Acid-catalysed rearrangements between 3,4-dihydro-2*H*-1,5-benzooxazocine and -benzothiazocine and their macrocyclic (16-membered, 24-membered and 32-membered) oligomers

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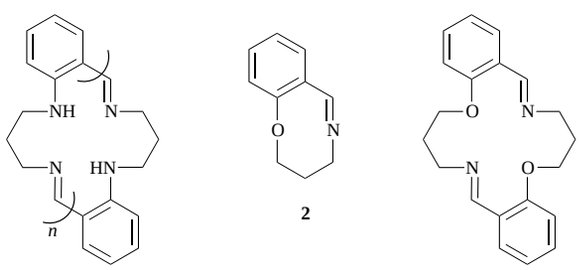
Treatment of 2-(3-azidopropoxy)benzaldehyde with triphenylphosphine in diethyl ether, followed by sequestration of the products with nickel(II) thiocyanate and subsequent liberation from the complex with aqueous ammonia, produces the 16-membered dimer of 3,4-dihydro-2*H*-1,5-benzooxazocine. The dioxadiaza diimine macrocycle 3 undergoes an acid-catalysed rearrangement in solution into an equilibrium mixture that includes the trioxatriaza triimine (24-membered) 8 and tetraoxatetraaza tetraimine (32-membered) 9 macrocycles, as well as the diimine. The oligomers in [^{2}H]chloroform differ in the ^{1}H NMR chemical shifts of the protons on the central carbon atoms of the propane-1,3-diyl links, thereby allowing an investigation of the factors involved in the rearrangements between the macrocyclic oligomers. Thus, the rearrangements of the macrocyclic polyimines into equilibrium mixtures of the various oligomers occurs with $t_{\frac{1}{2}}$ 7–10 min, but the position of the equilibrium in each case is dependent upon the imine equivalent concentration of the solution. 3,4-Dihydro-2*H*-1,5-benzothiazocine undergoes a similar rearrangement. The equilibrations have been ascribed to facile intermolecular transiminations between the oligomers in the presence of traces of acid and to the similarities of the thermodynamic stabilities of the 16-, 24- and 32-membered oligomers. The crystal and molecular structures of ammonium nitrate salts of the 16-membered diamine 11 and 32-membered tetraamine 10 derivatives of the corresponding macrocyclic benzooxazocines are reported.

Introduction

The importance of metal-ion size in the template synthesis of large macrocycles by condensation reactions is well known; an alteration in the metal employed in the cyclisation can produce an oligomeric macrocycle of different ring size by a kinetic or thermodynamic template effect.[1] If the macrocycles exist in a metal-independent equilibrium with higher cyclic oligomers however, the thermodynamic stabilities and solubility properties of the various oligomers may play the deciding role.

In our recent syntheses of imine macrocycles based on 1,2,3,4-tetrahydro-1,5-benzodiazocine, the 32-membered octaaza tetraimine **1c** was found to exist in a metal-independent acid-catalysed equilibrium with the 16-membered tetraaza diimine **1a** and 24-membered hexaaza triimine **1b**.[2] The equilibrium was dominated by the poor solubility of **1c**, which was the product obtained from mixtures of the oligomers in solutions containing traces of acid. The more soluble lower polyimines were isolated by selective sequestration or fractional crystallisation from equilibrium mixtures quenched with a non-protic solvent.

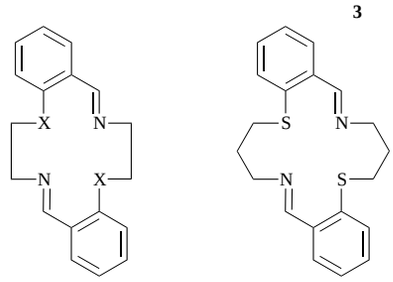
Acid-catalysed, metal-independent equilibria involving macrocyclic imines have been documented for the parent[3] and several substituted dihydrobenzo-azepines and -azocines,[2,4–10] and for certain other macrocyclic polyimines such as TAAB and TRI.[11] The equilibria, however, have not been observed previously for ring sizes larger than 16 members. For example, the closely related substituted benzoazepine dimers **4** (X = CH_2, O, S, AsMe)[3–8] rearrange into equilibrium monomer (7-membered) ⟷ dimer (14-membered) mixtures under slightly acidic conditions. In each case the monomer is strongly



1a (*n* = 1)
1b (*n* = 1)
1c (*n* = 3)

2

3



4 (X = CH_2, NH, O, S, AsMe)

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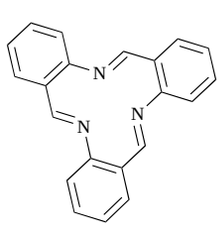
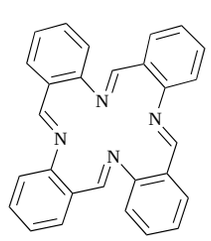


TRI



TAAB

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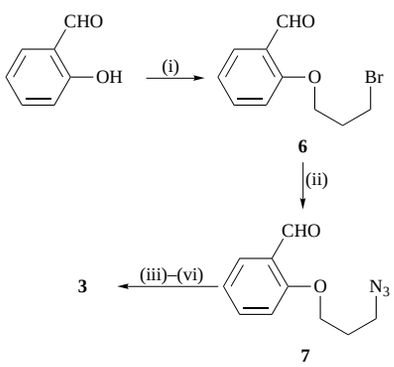
favoured in solution, but removal of solvent affords the dimer as a crystalline solid. For **4** (X = NH)[9] a similar rearrangement occurs in which the dimer is favoured; this was ascribed to the increased basicity of the amino groups present.[10] In contrast, the rearrangements between the benzodiazocine oligomers **1a**–**c** do not appear to involve the 8-membered monomer, but only the higher oligomers.

We have now prepared the 16-membered dioxadiaza diimine dimer **3** of 3,4-dihydro-2*H*-1,5-benzooxazocine **2**, as well as the 16-membered dithiadiaza diimine dimer of 3,4-dihydro-2*H*-1,5-benzothiazocine, **5**,[6] and investigated the acid-catalysed rearrangements in each case. The results are reported below; they indicate that acid-catalysed rearrangements involving 16-, 24- and 32-membered macrocycles of this type are common to 3,4-dihydro-2*H*-1,5-benzoheteroazocines containing NH-, O- and S-heteroatoms and originate in self-assembly processes in which rapid kinetics permit the formation of the thermodynamically most favoured products in each case.

Results and discussion

Benzoazocine oligomers

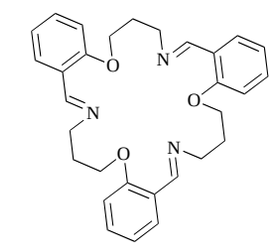
The 14-membered diimine 6,7,15,16-tetrahydrodibenzo[*f*,*m*][1,8,4,11]dioxadiazacyclotetradecine **4** (X = O) had been prepared previously in our laboratory from 2-(2-azidoethoxy)benzaldehyde by the aza-Wittig reaction.[8] The same reaction was employed for the preparation of the 16-membered dioxadiaza diimine 7,8,17,18-tetrahydro-6*H*,16*H*-dibenzo[*b*,*j*][1,9,5,13]dioxadiazacyclohexadecine **3** (Scheme 1). Because of



Scheme 1 *Reagents and conditions*: (i) $BrCH_2CH_2CH_2Br$, (ii) NaN_3, (iii) Ph_3P, Et_2O, (iv) $CHCl_3$, heat, 24 h, (v) $NiCl_2$, KSCN(aq.), (vi) NH_4OH

the triphenylphosphine oxide by-product in the reaction mixture and the facile rearrangement of **3** in solution, the diimine was isolated by selective sequestration with nickel(II) thiocyanate and subsequent liberation from the metal complex with aqueous ammonia.[6] The use of aqueous ammonia was necessary to bring about precipitation of **3** after release of the metal, thereby eliminating subsequent rearrangements in solution.

In our investigation of the acid-catalysed rearrangement of **3**, a concentrated solution of the macrocycle in [^{2}H]chloroform was monitored by ^{1}H NMR spectroscopy over several hours; the resonances characteristic of the diimine were gradually replaced by two sets of new resonances. The most diagnostic of these resonances were those arising from the protons on the central carbon atom of the propane-1,3-diyl link, in which minimal overlap occurred. Thus, the multiplet at δ 2.35, associated with **3**, was replaced by new multiplets at δ 2.11 and 2.25. As observed previously for other benzodiazocine rearrangements,[2] the new resonances suggested the presence of the triimine **8** and tetraimine **9**. The slow crystallisation of a concentrated chloroform solution of **3** afforded colourless crystals that exhibited new ^{1}H NMR resonances in [^{2}H]chloroform characteristic of one of the rearrangement products, including the diagnostic



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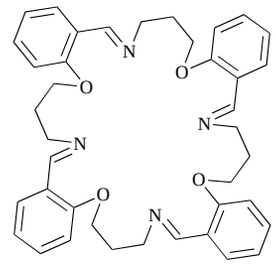

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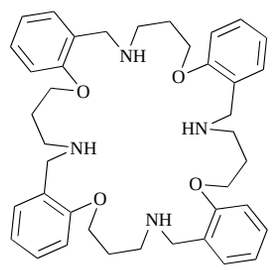

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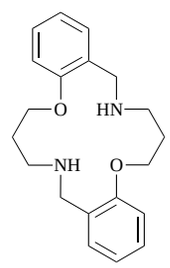

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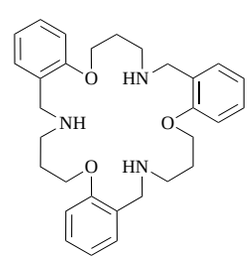


12

resonance at δ 2.11. The mass spectrum of the compound displayed a peak at *m*/*z* 644.0, which corresponded to the tetraimine **9**. The mass spectrum of **3** under similar conditions contained a molecular ion peak at *m*/*z* 321.1. Reduction of **9** with lithium aluminium hydride led to the corresponding, kinetically inert, tetraoxatetraamine **10**. Treatment of a methanolic solution of **10** with nitric acid led to the isolation of colourless crystals of **10**·4HNO_3·CH_3OH that were suitable for a single crystal X-ray structural determination. The molecular structure of the cation in **10**·4HNO_3·CH_3OH is shown in Fig. 1; within the unit cell each 32-membered tetraammonium macrocycle is associated with six nitrate ions, four of which are shared with cations in neighbouring cells.

The dioxadiaza diamine **11** was prepared by reduction of **3** under similar conditions. Although the ^{1}H NMR spectrum of **11** is very similar to that of **10**, the fragmentation pattern of **11** in the mass spectrum is significantly different; the spectrum contains a peak for the molecular ion at *m*/*z* 326.2, whereas **10** exhibits a peak at *m*/*z* 652.2. An X-ray crystal structure determination was performed on a crystal of **11**·2HNO_3. The molecular structure of one of two similar but independent cations in **11**·2HNO_3 is shown in Fig. 2. Each cation lies on a centre of inversion. The crystal contains discrete assemblies involving four of the 16-membered diammonium macrocycles juxtaposed about eight bridging nitrate ions.

Crystal data, information relating to data collection and refinement details for **11**·2HNO_3 and **10**·4HNO_3·CH_3OH are given in the Experimental section.‡

‡ Atomic coordinates, thermal parameters and bond lengths and angles have been deposited with the Cambridge Crystallographic Data Centre (CCDC). Any requests for this material should be accompanied by a full literature citation together with the reference number 207/157.

For details of the scheme, see Instructions for Authors, *J. Chem. Soc.*, *Perkin Trans. 1*, available *via* the RSC Web pages (http//www.rsc.org/authors).

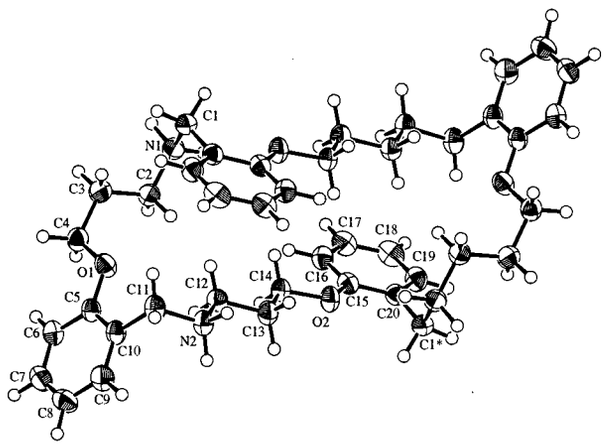


Fig. 1 ORTEP view of the cation in **10**·4HNO_3·CH_3OH showing atom-labelling scheme for non-hydrogen atoms. Thermal ellipsoids enclose 50% probability levels. The cation occupies a centre of inversion in the crystal.

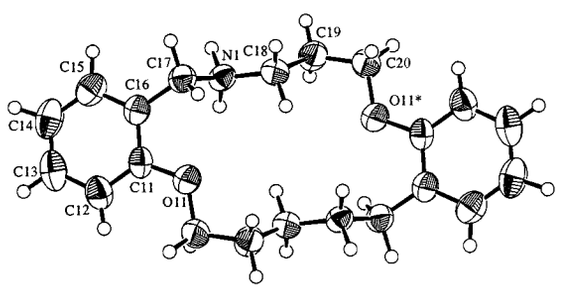
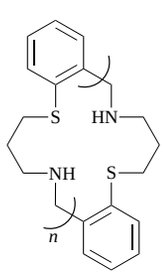


Fig. 2 ORTEP view of one of two similar, but independent cations in the unit cell of **11**·2HNO_3. Each cation lies on a centre of inversion. The atom-labelling scheme for non-hydrogen atoms in this particular cation is shown. Thermal ellipsoids enclose 50% probability levels.

Having established the identities of two of the three species involved in the equilibrium, *viz*. **3** and **9**, an attempt was made to isolate the third component, which exhibited a diagnostic ^{1}H NMR resonance at δ 2.25. The attempted fractional crystallisation from dichloromethane of a sample enriched in the unknown species was unsuccessful due to rearrangements. Thus, a concentrated, week-old solution of **3** was reduced with sodium cyanoborohydride in acetic acid–methanol. This led to the isolation of a mixture of the kinetically stable oxaaza polyamines **10**, **11** and **12** that were separated as their hydrochlorides on cation exchange resin by elution with aqueous methanolic hydrochloric acid of increasing acidity (1–4 M). The second band to be eluted from the column was identified as the triamine hydrochloride **12**·3HCl by its mass spectrum, which contained a peak at *m*/*z* 489.4 corresponding to the triamine. The first and third bands recovered from the column gave crystalline solids that had properties identical to those of the separately prepared **11**·2HCl and **10**·4HCl, respectively. Treatment of **12**·3HCl with aqueous sodium hydroxide produced free **12** as a colourless oil. In view of the isolation of **12**, the third species in the equilibrium mixture containing **3** and **9** was identified as the trioxatriaza triimine **8**.

Benzothiazocine oligomers

The dithiadiaza diimine **5** was prepared as described previously.[6] The diimine rearranges over several days in [^{2}H]chloroform, as indicated by the appearance of two new sets of resonances in the propane-1,3-diyl central methylene region and a single new azamethine peak in the ^{1}H NMR spectrum. Unlike the solution for **3** however, significant overlap of the resonances in the spectrum meant that a detailed analysis was not possible. Moreover, the poor stability of **5** in chloroform precluded the isolation of the higher oligomers by fractional crystallisation or selective sequestration with nickel(II). The cyanoborohydride reduction of a concentrated, week-old, chloroform solution of **5**, followed by an ion chromatogram mass spectrum of the oil after removal of solvent, nevertheless confirmed the presence of the dithiadiaza diamine (*m*/*z* 358.1), trithiatriaza triamine (*m*/*z* 537.2) and tetrathiatetraaza tetraamine (*m*/*z* 717.0) oligomers (mixture **13**). Pure **13** (*n* = 1) (the diamine) exhibited the peak at *m*/*z* 358.1 only. Because of poor solubility in water and aqueous alcohols, the mixture of polyamines **13** could not be separated by ion exchange chromatography of the corresponding hydrochlorides.



13 (*n* = 1,2,3)

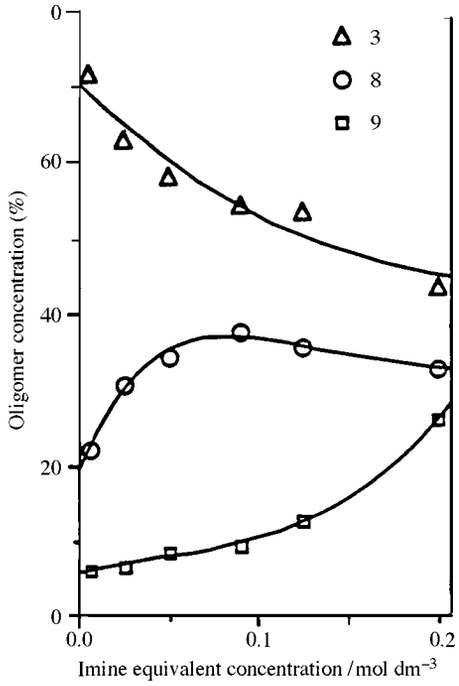


Fig. 3 Relative equilibrium proportions of oligomers of **2** in $CDCl_3$ solution as a function of imine equivalent concentration. The percentages were measured using the relative integrals of diagnostic ^{1}H NMR resonances at δ 2.11 (**3**), 2.25 (**8**) and 2.35 (**9**) after equilibration.

Acid-catalysed rearrangements between 3, 8 and 9

The $t_{\frac{1}{2}}$ values for rearrangements of **3** and **9** into equilibrium mixtures of **3**, **8** and **9** in [^{2}H]chloroform, as well as the positions of the resulting equilibria, were determined as functions of concentration by ^{1}H NMR spectroscopy. Imines **3** and **9** rapidly rearranged into equilibrium mixtures in solution. The spectra were recorded at 2–3 min intervals for the first 30 min after each solution was prepared, and then at increasing intervals over several hours. By this means the $t_{\frac{1}{2}}$ for **9** was found to be *ca.* 10 min, whereas for **3** it was *ca.* 7 min. Concentrations of 0.2 M imine equivalents (mol imine bonds per litre [^{2}H]chloroform) were used in both cases to normalise the comparisons.

The position of the equilibrium was found to be markedly dependent on the concentrations of the solutions employed (Fig. 3). The compounds equilibrated within several hours, but solutions were kept for *ca.* 15 h to ensure complete rearrangement. Fig. 3 shows the proportions of each oligomer (measured

using the integrals of the diagnostic central propane-1,3-diyl bridge ^{1}H NMR multiplets) as a function of the imine equivalent concentration. The diimine **3** was thermodynamically favoured in dilute solutions, but the tetraimine **9** became more favoured as the concentration of the solution was increased. At 0.006 M, the ratio of the integrals indicated **3**:**8**:**9** = 72:23:5. The percentage due to **3** fell whereas that of **9** rose as the concentration of the solution was increased over the range examined. The proportion of **8** increased to a maximum of 37% at 0.090 M, and then decreased slowly as the concentration was increased to 0.200 M. At 0.200 M the ratio of **3**:**8**:**9** determined in this way was 44:31:25. Thus, of every 100 imine-containing molecules in a 0.200 M [^{2}H]chloroform solution, 16 were tetraimine molecules (**9**), 26 were triimine molecules (**8**) and 58 were diimine molecules (**3**). Imine equivalent concentrations greater than 0.200 M could not be investigated because of broadening and overlap of the diagnostic ^{1}H NMR resonances employed.

Conclusion

The origin of equilibria involving 16-membered diimine, 24-membered triimine and 32-membered tetraimine oligomers of 3,4-dihydro-2*H*-1,5-benzooxazocines and -benzothiazocines, and 1,2,3,4-tetrahydro-1,5-benzodiazocines can be ascribed to facile acid-catalysed rearrangements between the macrocyclic imines that allow the establishment of thermodynamic mixtures of the respective oligomers. The diimine, triimine and tetraimine oligomers possess similar thermodynamic stabilities so that all three species are present under weakly acidic conditions. In the case of the benzooxazocines **3**, **8** and **9**, entropic factors determine the relative proportions of each oligomer, with the equilibrium position shifting in favour of the larger molecules as the concentration of the solution is increased. The difference in behaviour between the substituted benzoazepine dimers **4** (X = O, S, NH), in which the 7-membered monomer is always present, and the benzoazocine oligomers **1a**–**c**, **8** and **9**, and oligomers of **5**, in which the 8-membered monomer is not observed, suggests that rearrangements of the latter are governed by ring strain. The monomeric 7-membered benzoazepines are thermodynamically more stable than the 14-membered dimers, whereas the 8-membered benzooxazocines and benzothiazocines are significantly less stable than the corresponding 16-, 24- and 32-membered oligomers. These systems therefore represent a self-assembly process in which complex structures are spontaneously assembled from smaller building blocks; in each case the kinetic instability of the imine bonds in weakly acidic solutions permits the formation of the thermodynamically favoured higher oligomers. A mechanism for such rearrangements has been proposed previously.[2] The ease with which some of the oligomers can be isolated also suggests that the rearrangement is useful for the preparation of hitherto inaccessible 24- and 32-membered macrocyclic polyamines. Future work will be directed towards the isolation of the higher homochiral oligomers of 1,2,3,4-tetrahydro-1-methyl-5,1-benzoazarsocine, the 8-membered homologue of the 7-membered benzoazarsepines previously prepared in our laboratory.[7]

Experimental

^{1}H and ^{13}C NMR spectra were recorded at 20 °C on a Varian Gemini 300 spectrometer operating at 299.96 MHz. Chemical shifts are quoted as δ values in [^{2}H]chloroform relative to internal Me_4Si unless otherwise stated; coupling constants J are given in Hz. Elemental analyses and molecular weight measurements were performed by staff within the Research School of Chemistry. Melting points were determined on a Reichert melting point apparatus and are uncorrected. All reactions were performed under an inert atmosphere. The benzothiazocine dimer **5** and its diamine **13** (n = 1) were prepared as previously described.[6]

X-Ray crystallographic analysis of 11·2HNO$_3$

Crystal data: $C_{20}H_{28}N_4O_8$ (M = 452.46), colourless plate, triclinic, crystal dimensions 0.20 × 0.10 × 0.04 mm, D_c 1.378 g cm^{-3}, space group $P\bar{1}$ (no. 2), a = 10.082(2) Å, b = 12.007(2) Å, c = 9.782(1) Å, α = 105.89(1)°, β = 106.34(1)°, γ = 82.14(1)°, V = 1090.7(3) Å^3, Z = 2, F_{000} = 4480.00. All measurements were performed on a Rigaku AFC6R diffractometer with graphite monochromated Cu-Kα radiation (λ = 1.541 78 Å), μ = 9.13 cm^{-1}. The data were collected at 23.0 °C using the ω–2θ scan technique to a maximum 2θ value of 120.1°. Of the 3445 reflections collected, 3233 were unique (R_{int} = 0.054). The data were corrected for Lorentz and polarisation effects. The structure was solved by direct methods[12] and expanded using Fourier techniques.[13] The non-hydrogen atoms were refined anisotropically. The hydrogen atom coordinates were refined but their isotropic temperature factors were held fixed with a common value. The final cycle of full-matrix least-squares refinements was based on 1607 observed reflections [$I > 3.0\sigma(I)$] and 373 variable parameters. The final R factors were $R = \Sigma ||F_o| - |F_c||/\Sigma|F_o| = 0.057$, $R_w = [\Sigma w(|F_o| - |F_c|)^2/\Sigma wF_o]^{\frac{1}{2}} = 0.052$. The standard deviation of an observation of unit weight was 2.54. The maximum and minimum peaks on the final difference Fourier map corresponded to 0.47 and −0.36 e Å^{-3} respectively.

X-Ray crystallographic analysis of 10·4HNO$_3$·CH$_3$OH

Crystal data: $C_{41}H_{60}N_8O_{17}$ (M = 936.97), colourless block, triclinic (crystallised from methanol), crystal dimensions 0.18 × 0.08 × 0.16 mm, D_c 1.379 g cm^{-3}, space group $P\bar{1}$ (no. 2), a = 8.3422(8) Å, b = 10.533(1) Å, c = 13.979(1) Å, α = 94.871(9)°, β = 100.733(7)°, γ = 108.814(8)°, V = 1128.4(2) Å^3, Z = 1, F_{000} = 498.00. All measurements were performed on a Rigaku AFC6R diffractometer with graphite monochromated Cu-Kα radiation (λ = 1.541 78 Å), μ = 9.13 cm^{-1}. The data were collected at 23.0 °C using the ω–2θ scan technique to a maximum 2θ value of 120.1°. Of the 3581 reflections collected, 3370 were unique (R_{int} = 0.019). The data were corrected for Lorentz and polarisation effects. A correction for secondary extinction was applied [coefficient = 1.4(3) × 10^{-6}]. The structure was solved by direct methods[12] and expanded using Fourier techniques.[13] The non-hydrogen atoms were refined anisotropically except for the minor component of a disordered nitrate ion. A methanol molecule was included with half-occupancy over a centre of symmetry. Hydrogen atoms were refined isotropically. Methanol hydrogen atoms could not be located. The final cycle of full-matrix least-squares refinements was based on 2414 observed reflections [$I > 3.0\sigma(I)$] and 426 variable parameters. The final R factors were $R = \Sigma ||F_o| - |F_c||/\Sigma|F_o| = 0.048$, $R_w = [\Sigma w(|F_o| - |F_c|)^2/\Sigma w|F_o|^2]^{\frac{1}{2}} = 0.044$. The standard deviation of an observation of unit weight was 3.12. The maximum and minimum peaks on the final difference Fourier map corresponded to 0.33 and −0.25 e Å^{-3} respectively.

In the crystallographic structure determinations of **10**·4HNO$_3$·CH$_3$OH and **11**·2HNO$_3$ described above, neutral atom scattering factors were taken from Cromer and Waber.[14] Anomalous dispersion effects were included in F_c;[15] the values for $\Delta f'$ and $\Delta f''$ were those of Creagh and McAuley.[16] The values for mass attenuation coefficients are those of Creagh and Hubbell.[17] All calculations were performed using the TEXSAN crystallographic software package from the Molecular Structure Corporation.[18]

2-(3-Bromopropoxy)benzaldehyde 6

This compound was prepared in 50% yield by a similar procedure to that described for the ethylene analogue[8] and was isolated as a pale yellow oil, bp 122–124 °C (0.1 mmHg) (Found: C, 50.0; H, 4.6. $C_{10}H_{11}BrO_2$ requires C, 49.4; H, 4.6%); δ_H(299.95 MHz; $CDCl_3$; Me_4Si) 2.38 (2 H, t, J 7, $CH_2CH_2CH_2$), 3.63 (2 H, t, J 7, OCH_2), 4.21 (2 H, t, J 7, CH_2Br), 7.02 (2 H, m, ArH), 7.54 (1 H, m, ArH), 7.62 (1 H, d, J 7, ArH) and 10.48 (1

H, s, CHO); δ_C(299.95 MHz; $CDCl_3$) 29.82 ($CH_2CH_2CH_2$), 32.01 (OCH_2), 65.85 (CH_2Br), 112.54 (ArC), 120.92 (ArC), 128.40 (ArC), 136.05 (ArC), 160.91 (ArC) and 189.38 (CHO); *m*/*z* (EI) 244.0 ($M^{\cdot+}$).

2-(3-Azidopropoxy)benzaldehyde 7

This compound was prepared by the method used for the ethylene analogue.[8] The crude product was filtered through a short silica gel column with dichloromethane as eluent and the eluate was evaporated to leave a pale brown oil. Dissolution of the oil in diethyl ether and cooling of the solution in a dry ice–methanol bath gave colourless crystals of the pure products that were separated and stored at −20 °C. Yield: 89% of a colourless oil (at room temperature) (Found: C, 58.5; H, 5.5; N, 20.8. $C_{10}H_{11}N_3O_2$ requires C, 58.5; H, 5.4; N, 20.5%); δ_H(299.95 MHz; $CDCl_3$; Me_4Si) 2.14 (2 H, t, *J* 7, $CH_2CH_2CH_2$), 3.57 (2 H, t, *J* 7, OCH_2), 4.19 (2 H, t, *J* 7, CH_2N_3), 7.01 (2 H, m, ArH), 7.56 (1 H, t, *J* 7, ArH), 7.83 (1 H, d, *J* 7, ArH) and 10.50 (1 H, s, CHO); δ_C(299.95 MHz; $CDCl_3$) 28.68 ($CH_2CH_2CH_2$), 48.13 (OCH_2), 65.09 (CH_2Br), 112.49 (ArC), 121.01 (ArC), 128.61 (ArC), 135.08 (ArC), 160.96 (ArC) and 189.52 (CHO); *m*/*z* (EI) 121.0 ($M^{\cdot+}$).

7,8,17,18-Tetrahydro-6*H*,16*H*-dibenzo[*b*,*j*][1,9,5,13]dioxadiazacyclohexadecine 0.6 hydrate, 3·0.6H_2O

The azide **7** (3.14 g, 15.3 mmol) was dissolved in diethyl ether (30 ml) and triphenylphosphine (4.01 g, 15.3 mmol) was added. The mixture was stirred for 3 h until nitrogen evolution had ceased. The phosphine oxide was filtered off and washed with diethyl ether. The filtrate and washings were evaporated to leave a yellow oil that solidified over 15 h. The crude product was dissolved in chloroform (250 ml) and the solution was heated under reflux for 24 h. An aqueous methanol solution (20 ml, 50%) of $NiCl_2·6H_2O$ (1.95 g) and KSCN (2.00 g) was added to the chloroform solution and heating was continued for 1 h. The organic layer was separated and the pale purple complex, [Ni(SCN)$_2$(**3**)] (2.30 g, 66%), was filtered off, washed with chloroform and diethyl ether, and dried. The complex was suspended in aqueous ammonia (350 ml, *ca.* 20%) and the mixture was stirred for 4 days in a sealed vessel. During this period the free diimine separated as a colourless microcrystalline solid. It was filtered off, washed with a small portion of cold aqueous ammonia followed by water, and dried for 4 h (60 °C, 0.01 mmHg). The stoichiometry of the fractional hydrate obtained did not alter with further drying. Yield: 1.88 g {87% based on [Ni(SCN)$_2$(**3**)]}; mp 155–184 °C (Found: C, 72.1; H, 7.0; N, 8.4. $C_{20}H_{22}N_2O_2·0.6H_2O$ requires C, 72.1; H, 7.0; N, 8.4%); δ_H(299.95 MHz; $CDCl_3$; Me_4Si) 1.80 (1.2 H, br m, H_2O), 2.35 (4 H, m, $CH_2CH_2CH_2$), 3.97 (4 H, m, OCH_2 or NCH_2CH_2), 4.02 (4 H, m, OCH_2 or NCH_2CH_2), 6.98 (4 H, m, ArH), 7.32 (2 H, m, ArH), 7.91 (2 H, d, *J* 7, ArH) and 8.98 (2 H, s, NCH); δ_C(299.95 MHz; $CDCl_3$) 29.14 ($CH_2CH_2CH_2$), 58.21 (OCH_2 or NCH_2CH_2), 65.56 (OCH_2 or NCH_2CH_2), 114.73 (ArC), 121.56 (ArC), 126.78 (ArC), 131.95 (ArC) and 158.47 (ArC); *m*/*z* (EI) 321.1 ($M^{\cdot+}$).

7,8,17,18,27,28-Hexahydro-6*H*,16*H*,26*H*-tribenzo[*b*,*j*,*r*]-[1,9,17,5,13,21]trioxatriazacyclotetracosine 8

A solution of **3**·0.6H_2O (0.05 g, 0.15 mmol) in [^{2}H]chloroform (0.6 ml) was allowed to stand overnight whereupon the ^{1}H NMR spectrum of the solution included resonances consistent with **8**; δ_H(299.95 MHz; $CDCl_3$; Me_4Si) 2.25 (6 H, m, *J* 7, $CH_2CH_2CH_2$), 3.85 (6 H, t, *J* 7, OCH_2 or NCH_2CH_2), 4.19 (6 H, t, *J* 7, OCH_2 or NCH_2CH_2), 6.92 (6 H, m, ArH), 7.32 (3 H, m, ArH), 7.95 (3 H, d, *J* 7, ArH) and 8.82 (3 H, s, ArCHN).

7,8,17,18,27,28,37,38-Octahydro-6*H*,16*H*,26*H*,36*H*-tetrabenzo-[*b*,*j*,*r*,*z*][1,9,17,25,5,13,21,29]tetraoxatetraazacyclodotriacontine 0.3 hydrate, 9·0.3H_2O

The triimine **3**·0.6H_2O (1.00 g, 3.0 mmol) was dissolved in 1:1 chloroform–dichloromethane (6 ml) and the solution was allowed to stand overnight in a sealed vessel. Upon the addition of diethyl ether (14 ml), **9** separated as colourless crystals. The product was isolated, washed with a small quantity of cold diethyl ether, and dried (60 °C, 0.01 mmHg) for 1 h. The stoichiometry of the fractional hydrate obtained did not alter with further drying. Yield: 0.20 g (0.31 mmol), mp 215–220 °C (Found: C, 73.9; H, 6.8; N, 8.5. $C_{40}H_{44}N_4O_4·0.3H_2O$ requires C, 73.9; H, 6.9; N, 8.6%); δ_H(299.95 MHz; $CDCl_3$; Me_4Si) 1.75 (0.6 H, br m, H_2O), 2.11 (8 H, m, $CH_2CH_2CH_2$), 3.80 (8 H, t, *J* 7, OCH_2 or NCH_2CH_2), 4.06 (8 H, t, *J* 7, OCH_2 or NCH_2CH_2), 6.86–6.95 (8 H, m, ArH), 7.33 (4 H, t, *J* 7, ArH), 7.91 (4 H, d, *J* 7, ArH) and 8.81 (4 H, s, ArCHN); δ_C(299.95 MHz; $CDCl_3$) 30.42 ($CH_2CH_2CH_2$), 58.44 (OCH_2 or NCH_2CH_2), 65.09 (OCH_2 or NCH_2CH_2), 111.84 (ArC), 120.65 (ArC), 127.09 (ArC), 131.96 (ArC) and 157.94 (ArC); *m*/*z* (EI) 644.0 ($M^{\cdot+}$); M_r (osmometry in CH_2Cl_2) Calc. 644.8, Found 650.2.

7,8,9,10,17,18,19,20-Octahydro-6*H*,16*H*-dibenzo[*b*,*j*][1,9,5,13]-dioxadiazacyclohexadecine dihydrochloride hydrate, 11·2HCl·H_2O

Lithium aluminium hydride (1.06 g, 28 mmol) was suspended in anhydrous tetrahydrofuran (300 ml). The mixture was cooled (0 °C) and treated with **3** (3.00 g, 9.0 mmol) in small portions over 1 h, after which it was warmed to room temperature and stirred for 2 h. The following reagents were added to the reaction mixture sequentially at 0 °C: water (1.06 ml), 4 M NaOH (1.06 ml), water (3.18 ml). The mixture was then filtered and the precipitate of aluminium oxides was washed with tetrahydrofuran (50 ml). The filtrate was evaporated *in vacuo* to dryness; a pale yellow oil remained that could not be crystallised or distilled without decomposition. Dissolution of the oil in methanol and the dropwise addition of concentrated hydrochloric acid led to the precipitation of the *dihydrochloride* as a microcrystalline solid. The product was isolated, washed with cold methanol and dichloromethane, and dried for 1 h (60 °C, 0.01 mmHg). Yield: 3.01 g (7.2 mmol) (80%), mp 266–270 °C (Found: C, 57.4; H, 7.5; N, 6.5. $C_{20}H_{26}N_2O_2·2HCl·H_2O$ requires C, 57.6; 7.2; 6.7%); δ_H(299.95 MHz; 2:1 CD_3OD–D_2O; Me_4Si) 2.42 (4 H, br m, $CH_2CH_2CH_2$), 3.45 (4 H, m, OCH_2 or NCH_2CH_2), 4.30 (4 H, m, OCH_2 or NCH_2CH_2), 4.52 (4 H, s, Ar-CH_2-N), 7.21 (4 H, m, ArH) and 7.61 (4 H, m, ArH); δ_C(299.95 MHz; 2:1 CD_3OD–D_2O) 26.74 ($CH_2CH_2CH_2$), 45.81 (OCH_2 or NCH_2CH_2), 48.11 (OCH_2 or NCH_2CH_2), 65.67 ($ArCH_2N$), 112.40 (ArC), 122.36 (ArC), 132.70 (ArC), 133.25 (ArC) and 158.15 (ArC); *m*/*z* (EI) 326.2 (**11**$^{\cdot+}$). The free *diamine* was liberated from the salt by treatment with saturated aqueous sodium hydroxide. The colourless oil that separated had the following spectroscopic properties: δ_H(299.95 MHz; $CDCl_3$; Me_4Si) 1.85 (0.2 H, br m, H_2O), 2.03 (4 H, m, $CH_2CH_2CH_2$), 2.87 (4 H, m, OCH_2 or NCH_2CH_2), 3.86 (4 H, s, NCH_2Ar), 3.98 (4 H, m, OCH_2 or NCH_2CH_2), 6.83 (2 H, d, *J* 7, ArH), 6.91 (2 H, t, *J* 7, ArH) and 7.26 (4 H, m, ArH); δ_C(299.95 MHz; $CDCl_3$) 29.94 ($CH_2CH_2CH_2$), 46.87 (OCH_2 or NCH_2CH_2), 49.97 (OCH_2 or NCH_2CH_2), 66.00 ($ArCH_2N$), 110.80 (ArC), 120.46 (ArC), 128.58 (ArC), 130.92 (ArC) and 157.13 (ArC); *m*/*z* (EI) 326.2 ($M^{\cdot+}$).

7,8,9,10,17,18,19,20,27,28,29,30-Dodecahydro-6*H*,16*H*,26*H*-tribenzo[*b*,*j*,*r*][1,9,17,5,13,21]trioxatriazacyclotetracosine trihydrochloride sesquihydrate, 12·3HCl·1.5H_2O

Crystalline **3** (4.00 g, 12 mmol) was dissolved in chloroform (40 ml) and the solution was set aside for one week. Sodium cyanoborohydride (3.43 g, 55.6 mmol) was then added to the solution with stirring, followed by the immediate addition of 1:1 methanol–acetic acid (250 ml). The mixture was stirred for 1 h and then cooled to 0 °C. Saturated aqueous sodium hydroxide (250 ml) was slowly added and the mixture was extracted with dichloromethane (3 × 150 ml). The organic layer was separated, dried over $MgSO_4$, and evaporated to dryness, leaving a

colourless oil. The oil was dissolved in a methanol–hydrochloric acid solution (66% by volume methanol, 1 M acid) and the solution was chromatographed on DOWEX 50W-X2 ion exchange resin by elution with 2:1 methanol–hydrochloric acid of increasing acidity (1–4 M in acid). The *triamine trihydrochloride* was eluted as the second band from the column with the eluent 3.2–3.4 M in acid. The colourless solid remaining after removal of the solvent was purified by Soxhlet extraction into methanol. Yield of **12**·3HCl·1.5H_2O: 1.30 g (2.1 mmol) (17% of the original mixture), mp 146–148 °C (Found: C, 57.6; H, 7.6; N, 6.6. $C_{30}H_{39}N_3O_3$·3HCl·1.5H_2O requires C, 57.6; H, 7.2; N, 6.7%); δ_H(299.95 MHz; 2:1 CD_3OD–D_2O; Me_4Si) 2.50 (6 H, m, $CH_2CH_2CH_2$), 3.44 (2 H, br m, NH or OH), 3.62 (6 H, m, OCH_2 or NCH_2CH_2), 4.35 (6 H, m, OCH_2 or NCH_2CH_2), 4.44 (6 H, s, $ArCH_2N$), 7.22 (6 H, m, ArH) and 7.60 (6 H, m, ArH); δ_C(299.95 MHz; 2:1 CD_3OD–D_2O) 26.59 ($CH_2CH_2CH_2$), 46.32 (OCH_2 or NCH_2CH_2), 47.45 (OCH_2 or NCH_2CH_2), 66.31 ($ArCH_2N$), 112.90 (ArC), 120.02 (ArC), 122.38 (ArC), 132.58 (ArC) and 157.72 (ArC); *m*/*z* (EI) 489.4 (**12**$^{\bullet+}$). Addition of saturated aqueous sodium hydroxide to the hydrochloride, followed by extraction of the mixture with dichloromethane, produced, after separation of the organic phase (which was dried over $MgSO_4$) and evaporation to dryness, **12**·1.5H_2O as a colourless oil that could not be crystallised or distilled (Found: C, 69.6; H, 8.3; N, 8.4. $C_{30}H_{39}N_3O_3$·1.5H_2O requires C, 69.7; H, 8.2; N, 8.2%); δ_H(299.95 MHz; $CDCl_3$; Me_4Si) 2.00 (11 H, m, NH, H_2O and $CH_2CH_2CH_2$), 2.80 (6 H, t, *J* 7, OCH_2 or NCH_2CH_2), 3.81 (6 H, s, $ArCH_2N$), 4.05 (6 H, t, *J* 7, OCH_2 or NCH_2CH_2), 6.86 (6 H, m, ArH) and 7.24 (6 H, m, ArH); δ_C(299.95 MHz; $CDCl_3$) 29.62 ($CH_2CH_2CH_2$), 46.15 (OCH_2 or NCH_2CH_2), 49.39 (OCH_2 or NCH_2CH_2), 66.00 ($ArCH_2N$), 111.01 (ArC), 120.42 (ArC), 128.27 (ArC) and 129.74 (ArC); *m*/*z* (EI) 489.5 (M$^{\bullet+}$).

7,8,9,10,17,18,19,20,27,28,29,30,37,38,39,40-Hexadecahydro-6*H*,16*H*,26*H*,36*H*-tetrabenzo[*b*,*j*,*r*,*z*][1,9,17,25,5,13,21,29]-tetraoxatetraazacyclodotriacontine 0.2 hydrate, 10·0.2H_2O

Lithium aluminium hydride (0.14 g, 3.7 mmol) was suspended in anhydrous tetrahydrofuran (150 ml) and the mixture was cooled (0 °C). Solid **9** (0.55 g, 0.85 mmol) was added to the mixture in small portions over 1 h. The mixture was then warmed to room temperature, heated under reflux for 4 h, and stirred overnight. The following reagents were then added sequentially to the reaction mixture at 0 °C: water (0.14 ml), 4 M NaOH solution (0.14 ml), water (0.43 ml). The mixture was filtered and the grey precipitate of aluminium oxides was washed with tetrahydrofuran. The filtrate and washings were evaporated to dryness and diethyl ether was added to induce crystallisation of the colourless product. Yield: 0.45 g (0.68 mmol) (81%); mp 149–150 °C (Found: C, 73.0; H, 8.1; N, 8.3. $C_{40}H_{52}N_4O_4$·0.2H_2O requires C, 73.2; H, 8.1; N, 8.5%); δ_H(299.95 MHz; $CDCl_3$; Me_4Si) 1.80 (4.3 H, br m, NH and H_2O), 1.97 (8 H, m, $CH_2CH_2CH_2$), 2.74 (8 H, t, *J* 7, OCH_2 or NCH_2CH_2), 3.76 (8 H, s, $ArCH_2N$), 4.04 (8 H, t, *J* 7, OCH_2 or NCH_2CH_2), 6.86 (8 H, m, ArH) and 7.20 (8 H, m, ArH); δ_C(299.95 MHz; $CDCl_3$) 29.87 ($CH_2CH_2CH_2$), 46.28 (OCH_2 or NCH_2CH_2), 49.60 (OCH_2 or NCH_2CH_2), 66.06 ($ArCH_2N$), 111.01 (ArC), 120.31 (ArC), 128.29 (ArC), 129.75 (ArC) and 156.93 (ArC); *m*/*z* (EI) 652.2 (M$^{\bullet+}$); M_r (osmometry in CH_2Cl_2) Calc. 652.9, Found 659.

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