, 2H, *J* 5.7 Hz, NCH_2; 3.86, s, 3H, $COCH_3$; 4.41, t, *J* 5.5 Hz, 2H, CH_2OS; 6.67, dd, *J* 7.2, 8.1 Hz, 1H, Ar; 6.73, br d, *J* 8.4 Hz, 1H, Ar; 7.38, dt, *J* 8.4, 0.9 Hz, 1H, Ar; 7.92, dd, *J* 7.8, 1.5 Hz, 1H, Ar; 7.97, br s, 1H (exchanges with D_2O), NH. ^{13}C NMR ($CDCl_3$) δ 37.6, 42.0, 51.7, 67.6, 110.9, 111.1, 115.8, 131.8, 134.6, 149.7, 168.7.

Synthesis of Diester (14)

Ethyl thiosalicylate (28.7 g, 0.15 mol), the mesylate (13) (43.05 g, 0.15 mol) and potassium carbonate (43.53 g, 0.32 mol) were added to ethanol (700 mL) and the mixture was heated at reflux under nitrogen for 3 h. The reaction mixture was cooled, poured into water (2 L), and the crude product was removed by filtration and washed with water. The *diester* (14) was recrystallized from a mixture (5:1) of ethanol and chloroform (36.2 g, 64%) (Found (ES): $[M + Na]^+$, 382.1093. $C_{19}H_{21}NO_4$ requires $[M + Na]^+$, 382.1083). ^{1}H NMR ($CDCl_3$) δ 1.41, t, *J* 7.1 Hz, 3H, C**H**$_3$CH$_2$O; 3.22, m, 2H, SCH_2; 3.56, m, 2H, NCH_2; 4.40, q, *J* 7.1 Hz, 2H, CH_3C**H**$_2$; 6.62, m, 1H, Ar; 6.68, br d, *J* 8.5 Hz, 1H, Ar;

7.19, m, 1H, Ar; 7.32–7.46, m, 3H, Ar; 7.9, m, 3H, Ar. ^{13}C NMR ($CDCl_3$) δ 14.4, 31.7, 41.7, 51.5, 61.2, 110.4, 110.9, 115.0, 124.4, 126.4, 129.2, 131.0, 131.7, 132.0, 134.5, 139.7, 150.3, 166.4, 168.8.

Synthesis of Diol (15)

A suspension of the diester (14) (33.5 g, 0.09 mol) was slowly added to a stirred suspension of lithium aluminium hydride (7.8 g, 0.2 mol) in dry, freshly distilled tetrahydrofuran (500 mL) under a nitrogen atmosphere, at 0°C. The mixture was stirred overnight and cooled, after which the excess lithium aluminium hydride was hydrolysed by dropwise addition of water (7.8 mL), 10% sodium hydroxide (12.3 mL) and water (12.3 mL). The mixture was stirred at room temperature for 1 h. The solution was filtered and the precipitate washed several times with dichloromethane. Evaporation of the filtrate yielded a pale yellow oil, which was dissolved in dichloromethane and eluted with the same solvent through a short silica gel column. Removal of the solvent yielded the product (15) as an off-white *solid* that was recrystallized from a mixture of dichloromethane/cyclohexane (24.2 g, 90%) (Found (ES): $[M + Na]^+$, 312.1025. $C_{16}H_{19}NO_2S$ requires $[M + Na]^+$, 312.1029). ^{1}H NMR ($CDCl_3$) δ 3.12, br t, *J* 6.0 Hz, 2H, SCH_2; 3.26, br t, *J* 6.0 Hz, 2H, $NHCH_2$; 4.46, s, 2H, CH_2OH; 4.65, s, 2H, CH_2OH; 6.53, br d, *J* 8.1 Hz, 1H, Ar; 6.62, dt, *J* 7.2, 0.9 Hz, 1H, Ar; 6.95, dd, *J* 7.2, 1.5 Hz, 1H, Ar; 7.10–7.22, m, 3H, Ar; 7.30, dd, *J* 6.6, 2.7 Hz, 1H, Ar; 7.38, dd, *J* 6.9, 1.5 Hz, 1H, Ar. ^{13}C NMR ($CDCl_3$) δ 34.3, 42.1, 63.5, 64.5, 110.6, 116.9, 124.7, 127.1, 128.3, 128.8, 129.2, 129.5, 131.1, 133.5, 141.5, 146.7.

Synthesis of Dialdehyde (16)

Barium manganate (66.0 g, 0.26 mol) was added to a stirred solution of diol (15) (4.4 g, 0.015 mol) in dry, freshly distilled dichloromethane (150 mL). The mixture was stirred overnight, then filtered through a small amount of silica gel and the black residue was washed several times with dichloromethane. Evaporation of the combined filtrates yielded (16) as an orange *solid*, which was recrystallized from a mixture of ethanol/chloroform (2.7 g, 62%) (Found: C, 66.9; H, 5.4; N, 5.0. $C_{16}H_{15}NO_2S$ requires C, 67.3; H, 5.3; N, 4.9%). ^{1}H NMR ($CDCl_3$) δ 3.23, m, 2H, SCH_2; 3.55, m, 2H, $NHCH_2$; 6.64, br d, *J* 9.0 Hz, 1H, Ar; 6.73, t, *J* 7.2 Hz, 1H, Ar; 7.33–7.56, m, 5H, Ar; 7.86, dd, *J* 7.8, 1.2 Hz, 1H, Ar; 8.54 br s, 1H, NH; 9.81, s, 1H, CHO; 10.42, s, 1H, CHO. ^{13}C NMR ($CDCl_3$) δ 32.8, 41.2, 110.3, 115.4, 118.6, 126.1, 129.3, 131.4, 133.8, 134.6, 135.7, 136.6, 139.8, 149.7, 191.0, 193.7.

Synthesis of Macrocycle (5)

2,2′-Diaminodiethylamine (0.93 g, 0.009 mol) in methanol (20 mL) was added very slowly to a stirred solution of dialdehyde (16) (2.56 g, 0.009 mol) in methanol (140 mL) with heating. The mixture was refluxed for 1 h, and then allowed to cool. Excess sodium borohydride (2.0 g, 0.053 mol) was added rapidly, followed by slow addition of ice, resulting in a total volume of 500 mL. The mixture was left stirring overnight, during which time an off-white gum separated out. The mixture was extracted with dichloromethane (3 × 100 mL) followed by a water wash (100 mL) of the combined extracts. The dichloromethane extract was then dried with anhydrous sodium sulfate. Removal of the solvent on the rotary evaporator yielded the *macrocycle* (5) as a solid, which was subsequently recrystallized from acetonitrile (2.1 g, 65%) (Found: C, 66.7; H, 7.5; N, 15.3. $C_{20}H_{28}N_4S$ requires C, 67.4; H, 7.9; N, 15.7%) (Found (ES): $[M + H]^+$, 357.2124. $C_{20}H_{28}N_4S$ requires $[M + H]^+$, 357.2107). ^{1}H NMR ($CDCl_3$) δ 1.75, br s, 4H, NH; 2.7, m, 4H, NCH_2; 2.8–2.9, m, 4H, NCH_2; 3.37, m, 2H, SCH_2; 3.52, m, 2H, $ArNHCH_2$; 3.79, s, 2H, $ArCH_2$; 3.78, s, 2H, $ArCH_2$; 6.63, m, 2H, Ar; 7.02, dd, *J* 7.8, 1.8 Hz, 1H, Ar; 7.10–7.25, m, 4H, Ar; 7.33, dd, *J* 8.1, 0.1 Hz, 1H, Ar. ^{13}C NMR ($CDCl_3$) δ 32.0, 41.9, 48.4, 49.5, 49.6, 49.8, 53.4, 54.3, 109.9, 116.4, 124.2, 125.2, 126.9, 127.9, 128.5, 129.7, 130.1, 137.3, 138.5, 147.7.

Synthesis of Intermediate (18)

The mesylate (13) (20.0 g, 0.073 mol) and salicylaldehyde (10.7 g, 0.088 mol) were heated with potassium carbonate (20.2 g, 146 mmol) in dimethylformamide (100 mL) for 4 h. The resulting mixture was poured into water (500 mL) and the mixture extracted with diethyl ether (3 × 200 mL). The combined organic extracts were washed with water (3 × 100 mL), dried over sodium sulfate, and then evaporated to yield the *ester* (18) as a viscous oil (17.8 g, 81%) (Found (ES): $[M + Na]^+$, 322.1048. $C_{17}H_{17}NO_4$ requires $[M + Na]^+$, 322.1050). ^{1}H NMR ($CDCl_3$) δ 3.73, br t, *J* 5.7 Hz, 2H, NCH_2; 3.86, s, 3H, OCH_3; 4.33, t, *J* 5.7 Hz, 2H, OCH_2; 6.64, dt, *J* 1, 7 Hz, 1H, Ar; 6.78, d, *J* 7.9 Hz, 1H, Ar; 6.99, d, *J* 8.1 Hz, 1H, Ar; 7.05, br t, *J* 7.5 Hz, 1H, Ar; 7.39, dt, *J* 1.6, 8.5 Hz, 1H, Ar; 7.53, dt, *J* 1.8, 8.8 Hz, 1H, Ar; 7.85, dd, *J* 1.8, 7.7 Hz, 1H, Ar; 7.92, dd, *J* 1.7, 8.1 Hz, 1H, Ar; 8.11, br s, NH, 1H; 10.52, s, CHO. ^{13}C NMR ($CDCl_3$) δ 42.0, 51.6, 67.1, 110.7, 111.0, 112.5, 115.2, 121.0, 125.2, 128.3, 131.8, 134.5, 135.6, 150.6, 160.8, 189.4.

Synthesis of Diol (19)

The ester (18) (10.09 g, 0.034 mol) in dry tetrahydrofuran (50 mL) was slowly added to a stirred suspension of lithium aluminium hydride (1.8 g, 0.047 mol) in dry tetrahydrofuran (500 mL) under a nitrogen atmosphere. The reaction mixture was stirred for 1 h, then cooled in an ice bath, and the excess lithium aluminium hydride quenched by successive dropwise additions of water (1.8 mL), 10% sodium hydroxide (2.9 mL) and again water (2.9 mL). The mixture was stirred overnight, then filtered through a small plug of Celite and the precipitate was washed several times with dichloromethane. Evaporation of the filtrate yielded the product as an oil. Rapid column chromatography on silica gel, using dichloromethane as eluent, yielded the pure diol (19) as a white, crystalline *solid* (5.0 g, 54%) (Found: C, 70.4; H, 7.0; N, 5.0. $C_{16}H_{19}NO_3$ requires C, 70.3; H, 7.0; N, 5.1%). ^{1}H NMR ($CDCl_3$) δ 3.56, br t, *J* 5.1 Hz, 2H, NCH_2; 4.26, t, *J* 5.1 Hz, 2H, $OC\mathbf{H}_2CH_2$; 4.59, s, 4H, CH_2OH; 6.67–6.73, m, 2H Ar; 6.88, d, *J* 8.1 Hz, 1H, Ar; 6.94, dt, *J* 0.8, 7.6 Hz, 1H, Ar; 7.02, dd, *J* 1.5, 7.3 Hz, 1H, Ar; 7.21–7.28, m, 3H, Ar. ^{13}C NMR ($CDCl_3$) δ 42.8, 61.1, 64.3, 66.3, 110.8, 111.3, 117.1, 121.0, 125.1, 129.1, 129.2, 129.3, 129.4, 129.7, 147.3, 156.5.

Synthesis of Dialdehyde (17)

Barium manganate (45.0 g, 0.18 mol) was added to a stirred solution of the diol (19) (3.0 g, 0.01 mol) in dry dichloromethane (120 mL). After 4 h, a further 10 g of barium manganate was added and the reaction mixture was stirred overnight, then filtered through silica gel. The residue was washed well with dichloromethane. Evaporation of the filtrates yielded the product (17) as a pale yellow *solid* (2.2 g, 74%) (Found: C, 71.0; H, 5.9; N, 5.3. $C_{16}H_{15}NO_3$ requires C, 71.4; H, 5.6; N, 5.2%). ^{1}H NMR ($CDCl_3$) δ 3.76, m, 2H, NCH_2; 4.31, br t, *J* 5.6 Hz, 2H, OCH_2; 6.75, t, *J* 7.4 Hz, 1H, Ar; 6.78, d, *J* 8.5 Hz, 1H, Ar; 6.98, d, *J* 8.4 Hz, 1H, Ar; 7.05, t, *J* 7.5 Hz, 1H; 7.41–7.56, m, 3H, Ar; 7.85, dd, *J* 1.8, 7.7 Hz, 1H, Ar; 8.65, br s, 1H, NH; 9.82, s, 1H, CHO; 10.50, s, 1H, CHO. ^{13}C NMR ($CDCl_3$) δ 41.4, 66.9, 110.6, 112.4, 115.6, 118.8, 121.2, 125.1, 128.4, 135.8, 135.9, 136.8, 150.3, 160.7, 189.6, 194.1.

Synthesis of Macrocycle (6)

2,2′-Diaminodiethylamine (0.38 g, 0.004 mol) was dissolved in methanol (5 mL) and added dropwise to a solution of the dialdehyde (17) (1.0 g, 0.004 mol) in methanol (100 mL). The reaction mixture was refluxed for 10 min and then sodium borohydride (0.45 g, 0.012 mol) was added slowly. Following the reduction, ice water (400 mL) was slowly added and the product separated out as a pale cream gum. The gum was extracted into dichloromethane (3 × 100 mL), followed by a water back-wash (50 mL) and dried over anhydrous sodium sulfate. Removal of the dichloromethane on the rotary evaporator yielded (6) as a white *solid*, which was recrystallized from acetonitrile (0.7 g, 56%) (Found: C, 70.4; H, 8.4; N, 16.0. $C_{20}H_{28}N_4O$ requires C, 70.6; H, 8.3; N, 16.5%). ^{1}H NMR ($CDCl_3$) δ 2.59–2.62, m, 4H, NCH_2; 2.72–2.75, m, 4H, NCH_2; 3.58, br m, 2H, NCH_2; 3.79, s, 2H; 3.80, s, 2H; 4.28, br t, *J* 4.3Hz, 2H, OCH_2; 6.47, br s, 1H, NH; 6.63–6.67, m, 2H, Ar; 6.68–6.93, m, 2H, Ar; 7.03, dd, *J* 7.2, 1.5 Hz, 1H, Ar; 7.16–7.25, m, 3H, Ar. ^{13}C NMR ($CDCl_3$) δ 43.2, 47.4, 48.4, 48.5, 48.5, 50.2, 53.7, 67.5, 109.9, 111.5, 116.5, 120.6, 124.2, 128.3, 128.5, 128.5, 129.9, 130.9, 147.7, 157.5.

Synthesis of Macrocycles (7) and (8)

N-(2-Aminoethyl)propane-1,3-diamine (1.08 g, 0.009 mol) in methanol (10 mL) was added slowly dropwise to a stirred solution of dialdehyde (16) (2.19 g, 0.008 mol) in methanol (500 mL). The mixture was refluxed for 45 min, then allowed to cool slightly and excess sodium borohydride (2.5 g, 0.07 mol) was added rapidly. The volume was reduced to 75 mL and ice water was added to a total volume of 500 mL. A yellow gum separated; this was extracted into dichloromethane (3 × 100 mL), followed by a water back-wash of the combined extracts. After drying the solution with anhydrous sodium sulfate, the dichloromethane was removed. The residue was shown (by ^{1}H NMR spectroscopy) to consist of a 60:40 mixture of macrocycles (7) and (8) (2.59 g; 92% total yield). These were separated by column chromatography on silica gel using a mixture of chloroform and triethylamine (gradual increase of triethylamine from 0 to 20%).

Macrocycle (7) (Diagram 3), containing the propyl portion of the triamine closest to the thioether group, was the less polar of the two and eluted first from the column (Found (ES): $[M + H]^+$, 371.2255. $C_{21}H_{30}N_4S$ requires $[M + H]^+$, 371.2264). The numbering system used for the NMR assignments for (7) is given in Diagram 3; the assignments are listed in Table 1.

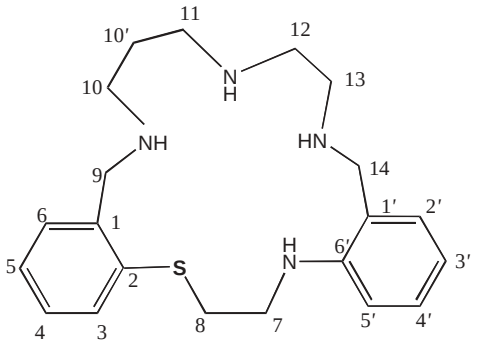


Diagram 3

NMR assignments for (8) were made by analogy with those obtained for isomer (7). ^{1}H NMR ($CDCl_3$) δ 1.68, m, 2H, NCH_2-C**H**$_2$$CH_2NHCH_2Ar$; 2.52, br s, 4H, NH; 2.78–2.67, m, 8H, NC**H**$_2$$CH_2CH_2NHCH_2Ar$, NCH_2CH_2C**H**$_2$$NHCH_2Ar$ and NCH_2C**H**$_2$-NCH_2Ar, NC**H**$_2$$CH_2NHCH_2Ar$; 3.27, m, 2H, SCH_2; 3.52, m, 2H, $ArNHCH_2$; 3.75, s, 2H, $NCH_2CH_2CH_2NC$**H**$_2$Ar; 3.84, s, 2H, NCH_2CH_2NC**H**$_2$Ar; 6.65, m, 2H, Ar; 7.02, br d, *J* 6.0 Hz, 1H, Ar; 7.15–7.27, 4H, m, Ar; 7.41, br d, *J* 6.6 Hz, 1H, Ar. ^{13}C NMR ($CDCl_3$) δ 28.6, 34.8, 46.7, 47.0, 47.1, 47.6, 52.1, 53.0, 53.1, 110.1, 116.4, 126.2, 128.1, 128.4, 128.6, 129.9, 130.2, 130.3, 136.6, 139.6, 147.3.

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