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Selective Derivatisations of Resorcarenes - 2. Multiple Regioselective Ring Closure Reactions

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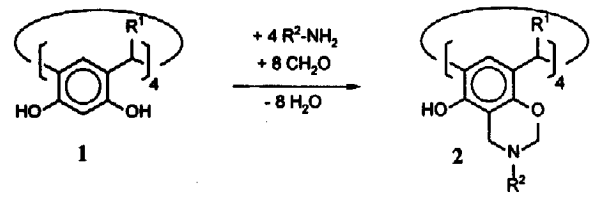
Abstract: The condensation of the C-pentyl resorcarene **1** with long chain aliphatic diamines **3a-d** and excess formaldehyde leads under high dilution conditions to tetrabenzoxazine derivatives **4a-d** in which pairs of adjacent oxazine rings are connected by an aliphatic chain. Six new rings are formed per resorcarene molecule during this reaction in a regioselective way. For one example (**4a**) the chiral cleft-like structure with C_2 symmetry was proved by single crystal X-ray analysis. Hydrolysis of the oxazine rings gives the secondary amine derivatives **5a,b** with C_{2V} symmetry in high yield. © 1997 Elsevier Science Ltd.

Introduction

Resorcarenes **1** are macrocyclic compounds easily available by acid catalysed condensation of resorcinol with various aldehydes. From four possible stereo isomers the all-cis isomer is often formed exclusively in high yield.[1,2] Due to this easy access resorcarenes **1** have been widely used as starting material for the synthesis of numerous sophisticated host molecules, such as cavitands,[3] carcerands,[4] and hemicarcerands[5] or of even larger molecular entities.[6]

These syntheses require the introduction of further functional groups by substitution of the resorcinol units in the 2-position, reactions which may be used also to enlarge the cavity of the [1$_4$]metacyclophane skeleton. Aminomethylation of **1** is possible by the reaction with formaldehyde and secondary amines.[7,8] With primary amines and an excess of formaldehyde further condensation occurs under regioselective formation of benzoxazines **2**.[9,10]



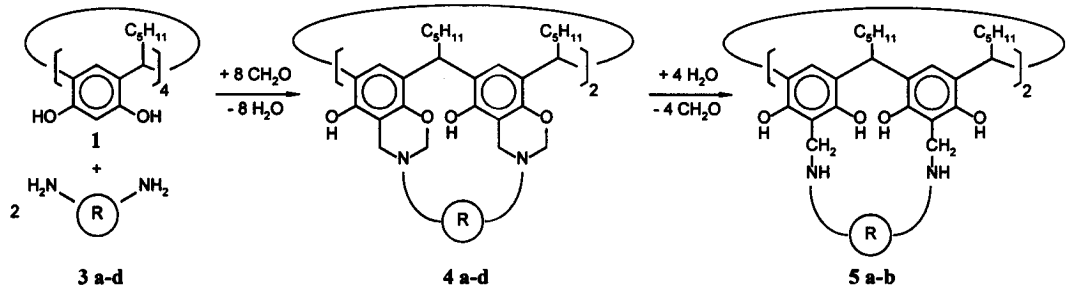
1 2

The driving force for this regioselectivity is obviously the tendency to form a maximum number of intramolecular O-H···O hydrogen bonds.[10] If chiral amines like 1-phenyl-, 1-cyclohexyl- or 1-(1-naphthyl)-ethylamine are used, just one of the two possible epimers is formed with high diastereoselectivity.[11-13]

We were interested to extend this condensation with formaldehyde also to aliphatic α,ω-di-amines **3**. Macrotricyclic compounds **4** should be available, in which two adjacent benzoxazine structures are connected by an additional bridge, providing that under high dilution conditions intermolecular reactions are sufficiently suppressed. From a preparative point of view such compounds, in which the C_4 symmetry is reduced to C_2 symmetry, could be interesting host molecules with a cleft like cavity. From a more general point of view it seemed interesting to see, if the regioselectivity found for various monoamines, would be observed also when additional constraints were introduced by this additional bridge.

Syntheses

The condensation of resorcarene **1** was carried out in ethanol with a moderate excess of diamine **3** (4 moles per mole of **1**) and a larger excess of formaldehyde (15 moles per mole of **1**) at 80°C, catalysed by a small amount of acetic acid. The products **4a-d** could be isolated by recrystallisation in yields between 57% (**4a**) and 7% (**4b**), while no defined reaction product was observed (or could be isolated) in the case of shorter or more rigid diamines, such as tetra- and hexamethylenediamine or *m*-xylylenediamine.



3 a-d 4 a-d 5 a-b

a R = -$(CH_2)_2$-O-$(CH_2)_2$-O-$(CH_2)_2$- **c** R = -$(CH_2)_2$-O-$(CH_2)_2$-O-$(CH_2)_2$-O-$(CH_2)_2$-
b R = -$(CH_2)_3$-O-$(CH_2)_4$-O-$(CH_2)_3$- **d** R = -$(CH_2)_6$-

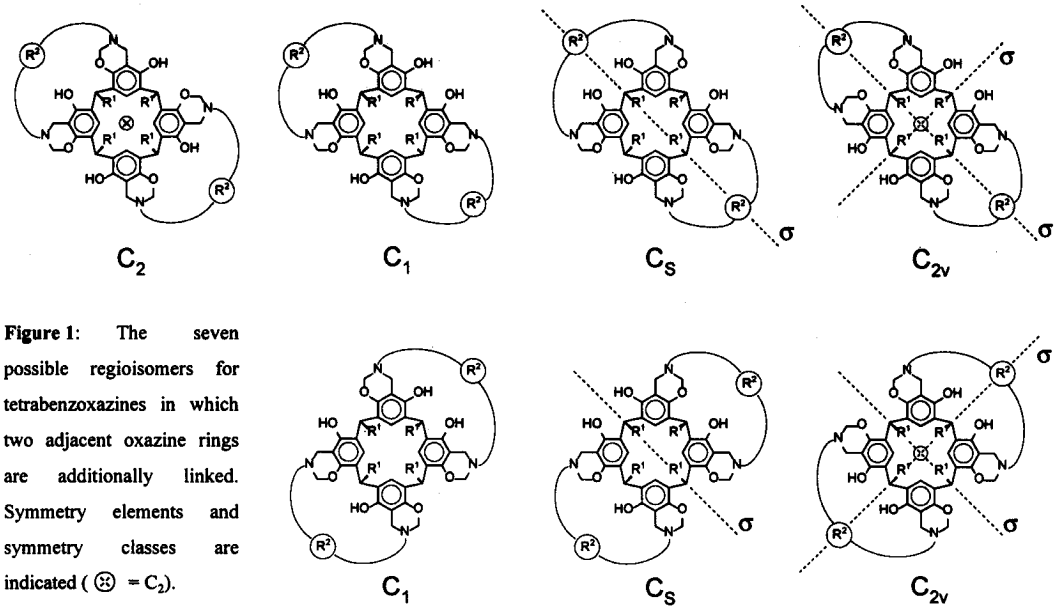


Figure 1: The seven possible regioisomers for tetrabenzoxazines in which two adjacent oxazine rings are additionally linked. Symmetry elements and symmetry classes are indicated (⊗ = C_2).

Mass spectrometry already suggested the formation of such a macrotricyclic structure, since the molecular ion was found (except for **4c**) with high abundance. Since in principle seven regioisomers are possible for tetrabenzoxazines of this type (see Fig. 1), the fact that only a single isomer could be detected is important.

The structure of **4a-d** follows definitely from their ^{1}H NMR spectra (compare Fig. 2), which show two singlets for OH and ArH protons, two triplets for the methine protons (Ar_2CHR), two (scarcely separated) pairs of doublets for the diastereotopic OCH_2N protons and two more strongly separated pairs of doublets for the

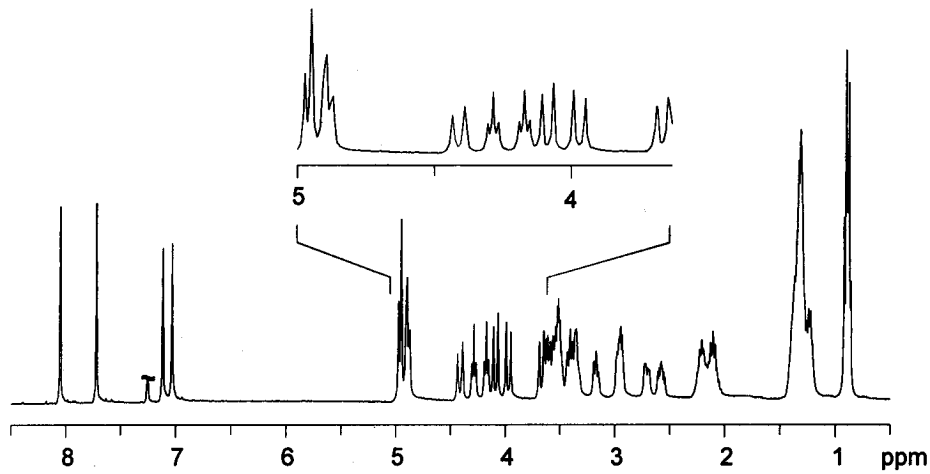


Figure 2: ^{1}H NMR spectrum (400 MHz) of compound **4a** in $CDCl_3$.

$ArCH_2N$ protons. This pattern excludes the two isomers with C_{2V} symmetry, which would have for instance four identical aryl protons. Also the two asymmetric isomers (C_1 symmetry) and the two isomers with C_S symmetry, which contain three different methine groups in a 1:2:1 ratio are not in agreement with the NMR spectra, unless some inprobable isochronism occured.

Since the molecular structure of **4a** was also confirmed by a single crystal X-ray analysis, the similarity of the NMR spectra can be regarded as an additional proof for the same structure in the case of **4b-d**. It is also evident that the differences between both different benzoxazine units become less pronounced, if the chain length of the bridge increases, like in **4b,c**.

The oxazine rings in compounds **4** can be hydrolysed to give secondary amines, which was demonstrated for two examples. Compounds **5**, obtained in essentially quantitative yield in form of their tetra-hydrochloride show the expected C_{2V} symmetry, which is especially evident from one sharp singlet for the aromatic protons.

Single Crystal X-Ray Analysis

Single crystals of **4a**, which were of sufficient quality for an X-ray analysis were grown from heptane-dichloromethane. Although the results are complicated by strong disorder and weak scattering power, the conclusions below are entirely justified.

The molecular structure and conformation of **4a** is shown in Figure 3. In fact, all four oxazine rings point in the same direction and pairs of adjacent oxazine rings are connected by the 3,6-dioxa-octano chains. Like in other cases[9,12] the nitrogen atoms of the oxazine rings point towards the resorcarene cavity, and the substitutents

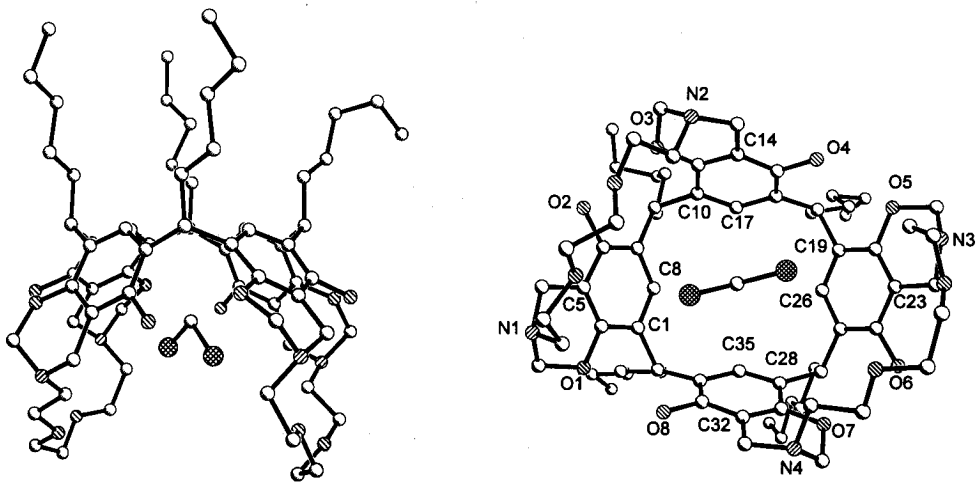


Figure 3: Molecular structure of compound **4a** • CH_2Cl_2 seen from two different directions; hydrogen atoms are omitted for clarity, the numbering scheme is indicated.

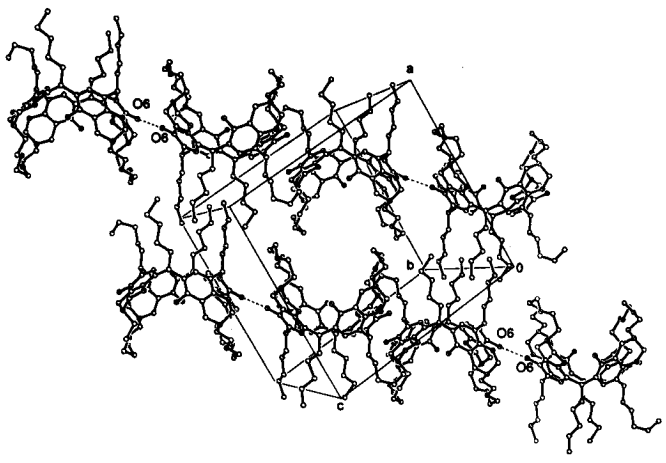


Figure 4: Packing of compound **4a**; all hydrogen atoms and dichloromethane are omitted for clarity

at the nitrogen atoms (the connecting chains) are in the axial position. Thus a molecular cleft is created by these two bridges in which a molecule of dichloromethane is deeply imbedded. Due to this inclusion the basic resorcarene skeleton is distorted to twofold symmetry (non crystallographic), since the two aromatic planes near the dichloromethane chlorines are pushed more outwards than the other two on the hydrogen side of dichloromethane. The interplanar angles between the aromatic rings and the reference plane of the four methine carbons are 42.4° (C5, C8), 60.3° (C14, C17), 43.8° (C23, C26), 61.7° (C32, C35). The distances between adjacent oxygens (O2···O3, O4···O5, etc.) are within the range of 2.80 - 2.85 Å indicating weak intramolecular O-H···O hydrogen bonds.

Figure 4 shows a section of the crystal lattice. The packing of the molecules is assisted by intermolecular contacts between the OH groups (O6) related by an inversion center with O···O distances of 2.92 Å which corresponds to very weak intermolecular hydrogen bonding. Pairs of molecules, related by another inversion centre are mutually filling the space between the pentyl chains attached to the methine carbons.

Conclusions

By condensation of resorcarenes **1** with diamines **3a-d** and formaldehyde six new cyclic structures are formed per molecule (four six-membered oxazine rings and two medium sized rings with 19 to 23 atoms) in a strictly regioselective manner. Chiral resorcarene derivatives **4a-d** with an enlarged, cleft-like cavity are available in this way. The yield varies between 57% for 1,8-diamino-3,6-dioxaoctane (**3a**) and 7% for 1,8-diaminooctane (**3b**). Considering the easy access of **1** and of similar resocarenes, chiral, cleft-like host molecules such as **3a** are thus available in two steps in reasonable quantities. The reaction failed with the diamines **3e-g** which are obviously too short and rigid to span the distance between adjacent oxazine rings. C_{2v} Symmetrical products in which two adjacent oxazine rings are oriented towards each other, an arrangement with a shorter distance between the nitrogene atoms were not observed. This underlines the importance of four intramolecular O-H···O hydrogen bonds, which are possible only in the C_2 symmetrical arrangement.

EXPERIMENTAL PART

Melting points were determined with a MEL TEMP 2 capillary melting point apparatus and are uncorrected. ^{1}H NMR (200/400 MHz) and ^{13}C NMR (50/100 MHz) spectra were recorded on a Bruker AC 200 and a Bruker AM 400 spectrometer, respectively. Coupling constants *J* are given in Hz. FD mass spectra were recorded with a Finnigan MAT 90 (5 kV/10 mA/min) spectrometer.

General procedure for the preparation of tetrabenzoxazines 4

To a solution of formaldehyde (35% aqueous solution, 1.5 ml, 17.5 mmol) and some drops of glacial acetic acid in ethanol (1 l) a solution of the resorcarene **1** (1 g, 1.3 mmol) in ethanol (25 ml) and a solution of the diamine **3** (5.4 mmol) in ethanol (25 ml) was slowly added (over 4 hrs with the help of a perfusor) at 80°C. The reaction mixture was refluxed for further 4 h. The red solution was evaporated in vacuum and the oily residue triturated with methanol. The white powder thus obtained was filtered off and recrystallised from chloroform-methanol. Further details are given for the individual compounds.

4a: 860mg (57%); mp 205-210°C (dec.); (Found: C, 70.28 H, 8.31 N, 4.85; $C_{68}H_{96}N_4O_{12}$ requires C, 70.32 H, 8.33 N, 4.82); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.04 (s, 2H, ArOH), 7.70 (s, 2H, ArOH), 7.10 (s, 2H, ArH), 7.02 (s, 2H, ArH), 4.95 (d, 4H, J 9.7, OCH_2N), 4.87 (d, 4H, J 9.9, OCH_2N), 4.40 (d, 2H, J 17.5, $ArCH_2N$), 4.27 (t, 2H, J 7.8, Ar_2CHR), 4.16 (t, 2H, J 7.8, Ar_2CHR), 4.07 (d, 2H, J 17.1, $ArCH_2N$), 3.95 (d, 2H, J 17.4, $ArCH_2N$), 3.66 (d, 2H, J 16.5, $ArCH_2N$), 3.61-3.31 (m, 16H, CH_2), 3.16 (m, 2H, CH_2), 2.93 (m, 4H, CH_2), 2.69 (m, 2H, CH_2), 2.57 (m, 2H, CH_2), 2.30-2.05 (m, 16H, CH_2), 1.45-1.20 (m, 24H, CH_2), 0.89 (t, 6H, J 7.1, CH_3), 0.86 (t, 6H, J 7.0, CH_3); ^{13}C NMR (50 MHz, $CDCl_3$) δ = 149.61, 149.44, 147.55, 147.23, 124.92, 124.30, 123.87, 123.52, 121.01, 120.81, 109.03, 108.25, 85.39, 81.98, 71.81, 70.87, 70.66, 68.59, 50.97, 50.56, 48.55, 45.19, 34.17, 32.92, 32.81, 32.60, 32.03, 31.98, 27.93, 27.82, 22.71, 22.63, 14.16; FD-MS, m/z 1160.7 (100%) [M^+, 1161.5].

4b: 440mg (29%); mp 148-150°C (dec.); (Found: C, 71.60 H, 8.81 N, 4.28; $C_{76}H_{112}N_4O_{12}$ requires C, 71.67 H, 8.86 N, 4.40); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.72 (s, 2H, ArOH), 7.71 (s, 2H, ArOH), 7.10 (s, 2H, ArH), 7.07 (s, 2H, ArH), 4.97 (dd, 2H, J 10.0 J 1.6, OCH_2N), 4.94 (d, 2H, J 10.0, OCH_2N), 4.85 (d, 2H, J 9.8, OCH_2N), 4.83 (d, 2H, J 9.8, OCH_2N), 4.23 (t, J 7.9, 2H, Ar_2CHR), 4.21 (t, J 7.9, 2H, Ar_2CHR), 4.10 (d, 2H, J 17.3, $ArCH_2N$), 4.04 (d, 2H, J 15.3, $ArCH_2N$), 3.71 (d, 2H, J 17.3, $ArCH_2N$), 3.65 (d, 2H, J 17.3, $ArCH_2N$), 3.55-3.52 (m, 2H, CH_2), 3.44-3.28 (m, 10H, CH_2), 3.24-3.19 (m, 4H, CH_2), 2.75-2.69 (m, 4H, CH_2), 2.62-2.55 (m, 4H, CH_2), 2.19-2.09 (m, 8H, CH_2), 1.80-1.72 (m, 8H, CH_2), 1.62-1.57 (m, 4H, CH_2), 1.47-1.40 (m, 4H, CH_2), 1.35-1.22 (m, 24H, CH_2), 0.88 (t, J 5.8, 6H, CH_3), 0.87 (t, J 5.8, 6H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 149.72, 149.61, 148.08, 147.85, 124.58, 124.27, 123.64, 123.51, 121.36, 121.24, 109.22, 108.76, 82.60, 81.51, 71.40, 70.39, 68.67, 67.67, 49.70, 48.79, 48.46, 47.17, 33.89, 33.66, 32.77, 32.73, 32.01, 28.90, 28.40, 27.85, 26.92, 25.99, 22.66, 14.11; FD-MS, m/z 1273.4 (100%) [M^+, 1273.7].

4c: 150mg (9%); mp 152-156°C (dec.); (Found: C, 69.08 H, 8.31 N, 4.54; $C_{72}H_{104}N_4O_{14}$ requires C, 69.20 H, 8.39 N, 4.48); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.73 (s, 2H, ArOH), 7.66 (s, 2H, ArOH), 7.08 (s, 2H, ArH), 7.07 (s, 2H, ArH), 4.97 (d, 2H, J 9.8, OCH_2N), 4.89-4.82 (m, 6H, OCH_2N), 4.23 (t, J 7.7, 2H, Ar_2CHR), 4.19 (t, J 7.9, 2H, Ar_2CHR), 4.06 (d, 2H, J 13.3, $ArCH_2N$), 4.02 (d, 2H, J 13.3, $ArCH_2N$), 3.70 (d, 2H, J 17.8, $ArCH_2N$), 3.65 (d, 2H, J 19.3, $ArCH_2N$), 3.62-3.39 (m, 18H, CH_2) 2.74-2.64 (m, 4H, CH_2), 2.54-2.51 (m, 2H, CH_2), 2.16-2.09 (m, 8H, CH_2), 1.81-1.70 (m, 8H, CH_2), 1.36-1.20 (m, 24H, CH_2), 0.88 (t, J 6.9, 6H, CH_3), 0.87 (t, J 6.9, 6H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ =

149.64, 148.05, 147.98, 124.48, 124.33, 123.67, 123.52, 121.26, 109.07, 108.69, 82.72, 82.46, 70.86, 70.75, 70.62, 69.50, 68.41, 49.10, 48.37, 47.48, 46.97, 33.90, 33.58, 32.79, 32.75, 31.99, 28.87, 28.27, 27.85, 22.68, 14.11.

4d: 100mg (7%); mp 215-217°C (dec.); (Found: C, 74.87 H, 9.01 N, 4.80; $C_{72}H_{104}N_4O_{14}$ requires C, 74.96 H, 9.09 N, 4.84); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.73 (s, 2H, ArOH), 7.33 (s, 2H, ArOH), 7.16 (s, 2H, ArH), 6.96 (s, 2H, ArH), 5.00 (dd, 2H, J 9.6 J 1.6, OCH_2N), 4.89 (d, 2H, J 9.7, OCH_2N), 4.87 (d, 2H, J 9.7, OCH_2N), 4.80 (d, 2H, J 9.6, OCH_2N), 4.26 (t, J 7.8, 2H, Ar_2CHR), 4.17 (t, J 8.0, 2H, Ar_2CHR), 4.07 (d, 2H, J 15.9, $ArCH_2N$), 4.30 (d, 2H, J 15.9, $ArCH_2N$), 3.72 (d, 2H, J 16.3, $ArCH_2N$), 3.68 (d, 2H, J 16.3, $ArCH_2N$), 2.75-2.49 (m, 8H, CH_2), 2.40-2.33 (m, 2H, CH_2), 2.21-2.00 (m, 12H, CH_2), 1.57-1.50 (m, 4H, CH_2), 1.42-1.16 (m, 34H, CH_2), 0.90 (t, J 7.0, 6H, CH_3), 0.87 (t, J 6.9, 6H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) 150.04, 149.23, 148.25, 147.73, 125.27, 123.73, 123.56, 123.52, 122.41, 120.49, 108.77, 108.30, 85.29, 81.76, 51.87, 51.20, 47.94, 43.84, 34.75, 33.17, 32.51, 32.07, 31.94, 27.89, 27.84, 27.71, 26.55, 25.92, 23.61, 22.70, 22.67, 22.62, 14.12; FD-MS, m/z 1153.0 (100%) [M^+, 1153.6].

Hydrolysis of the oxazine rings

Water and formaldehyde were removed by azeotropic distillation from a solution containing the tetrabenzoxazine (100 mg), 10 ml conc. hydrochloric acid and 10 ml water in 50 ml *n*-butanol. The remaining *n*-butanol was finally evaporated in vacuum. The yellow solid thus obtained was spectroscopically pure. For analytical purposes, it was recrystallised from methanol-chloroform.

5a: 80mg (74%); mp 195-197°C (dec.); ^{1}H NMR (200 MHz, DMSO-d_6) δ = 9.93, 9.55, 8.94, 8.10 (br s, each 4H, NH and OH), 7.58 (s, 4H, ArH), 4.28, 4.18 (br s, each 2H, Ar_2CHR), 3.64 (br s, 16H, CH_2), 3.00 (br s, 8H, CH_2), 2.27 (br s, 8H, CH_2), 1.30 (br s, 24H, CH_2), 0.86 (br s, 12H, CH_3); ^{13}C NMR (50 MHz, DMSO-d_6) 150.43, 150.31, 126.94, 126.47, 125.74, 109.31, 69.90, 65.57, 60.52, 46.24, 34.85, 34.65, 31.59, 27.78, 22.54, 22.46, 14.15.

5b: 85mg (79%); mp 173-175°C; ^{1}H NMR (200 MHz, DMSO-d_6) 9.61, 9.45, 8.71, 8.53 (br s, each 4H, NH and OH), 7.61 (s, 4H, ArH),), 4.09 (br s, 4H, Ar_2CHR), 3.56 (br s, 8H, CH_2), 3.45-3.30 (br s, 8H, CH_2 + H_2O), 2.87 (br s, 8H, CH_2), 2.29 (br s, 8H, CH_2), 1.88 (br s, 8H, CH_2), 1.51 (br s, 8H, CH_2), 1.30 (br s, 32H, CH_2), 0.85 (t, J 6.5 Hz, 12H, CH_3); ^{13}C NMR (50 MHz, DMSO-d_6) 150.32, 127.01, 126.73, 109.54, 69.99, 66.92, 44.63, 31.58, 27.76, 26.04, 25.61, 22.50, 14.16.

X-Ray analysis: Single crystals of **4a** were obtained from heptane-dichloromethane by slow evaporation. *Crystal data* $C_{68}H_{96}N_4O_{12}$ CH_2Cl_2 0.5 H_2O, Mw = 1254.41, monoclinic space group *P*21/n, a = 17.649(2), b = 21.389(2), c = 18.291(2), β = 94.65(1)°, V = 6882.0(1.3) Å^3, Z = 4, Dc = 1.211 Mg m^{-3}, μ (Cu-Kα) = 1.351 mm^{-1}, F (000) = 2696, crystal size = 0.40 × 0.30 × 0.30, Cu-Kα monochromatised radiation (λ_α= 1.54178 Å), T = 296(2) K; data collection with an Enraf-Nonius CAD4 diffractometer. The structure was solved by direct methods and refined on F^2 using SHELXL-93.[14] Due to the room temperature measurement, the quality of the crystal and the weak scattering power the obtained data were poor: 8976 unique reflections, 3762 > 2s(I). The low quality data and the severe disorder of the alkyl chains and of the crown ether bridges are responsible for the relatively high R-value (12.7 %). The atomic coordinates for the structure, as well as bond lenghts, bond angles and thermal parameters are available on request from the Director of the Cambridge Crystallographic Data Centre, University Chemical Laboratory, Lensfield Road, Cambridge CB2 1EW. Any request should be accompanied by the full literature citation for this publication.

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