Aust. J. Chem., 1995, **48**, 1917–1924

New Macrocyclic Ligands. VII* The Synthesis of Mixed-Donor Spiro-Linked Macrocycles

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Abstract

The syntheses of five new spiro-linked bis-macrocyles, incorporating four ether oxygen and four or six secondary nitrogen heteroatoms, are reported. Two strategies were employed—the first involved the condensation of a spiro tetraaldehyde with 2 equiv. of ethane-1,2-diamine or propane-1,3-diamine or 2,2′-diaminodiethylamine followed by *in situ* reduction of the resulting intermediate tetraimines. The second procedure began with pentaerythrityl tetraamine [$C(CH_2NH_2)_4$] which was then condensed with 2 equiv. of a dialdehyde moiety in which two ether oxygen atoms, bridged by either two or three methylene groups, were incorporated in its backbone. A related *in situ* reduction step to that employed in the first procedure then yielded the required double-ring macrocycles. For use in comparative studies, the corresponding single-ring macrocycles were also synthesized where they had not been reported previously.

Linked macrocyclic ligands that bind two metal ions in close proximity provide the potential for generating unusual spectral, magnetic, catalytic and chemical properties. In some instances they also show potential for modelling the cooperativity that occurs in particular metalloenzymes incorporating two metal centres.[1] However, relative to the metal ion chemistry of monocyclic ligands, that of linked ring systems has received much less attention.[2] Even so, a considerable number of linked ring macrocycles have now been reported, especially ones incorporating crown or aza crown moieties.[2–4] In the vast majority of these, the linkage(s) between rings consist of one or more atoms. In contrast, the number

* Part VI, *Aust. J. Chem.*, 1995, **48**, 1819.

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[2] Lindoy, L. F., 'The Chemistry of Macrocyclic Ligand Complexes' (Cambridge University Press: Cambridge 1989).
[3] Vögtle, F., and Weber, E., *J. Inclusion Phenom. Mol. Recognit. Chem.*, 1992, **12**, 75.
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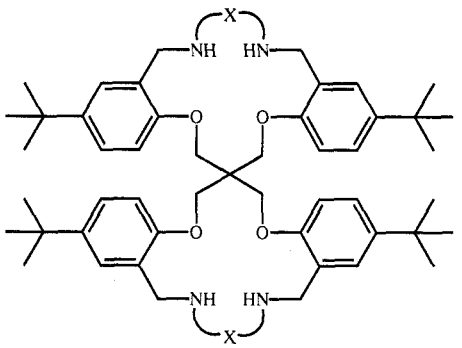
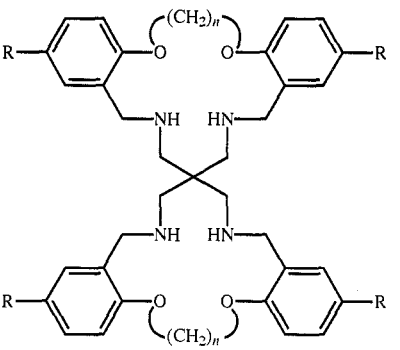
Manuscript received 22 June 1995 0004-9425/95/121917$05.00

of systems reported so far that incorporate a shared atom between adjacent rings remains quite small.[5,6] When the shared atom is an sp^3 carbon then the resulting tetrahedral arrangement will dispose the respective macrocyclic rings to adopt mutally orthogonal ('spiro-linked') alignments. Aspects of the metal ion chemistry of related (potentially binucleating) spiro-linked, open-chain ligands have also been investigated.[6,7]

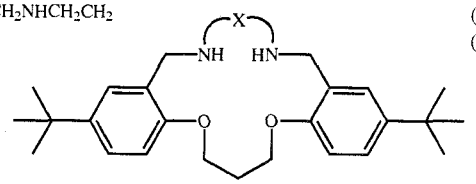
In this paper we describe the preparation of the new spiro-linked bis-macrocycles (1)–(3) and (4a,b). These rings are related both to each other as well as to the



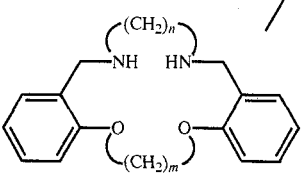
(1) X = CH_2CH_2
(2) X = $CH_2CH_2CH_2$
(3) X = $CH_2CH_2NHCH_2CH_2$



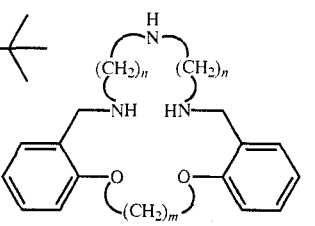
	R	*n*
(4a)	H	2
(4b)	Bu^t	3



(7) X = CH_2CH_2
(8) X = $CH_2CH_2CH_2$
(9) X = $CH_2CH_2NHCH_2CH_2$



(5)



(6)

[5] Weber, E., *Angew. Chem., Int. Ed. Engl.*, 1979, **18**, 219; Czugler, M., and Weber, E., *J. Chem. Soc., Chem. Commun.*, 1981, 472; Weber, E., *J. Org. Chem.*, 1982, **47**, 3478; Bouquant, J., Delville, A., Grandjean, J., and Laszlo, P., *J. Am. Chem. Soc.*, 1982, **104**, 686; Ouchi, M., Inoue, Y., Sakamoto, H., Yamahira, A., Yoshinaga, M., and Hakushi, T., *J. Org. Chem.*, 1983, **48**, 3168; McAuley, A., Subramanian, S., and Whitcombe, T. W., *J. Chem. Soc., Chem. Commun.*, 1987, 539; Bernhardt, P. V., Comba, P., Gahan, L. R., and Lawrance, G. A., *Aust. J. Chem.*, 1990, **43**, 2035.

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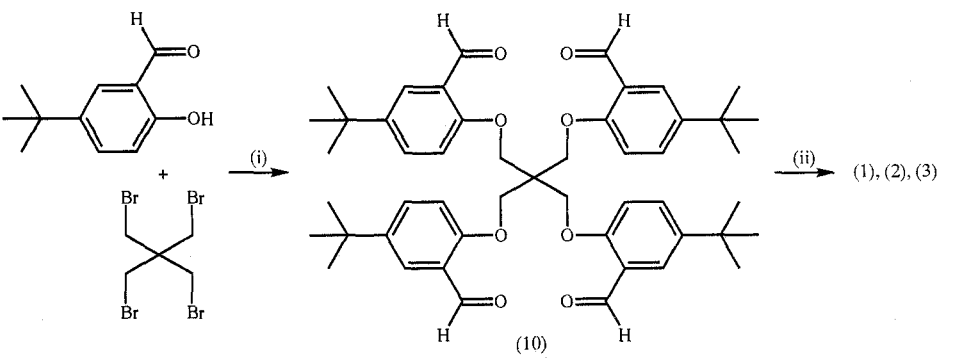
[7] Oehmke, R. W., and Bailar, J. C., *J. Inorg. Nucl. Chem.*, 1965, **27**, 2199; Phillip, A. T., *Aust. J. Chem.*, 1968, **21**, 2301; Gahan, L. R., Hart, K. E., Kennard, C. H. L., Kingston, M. A., Smith, G., and Mak, T. C. W., *Inorg. Chim. Acta*, 1986, **116**, 5; Dunlevy, T. M., Gahan, L. R., Hambley, T. W., Hanson, G. R., Markiewicz, A., Murray, K. S., Swann, I. L., and Pickering, S. R., *Aust. J. Chem.*, 1990, **43**, 1407; McAuley, A., Beveridge, K., Subramanian, S., and Whitcombe, T. W., *J. Chem. Soc., Dalton Trans.*, 1991, 1821.

corresponding 15- to 17-membered single-ring derivatives of type (5)[8] and (6).[9] The corresponding t-butyl-substituted derivatives (7)–(9) have also been synthesized as part of the present investigation. The behaviour of cyclic systems of types (5) and (6) towards a number of transition and post-transition ions has been the subject of detailed study by our group;[10,11] a special interest has been the potential of such rings for metal ion recognition. The work now reported represents the initial paper in an extension of the above program aimed at investigating a range of new multicomponent systems incorporating macrocycles as structural elements.

Results and Discussion

Two procedures were employed to produce the new spiro-linked macrocycles. The first method, used to obtain (1)–(3), is outlined in Scheme 1 and involves the reaction of pentaerythrityl tetrabromide [$C(CH_2Br)_4$] with 5-t-butylsalicylaldehyde in the presence of potassium carbonate suspended in dimethylformamide to give the tetraaldehyde (10) in high yield. This product was then reacted with the appropriate linear diamine. In each case the resulting tetraimine was reduced



Scheme 1. (i) K_2CO_3, dimethylformamide, 120°C overnight; (ii) diamine, $NaBH_4$.

[8] Grimsley, P. G., Lindoy, L. F., Lip, H. C., Smith, R. J., and Baker, J. T., *Aust. J. Chem.*, 1977, **30**, 2095.

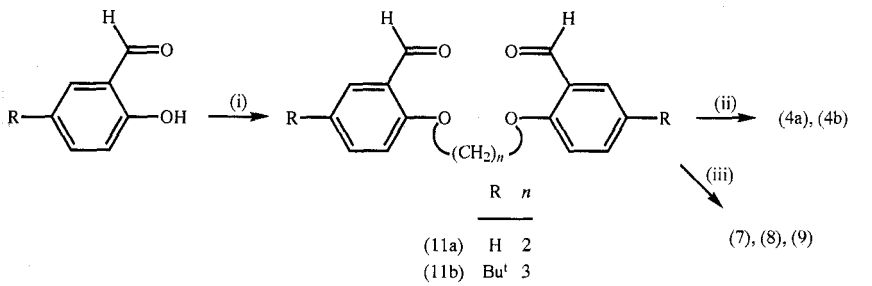
[9] Adam, K. R., Lindoy, L. F., Lip, H. C., Rea, J. H., Skelton, B. W., and White, A. H., *J. Chem. Soc., Dalton Trans.*, 1981, 74; Baldwin, D. S., Duckworth, P. A., Erickson, G. R., Lindoy, L. F., McPartlin, M., Mockler, G. M., Moody, W. E., and Tasker, P. A., *Aust. J. Chem.*, 1987, **40**, 1861.

[10] Lindoy, L. F., *Prog. Macrocyclic Chem.*, 1987, **3**, 53.

[11] Adam, K. R., Dancey, K. P., Leong, A. J., Lindoy, L. F., McCool, B. J., McPartlin, M., and Tasker, P. A., *J. Am. Chem. Soc.*, 1988; **110**, 8471; Adam, K. R., Antolovich, M., Baldwin, D. S., Brigden, L. G., Duckworth, P. A., Lindoy, L. F., Bashall, A., McPartlin, M., and Tasker, P. A., *J. Chem. Soc., Dalton Trans.*, 1992, 1869; Adam, K. R., Antolovich, M., Baldwin, D. S., Duckworth, P. A., Leong, A. J., Lindoy, L. F., McPartlin, M., and Tasker, P. A., *J. Chem. Soc., Dalton Trans.*, 1993, 1013; Adam, K. R., Arshad, S. P. H., Baldwin, D. S., Duckworth, P. A., Leong, A. J., Lindoy, L. F., McCool, B. J., McPartlin, M., Tailor, B. A., and Tasker, P. A., *Inorg. Chem.*, 1994, **33**, 1194; Adam, K. R., Baldwin, D. S., Duckworth, P. A., Lindoy, L. F., McPartlin, M., Bashall, A., Powell, H. R., and Tasker, P. A., *J. Chem. Soc., Dalton Trans.*, 1995, 1127.

in situ with sodium borohydride to give the desired double-ring macrocycle. The yields for these bis-macrocyclizations [39, 54 and 60%, respectively, for (1), (2) and (3)] appear reasonable considering the double nature of the condensation reaction. Moderate dilution conditions were found satisfactory for the synthesis of (2) but much higher dilution conditions were required for (1) and (3). Furthermore, macrocycle (2) was readily purified by recrystallization but this proved more difficult for (1) and (3)—these latter compounds were purified by crystallization of their protonated salts.

It is noted that previous workers have shown that the use of linear polyamines in Schiff-base reactions may result in a non-terminal (secondary) amine reacting in concert with a primary amine and the aldehyde to yield an aminal derivative.[1,12] Nevertheless, reduction of such species is known to generate the desired linear amine backbone incorporating only secondary amines. In view of the above, possible formation of an aminal intermediate cannot be ruled out in the preparation of (3).



Scheme 2. (i) For (11b): 1,3-dibromopropane, K_2CO_3, dimethylformamide, 120°C overnight. (ii) For (4a): (11a), pentaerythrityl tetraamine, MeOH, $NaBH_4$. For (4b): (11b), pentaerythrityl tetraamine, tetrahydrofuran, 4 Å molecular sieves, $LiAlH_4$. (iii) High dilution, 4 Å molecular sieves. For (7): (11b), ethane-1,2-diamine, $NaBH_4$. For (8): (11b), propane-1,3-diamine, $NaBH_4$. For (9): (11b), 2.2′-diaminodiethylamine, $NaBH_4$.

The second procedure (Scheme 2) was used to synthesize (4a,b). The preparation of dialdehyde (11a) has been reported previously[13] while (11b) was prepared by alkylation of 5-t-butylsalicylaldehyde with 1,3-dibromopropane under similar conditions to those described for the synthesis of the tetraaldehyde (10). Ring closure was carried out by condensation of either (11a) or (11b) with pentaerythrityl tetraamine [$C(CH_2NH_2)_4$] followed by *in situ* reduction of the tetraimine. Compound (4a) was obtained in moderate yield (49%) by cyclization of (11a) and pentaerythrityl tetraamine in methanol followed by sodium borohydride reduction under similar moderate dilution conditions to those used in the synthesis of (2).

Our initial attempts to effect cyclization of (11b) with pentaerythrityl tetraamine in methanol and subsequent reduction with sodium borohydride did not yield isolable quantities of (4b). However, (4b) was obtained successfully when the above condensation reaction was performed in dry tetrahydrofuran in the presence of 4 Å molecular sieves (to facilitate imine formation by scavenging water). Reduction of the intermediate tetraimine with lithium aluminium hydride, followed by chromatography, yielded (4b) in 37% yield.

[12] Menif, R., Martell, A. E., Squattrito, P. J., and Clearfield, A., *Inorg. Chem.*, 1990, **29**, 4723; Pietraszkiewicz, M., and Gasiorowski, R., *Chem. Ber.*, 1990, **123**, 405.
[13] Armstrong, L. G., and Lindoy, L. F., *Inorg. Chem.*, 1975, **14**, 1322.

Related Schiff-base condensation and sodium borohydride reduction procedures to those just described were employed to obtain the monocyclic derivatives (7)–(9) (Scheme 2). In all cases, physical measurements (^{1}H and ^{13}C n.m.r., high-resolution mass spectra) were in accordance with the (monomeric) structures proposed for these latter compounds. These same compounds provided spectral comparisons for the spiro-linked bis-macrocycles described above. In general, n.m.r. spectra for the spiro-linked and monocyclic systems were strictly comparable. Minor differences observed (see Experimental) are most reasonably attributed to the greater conformational rigidity expected for the spiro-linked systems.

Experimental

^{1}H and ^{13}C n.m.r. spectra were determined on a Bruker AM300 spectrometer at 300 and 75 MHz respectively. All n.m.r. spectra were recorded in (D)chloroform solution. High-resolution mass spectra (electron impact and liquid secondary ion mass spectra) were determined by Dr N. Davies, Central Science Laboratory, University of Tasmania. All melting points are uncorrected. Dialdehyde (11a),[13] 5-t-butylsalicylaldehyde[14] and pentaerythrityl tetraamine[15] were prepared by literature procedures. Pentaerythrityl tetrabromide was purchased from Aldrich and used without further purification. Dimethylformamide was distilled from a mixture of 4 Å and 13X molecular sieves. Tetrahydrofuran was distilled from sodium benzophenone ketyl.

Tetraaldehyde (10)

Potassium carbonate (14·8 g, 107 mmol), pentaerythrityl tetrabromide (9·3 g, 24 mmol) and 5-t-butylsalicylaldehyde (19·1 g, 107 mmol) were dissolved in dry dimethylformamide (200 ml) under a blanket of nitrogen. The reaction mixture was heated at 120°C overnight then cooled to room temperature. The solution was poured into an ice/water mixture (1 : 1); the resulting precipitate was collected, suspended in n-hexane (400 ml) and stirred for 5 min. The fine orange precipitate was collected and recrystallized from toluene to yield a colourless *solid* (17·1 g, 92%), m.p. 76–77° (Found: C, 75·7; H, 7·9. $C_{49}H_{60}O_8$ requires C, 75·7; H, 7·8%. Found: MH^+, 777·4347. $C_{49}H_{61}O_8$ requires *m/z* 777·4366). ^{1}H n.m.r. δ 1·28, 36H, s, $C(CH_3)_3$; 4·55, 8H, s, CH_2O; 7·02, 4H, d, *J* 8·8 Hz; 7·59, 4H, dd, *J* 2·6, 8·8 Hz; 7·80, 4H, d, *J* 2·6 Hz; 10·36, 4H, s, CHO. ^{13}C n.m.r. δ 31·2, CH_3; 34·2, $\mathbf{C}(CH_3)_3$; 45·6, $\mathbf{C}(CH_2O)_4$; 66·6, CH_2O; 112·3, 124·2, 126·4, 133·5, 144·4, 158·1, aromatics; 189·1, CHO.

Macrocycle (1)

Separate solutions of tetraaldehyde (10) (1·0 g, 1·3 mmol) dissolved in h.p.l.c. grade acetonitrile (200 ml) and ethane-1,2-diamine (0·16 g, 2·6 mmol) dissolved in absolute ethanol (200 ml) were added dropwise to refluxing absolute ethanol (200 ml) containing 4 Å molecular sieves over a 5 h period. The mixture was refluxed overnight then cooled to room temperature. Sodium borohydride (2·0 g, 52 mmol) was added and the mixture refluxed for a further 3 h. After cooling, the suspension was filtered and the collected solid washed with ethanol (3×50 ml). The solvent was evaporated to yield a gum which was dissolved in dichloromethane (100 ml) and washed with 1 M NaOH (50 ml). The organic layer was collected, dried (Na_2SO_4), filtered and the solvent removed to yield a pale yellow solid. This was dissolved in an ethanol/diethyl ether (1 : 4) mixture (5 ml), then concentrated hydrochloric acid (0·5 ml) was added with stirring. After cooling at 2° for 1 h, the hydrochloride salt that precipitated was collected and washed with ice-cold acetonitrile (10 ml). The hydrochloride salt was recrystallized from methanol. It was converted into the free base by suspending it in water (10 ml), adding concentrated sodium hydroxide until the aqueous phase reached pH 12, then extracting the free base into dichloromethane (3×20 ml). The combined organic portions were dried (Na_2SO_4),

[14] Kerr, J. M., Suckling, C. J., and Bamfield, P., *J. Chem. Soc., Perkin Trans. 1*, 1990, 887.
[15] Litherland, A., and Mann, F. G., *J. Chem. Soc.*, 1938, 1588; McAuley, A., Subramanian, S., and Whitcombe, T. W., *Can. J. Chem.*, 1989, **67**, 1650.

filtered and the solvent was evaporated to yield (1) as a colourless waxy *solid* (0·42 g, 39%), m.p. 128–129° (Found: MH^+, 833·5946. $C_{53}H_{77}N_4O_4$ requires *m/z* 833·5945). ^1H n.m.r. δ 1·29, 36H, s, Bu^t; 1·91, 4H, br s, NH; 2·71, 8H, s, CH_2N; 3·71, 8H, s, $ArCH_2$; 4·41, 8H, s, CH_2O; 6·92, 4H, d, *J* 8·6 Hz; 7·18, 4H, d, *J* 2·4 Hz; 7·24, 4H, dd, *J* 2·4, 8·6 Hz. ^{13}C n.m.r. δ 31·5, CH_3; 34·1, **C**$(CH_3)_3$; 45·1, **C**$(CH_2O)_4$; 47·6, NCH_2; 50·2, NCH_2; 69·3, CH_2O; 113·7, 125·4, 128·3, 128·8, 144·4, 155·1, aromatics.

Macrocycle (2)

Tetraaldehyde (10) (5·0 g, 6·4 mmol) was dissolved in h.p.l.c. grade methanol (300 ml) and heated to reflux under a nitrogen atmosphere. Propane-1,3-diamine (0·96 g, 12·9 mmol) dissolved in h.p.l.c. grade methanol (30 ml) was then added to the solution and reflux continued for 1 h. Sodium borohydride (1·02 g, 27·0 mmol) was then added in small portions and, after a further 1 h at reflux, the reaction mixture was allowed to cool to room temperature. A mixture of ice/water (300 ml) was added slowly to the reaction mixture and a white precipitate formed. This was collected and recrystallized from a mixture of acetonitrile (100 ml) and chloroform (3 ml) to yield (2) as a colourless crystalline *solid* (3·0 g, 54%), m.p. 212–214° (Found: C, 76·6; H, 9·3; N, 6·3. $C_{55}H_{80}N_4O_4$ requires C, 76·7; H, 9·4; N, 6·5%. Found: MH^+, 861·6266. $C_{55}H_{81}N_4O_4$ requires *m/z* 861·6257). ^1H n.m.r. δ 1·28, 36H, s, $C(CH_3)_3$; 1·58, 4H, quin, $J \approx 6$ Hz, NCH_2CH_2; 1·70, 4H, br s, NH; 2·62, 8H, t, $J \approx 6$ Hz, NCH_2CH_2; 3·73, 8H, s, $ArCH_2$; 4·40, 8H, s, CH_2O; 6·88, 4H, d, *J* 8·6 Hz; 7·19, 8H, m. ^{13}C n.m.r. δ 29·4, NCH_2CH_2; 31·5, CH_3; 34·0, **C**$(CH_3)_3$; 45·8, **C**$(CH_2O)_4$; 48·2, 51·0, CH_2N; 68·2, CH_2O; 113·6, 125·3, 128·1, 129·0, 144·2, 155·0, aromatics.

Macrocycle (3)

Separate solutions of tetraaldehyde (10) (1·0 g, 1·3 mmol) dissolved in h.p.l.c. grade acetonitrile (200 ml) and 2,2′-diaminodiethylamine (0·27 g, 2·6 mmol) dissolved in absolute ethanol (200 ml) were simultaneously added dropwise to refluxing absolute ethanol (200 ml) containing 4 Å molecular sieves over a 5 h period. The mixture was heated at reflux overnight, then cooled to room temperature. Sodium borohydride (2·0 g, 52 mmol) was added and the mixture refluxed for a further 3 h. After cooling, the suspension was filtered and the collected solid washed with ethanol (3×50 ml). The solvent was evaporated to yield a gum which was redissolved in dichloromethane (100 ml); the resulting solution was washed with 1 M NaOH (50 ml). The organic phases were combined, dried (Na_2SO_4), filtered and the solvent was removed to yield a pale yellow solid. This was dissolved in absolute ethanol (7 ml) and concentrated hydrochloric acid (0·5 ml) was added. The solution was let stand at 2° for 1 h and the hydrochloride salt that had precipitated was collected and washed with ice-cold acetonitrile (50 ml). This hydrochloride salt was then dissolved in a mixture of 1:1 ethanol/water (40 ml) and a saturated aqueous solution of potassium hexafluorophosphate (15 ml) was added dropwise. The volume of the mixture was reduced to 15 ml on a rotary evaporator, then let stand at 2° for 1 h. The white hexafluorophosphate salt that formed was washed with water (2×10 ml), air-dried, then washed with diethyl ether (2×10 ml). The free ligand was obtained by using an identical procedure to that described for macrocycle (1). It was obtained as a colourless waxy *solid* (0·72 g, 60%), m.p. 208° (Found: MH^+, 919·6774. $C_{57}H_{87}N_6O_4$ requires *m/z* 919·6789). ^1H n.m.r. δ 1·27, 36H, s, $C(CH_3)_3$; 2·49, 16H, m, NCH_2CH_2N; 2·86, 6H, br s, NH; 3·69, 8H, s, $ArCH_2$; 4·46, 8H, s, CH_2O; 6·95, 4H, d, *J* 8·6 Hz; 7·14, 4H, d, *J* 2·4 Hz; 7·27, 4H, dd, *J* 2·4, 8·6 Hz. ^{13}C n.m.r. δ 31·4, CH_3; 34·0, **C**$(CH_3)_3$; 44·9, **C**$(CH_2O)_4$; 47·6, 47·9, 50·0, CH_2N; 68·1, CH_2O. 111·7, 125·7, 126·5, 128·1, 144·0, 154·5, aromatics.

Dialdehyde (11b)

A mixture of 5-t-butylsalicylaldehyde (3·35 g, 18·73 mmol), potassium carbonate (2·60 g, 18·73 mmol) and 1,3-dibromopropane (1·90 g, 9·37 mmol) in dry dimethylformamide (50 ml) was heated at 120°C overnight. The solvent was removed and the resulting mixture partitioned between methylene chloride (30 ml) and 2 M sodium hydroxide (40 ml). After separating the organic phase, the aqueous phase was reextracted with methylene chloride (3×20 ml) and the organic fractions were combined, then dried (Na_2SO_4) and the solvent was removed. The residue was purified by chromatography on silica gel with 10% ethyl acetate/petrol as the

eluent. The dialdehyde (11b) was obtained as a yellow *oil* (2·94 g, 77%) (Found: $M^{+\bullet}$, 396·2298. $C_{25}H_{32}O_4$ requires $M^{+\bullet}$, 396·2298). ^{1}H n.m.r. δ 1·30, 18H, s, $C(CH_3)_3$; 2·39, 2H, quin, OCH_2CH_2; 4·29, 4H, t, OCH_2; 6·95, 2H, d, J 8·7 Hz; 7·57, 2H, dd, J 2·6, 8·7 Hz; 7·84, 2H, d, J 2·6 Hz; 10·48, 2H, s, CHO. ^{13}C n.m.r. δ 29·1, OCH_2CH_2; 31·2, $C(CH_3)_3$; 34·2, CH_3; 64·6, OCH_2; 112·1, 124·1, 125·0, 133·2, 143·8, 159·0, aromatics; 189·8, CHO.

Macrocycle (4a)

To a solution of (11a) (795 mg, 2·93 mmol) in h.p.l.c. grade methanol (30 ml) was added pentaerythrityl tetraamine (194 mg, 1·46 mmol) dissolved in h.p.l.c. grade methanol (10 ml). The reaction mixture was refluxed for 2 h, then cooled to 50°. Sodium borohydride (450 mg, 11·90 mmol) was added in small portions. The vigorously stirred, clear mixture was cooled to 2° and a slurry of ice and water (75 ml) was added slowly. The crude product separated as a white solid which was recrystallized from acetonitrile (35 ml) to yield (4a) as a colourless crystalline *solid* (510 mg, 49%), m.p. 217–220° (Found: C, 72·9; H, 7·2; N, 9·2. $C_{37}H_{44}N_4O_4$ requires C, 73·0; H, 7·3; N, 9·2%. Found: MH^+, 609·3435. $C_{37}H_{45}N_4O_4$ requires m/z 609·3441). ^{1}H n.m.r. δ 1·85, 4H, br s, NH; 2·31, 8H, s, NCH_2; 3·72, 8H, s, $ArCH_2$; 4·35, 8H, s, OCH_2; 6·84, 4H, br d, J 7·8 Hz; 6·88, 4H, br t, J *c.* 7·5 Hz; 7·11, 4H, dd, J 1·6, *c.* 7·5 Hz; 7·22, 4H, dt, J 1·6, 7·5 Hz. ^{13}C n.m.r. δ 41·0, $C(CH_2)_4$; 52·0, CH_2N, $ArCH_2$; 65·6, OCH_2; 109·9, 120·4, 128·3, 128·4, 131·1, 157·0, aromatics.

Macrocycle (4b)

A solution of anhydrous pentaerythrityl tetraamine (215 mg, 1·60 mmol) in dry tetrahydrofuran (10 ml) was added to dialdehyde (11b) (1·30 g, 3·22 mmol) dissolved in dry tetrahydrofuran (50 ml) containing a suspension of powdered 4 Å molecular sieves (0·5 g). This suspension was heated at reflux for 4 h, cooled and lithium aluminium hydride (245 mg, 6·4 mmol) was then slowly added. Refluxing was continued for a further 1 h. After cooling, excess lithium aluminium hydride was destroyed by the sequential addition of water (0·23 ml), 20% w/v sodium hydroxide (0·23 ml), then water (0·69 ml). The white gelatinous precipitate was filtered off, and washed with hot methylene chloride (3×20 ml). The combined organic extracts were washed with saturated brine (20 ml) and H_2O (20 ml), then dried (Na_2SO_4), filtered and the solvent was evaporated to yield a viscous oil which crystallized on storage. This material was recrystallized from acetonitrile/chloroform to yield (4b) as colourless *needles* (510 mg, 37%), m.p. 199–202° (Found: C, 75·4; H, 9·3; N, 6·5. $C_{55}H_{80}N_4O_4.H_2O$ requires C, 75·1; H, 9·4; N, 6·4%. Found: MH^+, 861·6258. $C_{55}H_{81}N_4O_4$ requires m/z 861·6258). ^{1}H n.m.r. δ 1·27, 36H, s, $C(CH_3)_3$; 2·25, 4H, quin, OCH_2CH_2; 2·57, 8H, s, $C(CH_2N)_4$; 3·71, 8H, s, $ArCH_2$; 4·18, 8H, t, OCH_2; 6·86, 4H, d, J 8·5 Hz; 7·16, 4H, d, J 2·4 Hz; 7·27, 4H, dd, J 2·4, 8·5 Hz. ^{13}C n.m.r. δ 29·6, OCH_2CH_2; 31·4, $C(CH_3)_3$; 34·0, $C(CH_3)_3$; 39·3, $C(CH_2N)_4$; 50·1, 52·6, $C(CH_2N)_4$, $ArCH_2$; 66·0, OCH_2; 112·7, 125·8, 128·5, 129·1, 144·0, 155·0, aromatics.

Macrocycle (7)

This compound was prepared by condensation of ethane-1,2-diamine (0·16 g, 2·6 mmol) and dialdehyde (11b) (0·98 g, 2·6 mmol) followed by *in situ* reduction with sodium borohydride (2·0 g, 52 mmol) as described for (1). The crude product was purified by chromatography (silica gel, elution with $MeOH/CHCl_3/NH_4OH$, 3:96:1) to afford the product as a waxy *solid* (0·88 g, 81%) (Found: $M^{+\bullet}$, 424·3077. $C_{27}H_{40}N_2O_2$ requires $M^{+\bullet}$, 424·3090). ^{1}H n.m.r. δ 1·28, 18H, s, $C(CH_3)_3$; 2·26, *c.* 2H, br s, NH; 2·32, *c.* 2H, quin, J 5·5 Hz, OCH_2CH_2; 2·78, s, 4H, NCH_2; 3·73, s, 4H, $ArCH_2$; 4·22, 4H, t, J 5·5 Hz, OCH_2; 6·83, 2H, d, J 8·8 Hz; 7·21, 2H, dd, J 2·8, 8·8 Hz; 7·25, 2H, d, J 2·8 Hz. ^{13}C n.m.r. δ 29·0, OCH_2CH_2; 31·4, CH_3; 34·0, $C(CH_3)_3$; 47·1, NCH_2; 50·0, NCH_2; 66·2, CH_2O; 112·1, 125·0, 128·2, 143·6, 154·9, aromatics.

Macrocycle (8)

This compound was prepared from propane-1,3-diamine (0·98 g, 13·2 mmol) and dialdehyde (11b) (5·3 g, 13·2 mmol) by a similar procedure to that described for (2). Two hours after sodium borohydride addition, the reaction solution was evaporated to dryness and the residue was then dissolved in dichloromethane (150 ml). This solution was then shaken with water

(100 ml), and the dichloromethane layer dried (Na_2SO_4). Evaporation of the methylene chloride yielded an orange oil which was purified by silica gel chromatography with a mixture of ethyl acetate/triethylamine (90:10) as eluent. The product was isolated as a waxy *solid* (2·4 g, 41%) (Found $M^{+\bullet}$, 438·3252. $C_{28}H_{42}N_2O_2$ requires $M^{+\bullet}$, 438·3246). ^1H n.m.r. δ 1·32, 18H, s, $C(CH_3)_3$; 1·72, 2H, quin, J 6·0 Hz, NCH_2CH_2; 1·85, 2H, br s, NH; 2·32, 2H, quin, J 5·8 Hz, OCH_2CH_2; 2·70, t, 4H, J 6·0 Hz, NCH_2; 3·80, 4H, s, $ArCH_2$; 4·29, 4H, t, J 5·8 Hz, CH_2O; 6·92, 2H, d, J 8·3 Hz; *c.* 7·27, 4H, m. ^{13}C n.m.r. δ 29·1, OCH_2CH_2; 30·0, NCH_2CH_2; 31·4, CH_3; 34·0, $C(CH_3)_3$; 47·5, 50·6, NCH_2; 65·9, CH_2O; 113·1, 125·0, 128·0, 128·8, 144·0, 155·0, aromatics.

Macrocycle (9)

This compound was prepared from 2,2′-diaminodiethylamine (0·14 g, 1·3 mmol) and dialdehyde (11b) (0·49 g, 1·3 mmol) by following the procedure described for the synthesis of (7). The product was obtained as a waxy *solid* (0·50 g, 81%) (Found: $M^{+\bullet}$, 467·3524. $C_{29}H_{45}N_3O_2$ requires $M^{+\bullet}$, 467·3512). ^1H n.m.r. δ 1·29, 18H, s, $C(CH_3)_3$; 2·2, *c.* 3H, br s, NH; 2·31, *c.* 2H, quin, J 6·0 Hz, OCH_2CH_2; 2·63, 8H, s, NCH_2CH_2N; 3·76, 4H, s, $ArCH_2$; 4·23, 4H, t, J 6·0 Hz, CH_2O; 6·89, 2H, d, J 8·6 Hz; 7·18, 2H, d, J 2·4 Hz; 7·23, 2H, dd, J 2·4, 8·6 Hz. ^{13}C n.m.r. δ 29·7, OCH_2CH_2, 31·4, CH_3; 33·8, $C(CH_3)_3$; 48·9, NCH_2; 49·1, NCH_2; 51·0, NCH_2; 64·0, CH_2O; 111·0, 124·9, 127·6, 127·8, 143·0, 154·7, aromatics.

Acknowledgments

We thank the Australian Research Council and the Australian Institute of Nuclear Science and Engineering for support. O.A.M. is the recipient of an Australian Postgraduate Research Award. J.N. acknowledges the Swiss National Science Foundation for the award of a Postdoctoral Fellowship.