Selective derivatisation of resorcarenes. Part 5. Acylation of tetrabenzoxazine derivatives†

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The reaction of the tetrabenzoxazines 2 with acetic anhydride under mild conditions leads selectively and exclusively to the tetraamides 3 in which the oxazine rings are opened; their structure was deduced from their ^{1}H NMR spectra and confirmed for one example by an X-ray single crystal structure analysis; acylation of the hydroxy groups was not observed.

Condensation of the all-*cis* isomers of resorcarenes **1**[1] with primary amines and an excess of formaldehyde leads in a strictly regioselective way to the C_4-symmetrical benzoxazine derivatives **2**[2] (Scheme 1), which are usually obtained in high yields.[3,4] This reaction provides not only an extension of the cavity, it also affords easy access to potential host molecules with inherent chirality. Whilst the regioselectivity has been proved by NMR spectroscopy and by several X-ray analyses,[3,4] the isolation of the single enantiomers has, as yet, not been possible. Recently, their chromatographic separation was achieved, using (3*S*,4*R*)Whelk-O1 and CHIRALPAK AD as chiral stationary phases.[5] However, it can also be shown that these compounds are easily enantiomerised (even) under the chromatographic conditions. Most probably this enantiomerisation[6] takes place, catalysed by traces of acid, *via* immonium cation intermediates, as shown in Scheme 2.[7] Thus, the derivatisation of the four remaining hydroxyl groups in **2** by *O*-alkylation or *O*-acylation should lead to stable enantiomers, since for an intermediate immonium cation only one adjacent hydroxyl group would be available for the regeneration of the benzoxazine ring.[8–10]

We attempted the acylation of **2a,b** with acetic anhydride (slight excess) in chloroform at room temperature in the presence of triethylamine and a catalytic amount of 4-dimethylaminopyridine.[11] The only products that we could isolate in moderate yield[12] were the tetraamides **3a,b** (Scheme 1), but no indication for *O*-acylation could be observed.[13] Thus, in agreement with the results for simple benzoxazines,[14] the more nucleophilic nitrogen (in comparison to oxygen), is acylated, while formaldehyde is hydrolytically eliminated from the N/O acetal.

The structure of the acylation products is already evident from their ^{1}H NMR spectra, which are only in agreement with the formation of a tetraamide. In addition to a singlet for the aromatic protons (around 7.2 ppm), there are two singlets for the phenolic hydroxyl groups at 11.5 and 8.7 ppm, suggesting hydrogen bonds of quite different strengths. In keeping with general experience, the low-field signal corresponds to a strong intramolecular hydrogen bond to the carbonyl oxygen, while the signal at higher field corresponds to a weaker hydrogen bond to the hydroxyl group of the adjacent resorcinol unit. Although the Ar–CH_2–N protons are diastereotopic, if the O–H···O–H···O=C hydrogen bonding system is kinetically stable, they appear as a singlet at 4.5 ppm.[15]

Single crystals of **3a**, suitable for X-ray analysis, were grown from dichloromethane–acetonitrile.[16] The molecular structure, the conformation and the numbering scheme are shown in Fig. 1, while Fig. 2 illustrates the crystal packing. The molecule lies on a fourfold crystallographic axis, which confirms the chiral, C_4 symmetrical conformation already suggested by the NMR spectra. The resorcarene skeleton therefore shows a perfect cone conformation with an interplanar angle between the resorcinol rings and the plane through the methine carbons of 130.1°. The strong hydrogen bonds between the OH group (O2) and the carbonyl oxygen (O3) are reflected by the very short O···O distance of 2.58 Å, while the weaker intramolecular hydrogen bonds between the OH groups (O1, O2B) of adjacent resorcinol rings lead to an O···O distance of a more usual length (2.74 Å). All other bond distances and angles are within the expected ranges. The CH_2–N–C=O arrangement is nearly planar (torsion angle C13–N1–C14–O3 = 8.75°; N atom 0.01 Å out of the plane of its ligands) and the cyclohexyl ring assumes the chair conformation. As shown in Fig. 2, these R^2 residues are oriented away from the

† For part 4 see: A. Shivanyuk, E. F. Paulus, V. Böhmer and W. Vogt, *J. Org. Chem.*, 1998, **63**, 6448.
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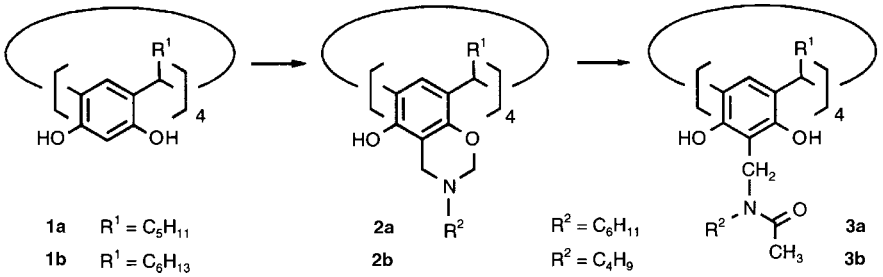
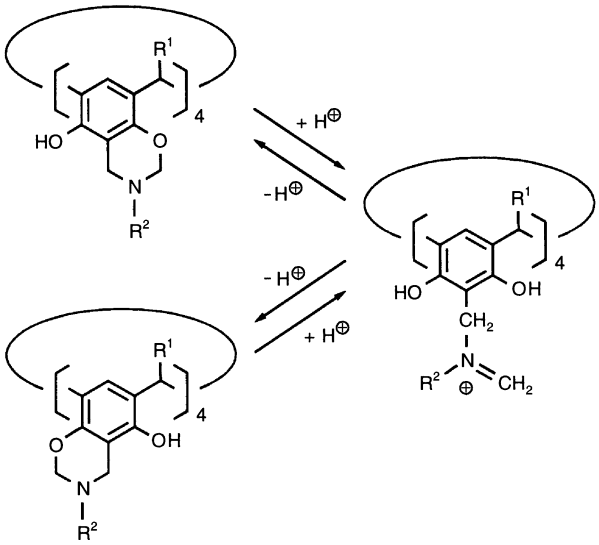
Non-SI unit employed: 1 kcal = 4.184 kJ.



Scheme 1



Scheme 2

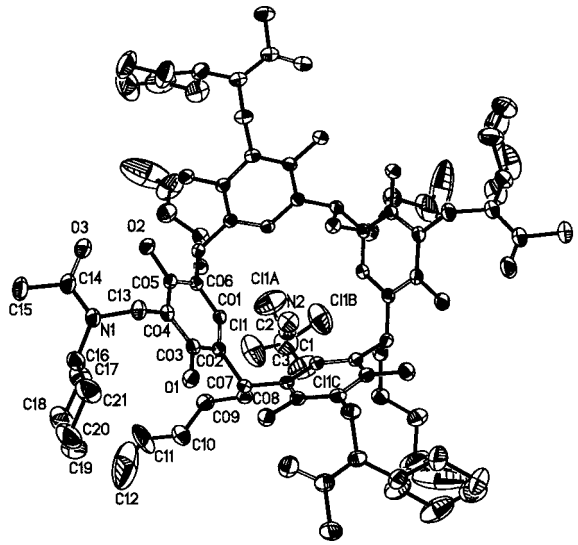


Fig. 1 Molecular conformation of **3a** in the crystalline state. The numbering scheme is indicated. Thermal ellipsoids are drawn on a 20% probability level.

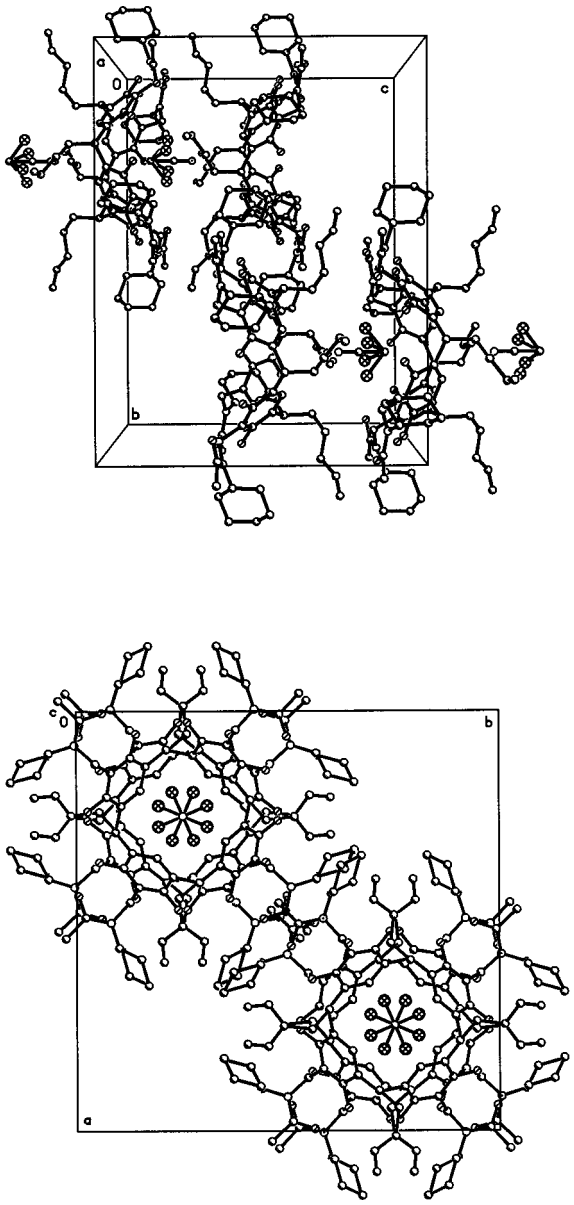


Fig. 2 Packing of **3a** projected along the *a* axis (above) and *c* axis (below). One solvent position can be occupied by acetonitrile (52%) or dichloromethane (48%) in two equally populated positions.

resorcarene cavity. Rotation around the Ar–CH_2 bond by about 180° would lead to an analogous hydrogen bonding system in a conformation with a more closed cavity. According to MM calculations,[17] such a conformation is even more stable, by 10.8 kcal mol^{-1}, due to a much more favourable van der Waals term, and might exist in solution, especially in the presence of suitable guests.

In the crystal lattice the molecules are arranged in infinite chains (molecular tubes)[18] along the *c* axis with an alternating sequence of the two enantiomeric conformations with reversed helicity of the hydrogen bonding system. Neighbouring chains point in opposite directions. Between the macrocycles one solvent molecule lies on the fourfold axis, acetonitrile with a probability of 52% and dichloromethane (48%), with the chlorine atoms equally distributed over two positions to obtain the fourfold symmetry.

In conclusion, the acylation of the tetrabenzoxazines **2** does not lead to tetraesters but to the tetraamides **3**, in which the oxazine rings are opened. This is in contrast to some reports in the literature,[8,9] but in agreement with studies on simple benzoxazines.[14] The tetraamides **3**, which can be modified by variation of the R^2 and of the acyl groups, may also be interesting as host molecules.

Acknowledgements

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References

1 For a recent review on resorcarenes see: P. Timmerman, W. Verboom and D. N. Reinhoudt, *Tetrahedron*, 1996, **52**, 417.

2 These compounds, more precisely tetrakis(3,4-dihydro-2*H*-1,3-benzoxazine)s, were first mentioned by Y. Matsushita and T. Matsui, *Tetrahedron Lett.*, 1993, **34**, 7433, without discussing their chirality and their potential regioisomers.

3 R. Arnecke, V. Böhmer, E. F. Paulus and W. Vogt, *J. Am. Chem. Soc.*, 1995, **117**, 3286.

4 K. Airola, V. Böhmer, E. F. Paulus, K. Rissanen, C. Schmidt, I. Thondorf and W. Vogt, *Tetrahedron*, 1997, **53**, 10709.

5 V. Böhmer, S. Caccamese, G. Principato and C. Schmidt, *Tetrahedron Lett.*, 1999, **40**, 5927.

6 For tetrabenzoxazines obtained from a chiral amine, this reaction means diastereomerisation, see: M. T. El Gihani, H. Heaney and A. M. Z. Slawin, *Tetrahedron Lett.*, 1995, **36**, 4905 and ref. 8, 9.

7 This is most probably also the first step in the easy exchange of N–CH_2–O for N–CD_2–O (or *vice versa*) in the presence of CD_2O (or CH_2O), and in complete hydrolysis to secondary amines under conditions where formaldehyde is removed.

8 W. Iwanek and J. Mattay, *Liebigs Ann. Chem.*, 1995, 1463.
9 R. Arnecke, V. Böhmer, S. Friebe, S. Gebauer, G. J. Krauss, I. Thondorf and W. Vogt, *Tetrahedron Lett.*, 1995, **36**, 6655.
10 While we were writing this manuscript, the successful tetrakis(*O*-methylation) in THF at −78 °C was reported, using a stoichiometric amount of *n*-butyllithium to deprotonate the hydroxy groups of tetrabenzoxazines and methyltriflate as the alkylating agent: P. C. Bulman Page, H. Heaney and E. P. Sampler, *J. Am. Chem. Soc.*, 1999, **121**, 6751.
11 These conditions were reported for the *O*-acylation of a similar tetrabenzoxazine [$R^1 = CH_3$, $R^2 = CH(CH_3)C_6H_5$], *cf.* ref. 8; the synthesis of such a tetraacetate by reaction with excess acetic anhydride in pyridine at room temperature was also described (R. Arnecke, PhD Thesis, Johannes Gutenberg-Universität, Mainz, 1996), a result that could not be reproduced either.
12 To a solution of tetrabenzoxazine **2** (0.4 mmol) in chloroform (40 ml), acetic anhydride (2 mmol), triethylamine (2 mmol) and a catalytical amount of 4-dimethylaminopyridine was added. After stirring for 24 h at room temperature the solvent was removed by evaporation and 10 ml methanol added. After several days at 4 °C the precipitate was filtered off and dried. **3a**: 100 mg (18%); mp: 196 °C; ^{1}H NMR (200 MHz, $CDCl_3$): δ 11.49 (s, 4H, OH), 8.68 (s, 4H, OH), 7.24 (s, 4H, ArH), 4.50 (s, 8H, NCH_2Ar), 4.32 (t, *J* 7.3, 4H, $RCHAr_2$), 3.57 (br t, 4H, $NCHR_2$), 2.18 (s, 12H, CH_3), 2.1–1.2 (m, 64H, CH_2), 0.84 (t, *J* 6.1 Hz, 12H, CH_3). **3b**: 90 mg (17%); mp: 174 °C; ^{1}H NMR (200 MHz, $CDCl_3$): δ 11.44 (s, 4H, OH), 8.67 (s, 4H, OH), 7.17 (s, 4H, ArH), 4.35 (m, 12H, NCH_2Ar and $RCHAr_2$), 3.66 (br s, 2H, CH_2), 3.36 (br s, 2H, CH_2), 2.10 (br s, 20H, CH_2 and CH_3), 1.27 (m, 48H, CH_2), 0.97 (t, *J* 7.1, 12H, CH_3), 0.84 (t, *J* 6.3 Hz, 12H, CH_3).
13 It may be possible to achieve an *additional* acylation of the (eight) hydroxyl groups in **3**, which was not the purpose of the present studies.
14 W. Burke, M. Kolbezen and W. Stephens, *J. Am. Chem. Soc.*, 1952, **74**, 3601.
15 An AB system was observed, for instance, in resorcarene derived secondary amines due to intramolecular O–H···N hydrogen bonds: D. A. Leigh, P. Linnane, R. G. Pritchard and G. Jackson, *J. Chem. Soc., Chem. Commun.*, 1994, 389.
16 Crystal data for **3a**: $C_{84}H_{124}N_4O_{12}\cdot(0.5CH_3CN, 0.5CH_2Cl_2)$, $M_W = 1444.86$, tetragonal, space group *P*4/*ncc*, $a = 22.036(1)$, $c = 17.001(2)$ Å, $V = 8255.3(1)$ Å^3, $Z = 4$, $D_X = 1.163$ g cm^{-3}, $F(000) = 3136$, $T = 293$ K. Data collection was performed on a computer controlled three-circle diffractometer equipped with a CCD area detector and a rotating anode (focus: 0.5 × 5 mm, 50 kV, 120 mA) using Mo-Kα radiation (graphite monochromator, $\lambda = 0.7107$ Å) Refinement of $(F_0^2 - F_c^2)^2$ based on all 3017 unique reflections led to $R = 0.0931$, $wR = 0.2349$ and $S = 1.049$; $R = 0.0787$ for $F_0 > 4\sigma(F_1)$. All calculations were done with SHELXTL-PLUS, SHELXS97 and SHELXL97 software (G. M. Sheldrick, Universität Göttingen). CCDC reference number 440/164. See http://www.rsc.org/suppdata/nj/a9/a907622k/ for crystallographic files in .cif format.
17 MM calculations were performed using the MMX force field as implemented in PCMODEL 5.13 (distribution by Serena Software, Dr. Kevin E. Gilbert, P.O. 3076, Bloomington, IN 47402). Geometry optimisation was accomplished with a conjugate gradient procedure. A dielectric constant of 1.5 D was used.
18 For resorcarenes as K^+-selective ion channels see: Y. Tanaka, Y. Kobuke and M. Sokabe, *Angew. Chem.*, 1995, **107**, 717.

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