

Unprecedented formation of lactone derivatives in thiacalix[4]arene series

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Distal bis(carboxymethoxy) derivatives of thiacalix[4]arene were found to undergo an unprecedented intramolecular cyclisation to yield lactone compounds **5a** or **5b**, the structure of lactones possessing nine-membered ring was proved by X-ray crystallography; inherent chirality of new compounds was demonstrated using separation on a chiral HPLC column.

The well-established chemistry of calix[*n*]arene family^{1,2} was recently 'rejuvenated' by the discovery of so called thiacalix[4]arenes.³ The presence of sulfur atoms instead of methylene groups makes thiacalix[4]arenes **1a** and **1b** very interesting molecules with some novel features compared with the chemistry of 'classical' calixarenes (Scheme 1). Thus, the preparation of appropriate tetrasulfoxide⁴ or tetrasulfone^{4a,5} derivatives proceed very easily by direct oxidation of sulfur. Unfortunately, the employment of thiacalix[4]arenes as building blocks or molecular scaffolds in supramolecular chemistry is still rather restricted by almost unknown chemistry of these compounds and the lack of general derivatization methods. As we found recently, simple tetraalkylated products⁶ exhibit interesting conformational behaviour⁷ that differ to a high degree from that of 'classical' calix[4]arene derivatives. In this paper we report on another example of different chemical behaviour of thiacalix[4]arene derivatives.

During our attempts at the preparation of diamides by the reaction of acyl chlorides **4a** or **4b** with various aromatic amines we isolated substantial amounts of unknown byproduct. Surprisingly, as we found, the same type of compounds can be prepared in high yields using the reaction of **4a** or **4b** in the presence of triethylamine in tetrahydrofuran. Thus, the stirring of **4a** (prepared from **3a** by the reaction with oxalyl chloride) with 6 eq. of Et₃N in THF at rt leads to the main product **5a** in 69% yield.⁸ The ¹H NMR spectrum of this compound (see ESI†) exhibits two singlets of Bu^t groups (0.88 and 1.40 ppm)

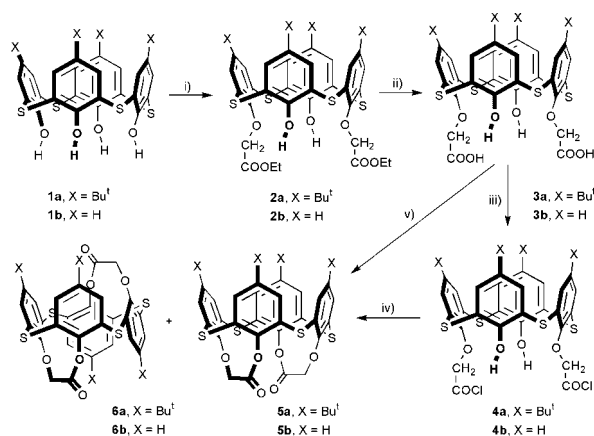
and four doublets with characteristic meta coupling (*J* ~ 2.2 to 2.7 Hz) in the aromatic region. Together with two doublets possessing typical geminal coupling constants (*J* ~ 12 Hz) at 4.63 and 5.52 ppm it reflects C₂ symmetry of the whole molecule. This was confirmed also by ¹³C NMR where the expected 18 signals were recognised. The above-mentioned findings can be explained by structure **5a** formed by the intramolecular reaction of acyl chloride with the neighbouring hydroxy group.

As we found, the same product can be prepared directly from diacid **3a** by reaction with a dehydration agent. Thus heating of **3a** with acetic anhydride led to **5a** in 50% yield while stirring the same acid with P₂O₅ in DCM solution gave **5a** in 66% yield, in both cases accompanied by 10% of byproduct **6a**. The splitting pattern and the number of signals in the ¹H NMR spectrum of **6a** is identical with that of **5a**. On the other hand, there is a dramatic change in the chemical shifts of methylene groups where corresponding protons are shifted up-field by 1.5 and 1.1 ppm respectively if compared with **5a**. This indicates a strong anisotropic shielding effect of aromatic units in good agreement with the proposed 1,2-alternate conformation. Albeit all our attempts to grow suitable crystals for X-ray analysis have failed, molecular modelling (MOPAC) confirmed the close proximity of C–H bonds and the plane of inverted aromatic units (see ESI). Interestingly, the corresponding derivative **6b** has not been observed in similar reactions of **3b**.

Bis(carboxymethoxy) derivatives **3a** and **3b** adopt a *cone* conformation both in the solution (proved by NMR) and in the solid state (X-ray crystallography). On the other hand, the formation of the 1,2-alternate product **6a** requires a previous rotation of the CH₂COOH substituent through the cavity which was never observed in the chemistry of 'classical' calixarenes. As we found very recently,⁹ in contrast to 'classical' calix[4]arene the propyl groups are not bulky enough to fully prevent such a rotation in the thiacalixarene series. Because the steric requirements of the carboxymethyl groups are apparently comparable or even lower than those of propyl, anticipated rotation of this group seems to be feasible.

The above described behaviour, the formation of lactones **5** or **6**, was observed only in the case of thiacalix[4]arene derivatives. The same reactions carried out with 'classical' calix[4]arene never gave similar cyclic products, probably due to the better preorganisation of thiacalixarene moiety for intramolecular cyclisation (bigger cavity).

The structure of **5a** possessing nine-membered lactone rings was unequivocally demonstrated using a single crystal X-ray diffraction¹⁰ (suitable single crystals were obtained by slow evaporation of EtOAc–CH₂Cl₂ solution). The presence of two bridges induces the distortion of the *cone* conformation and impresses an effective C₂ symmetry to the whole structure (Fig. 1). Four sulfur atoms are placed in the corners of a lozenge with shorter (S₂–S₄) and longer (S₁–S₃) diagonals being 6.9 and 8.3 Å, respectively. Two opposite aromatic rings are tilted outwards while the other two units are almost coplanar thus closing the cavity for potential inclusion of solvent molecule. As follows



Scheme 1 i) BrCH₂COOEt, acetone–K₂CO₃; ii) KOH, H₂O–EtOH; iii) (COCl)₂, CH₂Cl₂; iv) NEt₃, CH₂Cl₂; v) P₂O₅, CH₂Cl₂.

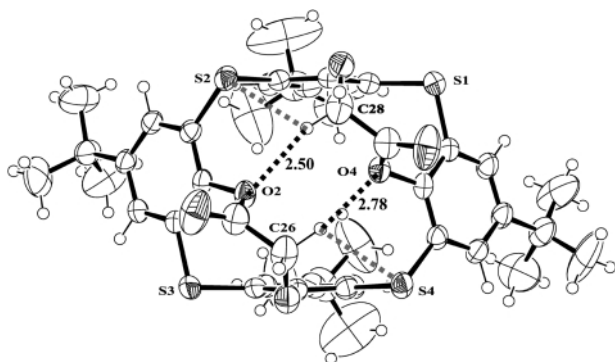


Fig. 1 X-ray structure (ORTEP drawing) of **5a** with indicated intramolecular hydrogen bonds.

from Fig. 1, the structure is supported by intramolecular hydrogen bonds (HBs) between lactone methylene hydrogens (H261, H282) and neighbour oxygen atoms O2, O4 with possible contribution of sulfur bridges S2, S4 (all distances shorter than 3 Å).

A very interesting feature of the derivative **5a** is represented by its molecular packing. The thiacalix[4]arene moieties are arranged along the *y* axis in such a way that they create an infinite network of molecules held together by the non-classical intermolecular hydrogen bonds. Every carbonyl oxygen is in a close contact with at least two hydrogen atoms of *tert*-butyl groups from a neighbouring thiacalix[4]arene unit (see ESI) with distances of 2.49 and 2.84 Å (two other hydrogens are slightly further than 3.0 Å). To the best of our knowledge such an arrangement has never been described in the calix[4]arene chemistry (Cambridge Structural Database).

Lactone **5b** also possesses very unusual crystal packing.¹¹ As is obvious from Fig. 2, derivative **5b** creates a kind of dimer with a net of close contacts between carbonyl oxygen and neighbour CH₂ groups of lactone functions (hydrogen bonds with the H...O=C distances 2.64–2.85 Å). These dimers are then interconnected by several additional HBs between carbonyl oxygens and aromatic hydrogens from neighbouring calixarene units (Ar–H...O=C distances ~2.70 Å). The network of molecules is held together by the intermolecular π - π interactions between the aromatic rings (upper rims) of thiacalix[4]arenes (Fig. 2). The average distance of the two coplanar rings (3.5 Å) is very similar to that in other thiacalixarene derivatives (3.41 Å) as described very recently.¹⁴

The inherent chirality of the new compounds was demonstrated using HPLC chromatography on a chiral column (*R,R*)-Wheelk-O 1, which is designed for the separation of systems possessing π - π and/or HB interactions. The column proved to be highly suitable for separating lactones **5a** and **5b**, especially because of the possibility of using chlorinated solvents which is important for the solubilization of the compounds. Thus,

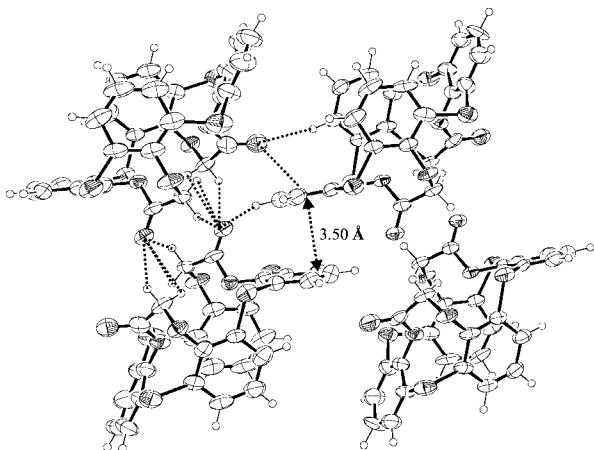


Fig. 2 Crystal packing of **5b** demonstrating intermolecular hydrogen bonding network, all indicated contacts are shorter than 3.00 Å.

derivative **5b** exhibits base-line separation with retention times 24.9 and 26.5 min for appropriate enantiomers (see ESI).

In conclusion, bis(carboxymethoxy) derivatives of thiacalix[4]arene were found to undergo an unprecedented intramolecular cyclisation to yield nine-membered lactone compounds **5a** or **5b**. The X-ray diffraction of these compounds revealed an interesting molecular packing, held together by the combination of π - π and HB interactions. The inherent chirality of the new compounds was demonstrated through separation on a chiral HPLC column.

Notes and references

† Electronic supplementary information (ESI) available: Figs. S1–S4 and experimental details. See <http://www.rsc.org/suppdata/cc/b1/b100906k/>

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- Preparation of **5a**, **5b** and **6a** see ESI†.
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- Crystallographic data for **5a**: C₄₄H₄₈O₆S₄; *M* = 801.100 g mol⁻¹, monoclinic system, space group *P2*₁/*c*, *a* = 20.044(1), *b* = 10.731(1), *c* = 20.490(1) Å, β = 102.17(1)°, *Z* = 4, *V* = 4308.2(5) Å³, *D*_c = 1.2351 g cm⁻³, μ (Cu K α) = 2.39 mm⁻¹, crystal dimensions of 0.6 × 0.3 × 0.2 mm. Data were measured at 293 K on an Enraf–Nonius CAD4 diffractometer with graphite monochromated Cu–K α radiation. The structure was solved by direct methods¹² and anisotropically refined by full matrix least-squares on *F*¹³ to final *R* = 0.0756 and *R*_w = 0.0828 using 5629 independent reflections (θ_{\max} = 67.94°). Lactone methylene hydrogens were found from difference Fourier maps, the other hydrogen atoms were located from expected geometry and were not refined. Psi scan was used for the absorption correction.
- Crystallographic data for **5b**: C₂₈H₁₆O₆S₄; *M* = 576.671 g mol⁻¹, monoclinic system, space group *P2*₁/*c*, *a* = 19.670(8), *b* = 9.503(2), *c* = 28.757(3) Å, β = 103.22(2)°, *Z* = 8 (2 in asymmetric unit), *V* = 5232(2) Å³, *D*_c = 1.464 g cm⁻³, μ (Cu K α) = 3.705 mm⁻¹, crystal dimensions of 0.5 × 0.3 × 0.2 mm. Data were measured at 293 K on an Enraf–Nonius CAD4 diffractometer with graphite monochromated Cu–K α radiation. The structure was solved by direct methods¹² and anisotropically refined by full matrix least-squares on *F*¹³ to final *R* = 0.0818 and *R*_w = 0.0733 using 3906 independent reflections (θ_{\max} = 64.94°). Lactone methylene hydrogens were found from difference Fourier maps, the other hydrogen atoms were located from expected geometry and were not refined. Psi scan was used for the absorption correction. CCDC 157253 and 157254. See <http://www.rsc.org/suppdata/cc/b1/b100906k/> for crystallographic files in .cif format.
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