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Synthesis of an optically active C_3-symmetric cage-like trisamide†

Ruxandra D. Ionescu and Torbjörn Frejd*

Department of Organic Chemistry, Lund University, PO Box 124, 221 00 Lund, Sweden.
E-mail: torbjorn.frejd@orgk1.lu.se

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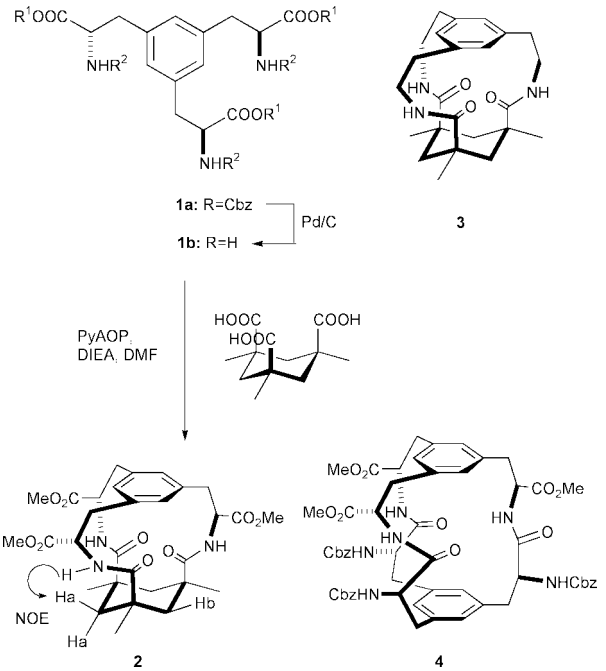
The synthesis of the optically active C_3-symmetric cage-like trisamide 2 was easily accomplished by the reaction of 1b with Kemp's triacid; structure elucidation revealed the presence of an array of H-bonds closing the structure as a capsule.

We have for some time been interested in constructing new C_3-symmetric molecules based on amino acid **1**.[1] The tripodal structure of this compound in combination with Kemp's triacid[2] with its unusual triaxial alignment of the carboxylic acid groups,[3] would make possible the synthesis of the cage-like structure **2**. A similar compound **3** was indeed suggested by Kemp and Petrakis in their paper from 1981,[2] but to the best of our knowledge, it has never been synthesised. In this communication, we describe the synthesis of **2**, as shown in Scheme 1.

The protected trisphenylalanine derivative **1a** was synthesised in three steps from commercially available trimesic acid as described previously.[4] Removal of the benzyloxycarbonyl protecting groups by hydrogenation over Pd/C, gave a quantitative yield of **1b**. Slow addition, *via* syringe pump, of a mixture of Kemp's triacid, PyAOP‡ and Hünig's base to **1b** provided **2** in 8–11% yield§ (Scheme 1). This rather low yield was to be expected, as judged from other similar reactions.[5]

Several attempts to improve the yield of the reaction were made by employing different coupling reagents. Replacing PyAOP with the combination EDC–HOBt had no positive effect on the yield and remaining HOBt was difficult to remove from the product during purification. EDC alone failed to provide any product, while HATU gave essentially the same yield as PyAOP. Further, using the PyAOP-procedure as above but increasing the rate of the addition of the coupling reagent or using smaller amounts of the solvent resulted in the formation of more polymeric material, which made purification difficult. Nor did slow addition of the coupling reagent and extending the reaction time (48–72 h), with or without heat, improve the situation; only polymeric material and decomposition of the coupling reagent was indicated by NMR-analysis.



Scheme 1

The free trisamine **1b** could possibly also combine with its corresponding trisacid under amide bond formation. As one of several combinations, one would expect a C_3-symmetric cage-like compound **4** to be formed in which the general structure of **1** served both as the 'top' and the 'bottom' of the cage. Unfortunately, **4** could not be identified in such experiments. Mass spectroscopy revealed only the formation of material with higher molecular weights in the range of oligomers. This outcome was not totally unexpected since the formation of **4** would require a considerable entropy drop of the system. On the other hand, we believe that in the reaction employing Kemp's acid, the preorganisation of its triaxial carboxylic acid groups[3] in the acidic state and also as triester,[2,3c,6] facilitated the formation of the cage.

Since all attempts to grow crystals of **2** useful for X-ray structure determination have hitherto failed, its structure was studied by molecular mechanics computation, NMR- and mass spectroscopy. According to molecular mechanics calculations (MM3),[7] starting from a large number of input structures based on molecular models, the structure of **2** having the cyclohexane ring in the chair conformation had the lowest energy found (Fig. 1). H-bonds between the amide protons of one arm and the carbonyl oxygens of the adjacent arms were clearly seen and the C_3-symmetric character of **2** was indeed reproduced.

It was also evident from the ^{1}H NMR spectrum that **2** was C_3-symmetric, since only one set of signals appeared. As expected, the shift of the various protons had changed as compared to those of **1b**. Thus, the α-proton signal was shifted down-field, from 3.97 ppm in **1b** to 5.25 ppm in **2**, and the multiplicity changed from a double doublet in **1b** to a triple doublet in **2**. This was attributed to the coupling to both the amide protons and the β-protons. In **1b**, no coupling between the α-proton and NH was observed and the signal of the α-proton was a double doublet as a result of its coupling only to the β-protons. For **2**, the N**H**–Hα coupling was clearly seen in the COSY spectrum.† Also the β-proton resonances showed changes in shift and appearance. From being a double doublet at 2.87 ppm, with a coupling constant of 7.2 Hz in **1b**, the corresponding signal in **2** was split into a double doublet at 3.48 ppm and a double doublet

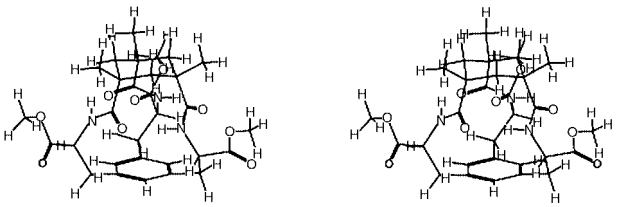


Fig. 1 Stereoview of **2** after steric energy minimization (MM3).[7]

† Electronic supplementary information (ESI) available: spectral data for **1b** and **2**. See http://www.rsc.org/suppdata/cc/b1/b101193f/

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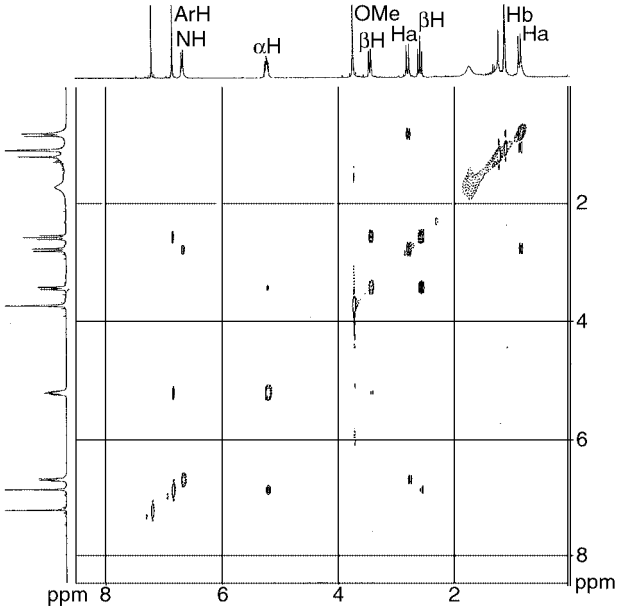

Fig. 2 NOESY spectrum of **2** in $CDCl_3$.

at 2.62 ppm ($J_{\alpha,\beta}$ = 6.9 Hz). One of these protons (at 3.48 ppm) presented a weak NOESY correlation to the α-proton, (Fig. 2). This observation supported the H-bonding in the MM3-model. As seen in Fig. 1, the α- and gauche β-protons are positioned 2.36 Å apart. These protons are located near the extension of the aromatic plane, *i.e.* in the down-field shift region, as can be seen in Fig. 1. The effect was confirmed by ^{1}H NMR. The anti relation between the two β-protons was expressed by the large geminal coupling constant ($J_{\beta-\beta}{}^1$ = 15.7 Hz). The signal originating from the methylene protons in Kemp's acid itself appeared at 2.54 ppm, while the corresponding proton resonance in **2** appeared as two different doublets, one at 2.83 ppm and the other at 0.89 ppm, with a large geminal coupling constant of 15.7 Hz. NOESY experiments revealed that the equatorially positioned protons (the signal at 2.83 ppm) presented a NOE enhancement effect to N**H**CO (Fig. 2). No such effect was observed for the axial protons (0.89 ppm). This observation also supports the H-bonding shown in the MM3-model. As seen in Fig. 1, the NH–Ha distance is only 2.0 Å. The array of NH···O=C hydrogen bonds closes the cage, thus hindering guest molecules to enter. Moreover, the space available inside the cage is probably too small to accommodate a guest particle. This was estimated by MM3[7] energy minimization of an imaginary inclusion complexes between a hydrogen or helium atom and the cage, which resulted in *ca.* 8 kcal mol^{-1} higher energy of both complexes as compared to the empty cage.

The protruding carboxylate groups of **2** may be used as attachment points for various structures *via* ester- or amide bonds. Compound **2** would then serve as a core of dendritic structures. Synthetic work in this direction as well as molecular recognition studies are in progress.

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Notes and references

‡ Abbreviations: PyAOP = [7-azabenzotriazol-1-yloxytris(pyrrolidino)-phosphonium hexafluorophosphate]; Hünig's base = *N*,*N*-diisopropyethylamine (DIEA), EDC = 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride, HOBt = 1-hydroxybenzotriazole hydrate, HATU = *O*-(7-azabenzotriazol-1-yl)-*N*,*N*,*N*′,*N*′-tetramethyluronium hexafluorophosphate.

§ Compounds **1b** and **2** were characterised by ^{1}H and ^{13}C NMR spectroscopy (400 MHz, 298 K) and by mass spectroscopy (FAB). NOESY experiment was used to make individual ^{1}H NMR assignment. Polarimetric measurements were performed at 20 °C.

Preparation of **1b**. Compound **1a**[4] (1.0 g, 1.27 mmol) was dissolved in MeOH (50 mL), Pd/C (50 mg) was added and the mixture was hydrogenated at 1 atm overnight. After removal of the catalyst by filtration through Celite, **1b** was obtained as an amorphous white powder (0.48 g, 99%). mp 207.0–208.8 °C. ν_{max}(KBr)/cm^{-1} 3409.9(NH), 2962.5, 1743.5(CO), 1674.1. ^{1}H NMR (300 MHz, CD_3OD) δ 6.81 (s, 3H), 3.97 (dd, J = 8.5 Hz, 3H), 3.51 (s, 9H), 2.87 (dd, J = 7.2 Hz, 6H). ^{13}C NMR (75 MHz, CD_3OD) δ 171.5, 137.9, 131.9, 55.9, 54.3, 37.8. $[\alpha]_D$ +16.3° (*c* 0.55, MeOH). HRMS (FAB + H$^+$) calculated for $C_{18}H_{27}N_3O_6$ 381.1900. Found 382.1967 [M$^+$ + H].

Preparation of **2**. A solution of Kemp's triacid (0.033 g, 0.13 mmol), PyAOP (0.20 g, 0.38 mmol) and DIEA (65 μL, 0.38 mmol) in DMF (10 mL) was added, *via* a syringe pump, to a solution of **1b** (0.050 g, 0.13 mmol) and DIEA (65 μL, 0.38 mmol) in DMF (90 mL), over 10 h. The reaction mixture was stirred for an additional 12 h at rt. The solvent was then removed under reduced pressure and the residue was dissolved in diethyl ether (20 mL). The organic phase was washed with 1 M HCl (10 × 10 mL) in order to remove remaining PyAOP. The volume of the organic phase was reduced and the crude product was chromatographed (CH_2Cl_2–MeOH 30:1, R_f = 0.5) to give **2** as a semi-solid (7 mg, 8%). ν_{max}(KBr)/cm^{-1} 3379.1(NHCO), 2954.7, 1895.2, 1743.5(CO), 1643.2, 1535.2. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.91 (s, 3H), 6.73 (d, J = 10.2 Hz, 3H), 5.27 (ddd, $J_{H\alpha-Hb}$ = 6.9 Hz, $J_{H\alpha-NH}$ = 10.2 Hz, 3H), 3.78 (s, 9H), 3.48 (dd, J = 6.9 Hz, 3H), 2.83 (d, J = 15.8 Hz, 3H), 2.62 (dd, J = 7.3 Hz, 3H), 1.15 (s, 9H), 0.89 (d, J = 15.6 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.0, 172.2, 135.3, 129.6, 52.4, 52.2, 43.6, 40.9, 37.2, 35.9. $[\alpha]_D$ −3.4° (*c* 0.35, MeOH). HRMS (FAB + Na$^+$) calculated for $C_{30}H_{39}N_3O_9Na$ 608.2584. Found 608.2588 [M$^+$ + Na].

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