One-pot synthesis of a shape-persistent endo-functionalised nano-sized adamantoid compound†

Michael Mastalerz

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A simple approach by reversible imine condensation to shape-persistent endo-functionalised nanocage compounds is presented.

The development of the directed synthesis of discrete nano-sized structures has been improved in recent years. Especially in supramolecular coordination chemistry the synthesis of three-dimensional cage compounds is already well established.[1] These supermolecules often have highly symmetrical shapes such as geometrical archemedian or platonic bodies.[2] Such compounds are widely used to encapsulate various guest molecules or behave as reaction vessel or container for sometimes "unusual" reactions.[3] Recently Fujita *et al*. introduced endohedral functionalised supramolecular nanoballs with polymerisable units in the interior.[4] After successful polymerisation the cage compound was cleaved to set the polymer free.

In comparison to supramolecular cages, based on coordination of transition metals, analogous shape-persistent covalent bound organic cage compounds are rare.[5] Until recently such compounds were only accessible through high level synthetic efforts. Dynamic reversible reactions provide the key to the directed synthesis of covalent bound structures with high efficiency by *Constitutional Dynamic Chemistry* (CDC) or *Dynamic Combinatorial Chemistry* (DCC).[6] Such reversible reactions include, for example, the boronic ester condensation,[7] the formation of Schiff base compounds[8] and combinations of both.[9] This strategy was used successfully for the synthesis of shape-persistent macrocycles with diameters in the range of nanometres.[10,11] The imine condensation was also a key step in the synthesis of molecular topologies such as helicates,[12] rotaxanes,[13] suitanes,[14] borromean rings,[15] solomonic knots,[16] and foldamers.[17]

Warmuth *et al*. introduced covalent bound nanocapsules on the basis of a one-pot synthesis of resorcinarene derivatives with diamines in high yields.[18] By extensive studies of the reaction conditions they were able to reach a high product selectivity.

Very recently Warmuth and coworkers published the synthesis of a chiral nanocube containing asymmetric units in the remote periphery of the vertexes.[19]

The research introduced here is based on a similar concept using rigid C_3-symmetrical units as building blocks for the synthesis of covalent bound nanocage compounds. The difference to most systems known today is the synergistic direction of six hydroxyl groups into the centre of the cavity. As rigid building blocks triamine **1**[20] and salicylic dialdehyde **2** were chosen first to give the endo-functionalised adamantoid nanocage compound **3** in 58% yield in a single step (Fig. 1 and Fig. 2).‡ No addition of templating metal salts or promoting acids was necessary. The reaction procedure is very simple: stirring a mixture of the reactants **1** and **2** in a ratio of 2 : 3 in THF at room temperature for seven days. The deep orange precipitate was filtered off, washed with some THF and dried *in vacuo* to give **3** with a purity sufficient for elemental analysis. The substance shows only peaks around m/z = 2218 and 2444 in the MALDI-TOF mass spectrum recorded in dithranol (Fig. 3). Whereas the isotopic pattern of the peaks at m/z = 2218 is in total agreement with the calculated pattern for **3**+H$^+$ the signals at m/z = 2443–2449 are supposed to be formed by a supramolecular 1 : 1 complex of **3** with the matrix dithranol. In the IR spectrum a sharp peak at 1625 cm^{-1} is caused by the stretching of the imine double bond. Another hint for the structure is a peak for λ_{max} at 377 nm in the UV–Vis. This band is comparable to that of similar salicyldiimines.[21]

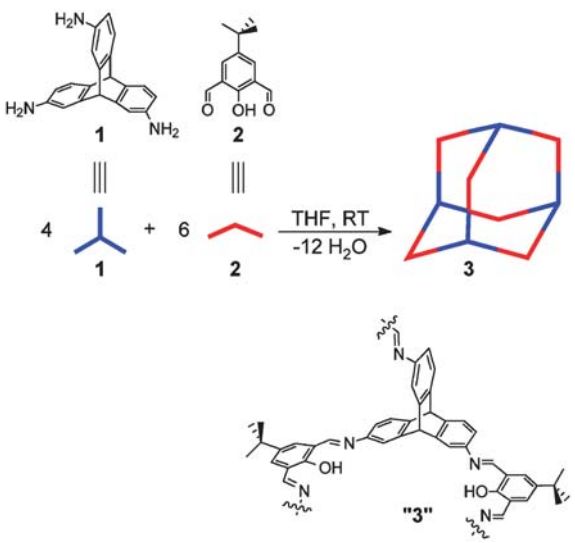

Fig. 1 One-pot synthesis of the adamantoid cage compound **3**. "**3**" is a part of the cage structure to clearly depict the formed imine bonds.

Although the yield is "only" 58%, this means that the conversion of each step is *ca*. 96%.

The mother liquor of the reaction mixture was investigated too by MALDI-TOF spectroscopy. Besides some nanocage

Ulm University, Institute of Organic Chemistry II and Advanced Materials, Albert-Einstein-Allee 11, D-89081 Ulm, Germany. E-mail: michael.mastalerz@uni-ulm.de; Tel: +49-731-50-22855

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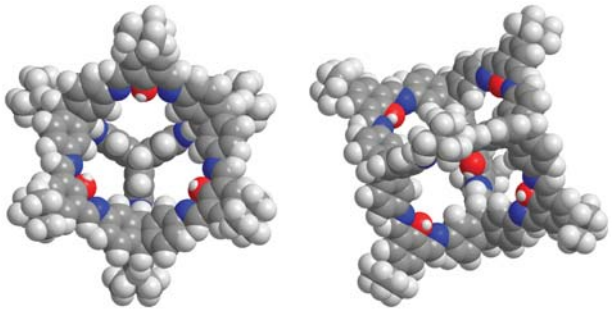


Fig. 2 MM2-optimised space filling model of **3** from two different perspectives. Grey: carbon, blue: nitrogen, red: oxygen, white: hydrogen.

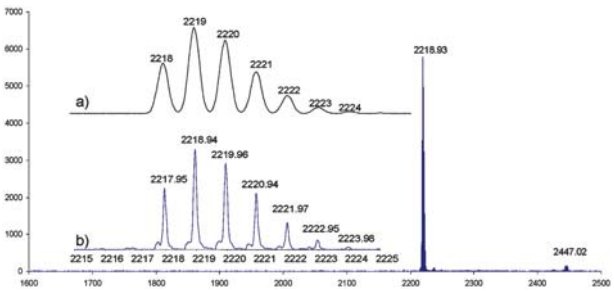
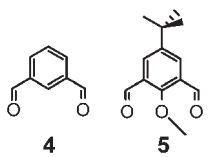


Fig. 3 MALDI-TOF MS of **3** in dithranol (matrix). (a) Simulated isotopic pattern for $\mathbf{3}+H^+$. (b) Zoomed out section of the mass peak region.

compound **3** peaks of partly condensed compounds could be detected. These compounds are intermediates in the formation of the cage compound **3**.

A directing or preorganising effect of the hydroxyl protons by hydrogen bonds to the nitrogen atoms of the formed imine bonds is supposed. Additionally, intramolecular hydrogen bonds of the hydroxyl protons of the salicylic dialdehyde may elevate the velocity of the reaction. To strengthen the hypothesis, first condensation experiments of triamine **1** with isophthalaldehyde **4** and protected aldehyde **5**, respectively were investigated. In the case of the reaction of **4** and **1** an insoluble polymeric material is obtained. This is a hint of the preorganising effect of the hydroxyl groups. However, when aldehyde **5** is used instead, even after 14 days only some peaks in the MALDI-TOF mass spectrum could be detected as nanocage compound. These peaks are still part of a complex mixture that cannot be separated yet, even by size exclusion chromatography.



4 **5**

According to an MM2 minimized structural model (Fig. 2) cage compound **3** displays an adamantoid T_d-symmetry[22] with the six endohedral directing hydroxyl groups. These hydroxyl groups build a regular octahedron with an O–O-distance of the opposite oxygen atoms of *ca.* 15.7 Å and an edge length of *ca.* 11.3 Å. The outer diameter is *ca.* 27.2 Å (between two

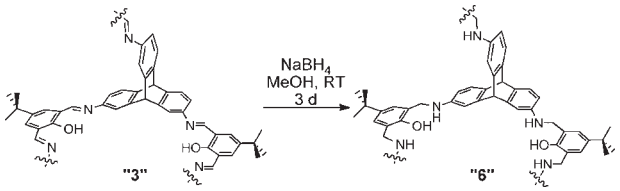


Fig. 4 Reduction of the twelve imine bonds shown exemplified at subunits (”**3**” and ”**6**”) of cage compounds **3** and **6**.

opposite *tert*-butyl groups). Although the structure is an open framework the minimal inner volume is estimated to be 678 Å^3.

To confirm the structure of **3** which is barely soluble in almost every common organic solvent the twelve imine bonds were reduced by sodium borohydride in methanol to get a more flexible compound (Fig. 4). After workup cage compound **6** was isolated in 76% yield.‡ And indeed compound **6** shows good solubility in most organic solvents.

In the ^{1}H NMR of **6** (Fig. 5) a broad doublet at 4.27 ppm appears that clearly can be assigned to the benzylic methylene protons. The amine protons give a broad pseudo-triplet at 5.10 ppm by coupling with the methylene protons, showing clearly that the reduction was successful. In addition the structure was confirmed by ^{13}C NMR, ESI-MS, IR and elemental analysis. However, the results from elemental analysis suggest that even after drying in high vacuum five water molecules are enclathrated inside the polar cavity.

Compound **6** is also a nanocage compound containing twelve hydroxyl or amine protons directing into the interior of the cavity. This makes the compound a potential host molecule for prospective complexation studies that have not been investigated in detail yet.

In conclusion, the first shape-persistent covalent bound adamantoid nanocage was synthesized in an effective and simple one-pot synthesis by a reversible imine condensation (Schiff base reaction). Additionally the compound contains rigid functional groups directing into the centre of the cavity.

Further studies on the kinetics and thermodynamics of the cage forming process, complexation of guest molecules and

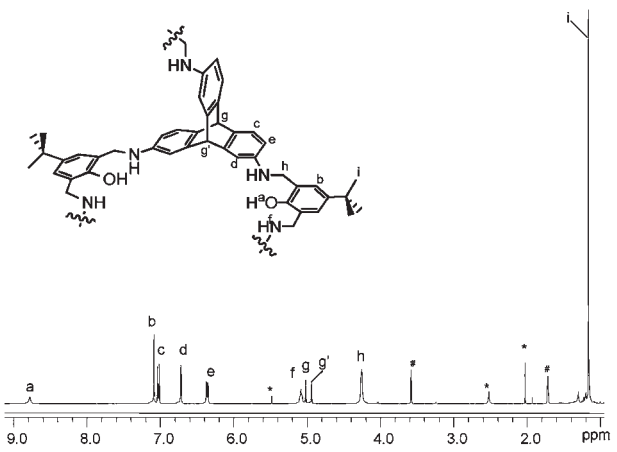


Fig. 5 ^{1}H NMR spectrum of **6** in THF-d8 (#). The signals labelled with the asterisks (*) are caused by enclathrated solvents (dichloromethane and water).

storage of volatile compounds are underway. Also more soluble derivatives of **3** will be synthesized as well as monodisperse metal clusters,[23] stabilized by the cage compounds.

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Notes and references

‡ Synthesis of **3**: A solution of **1**[20] (150 mg, 0.50 mmol) and **2** (156 mg, 0.75 mmol) in dry THF (30 mL) was stirred for 7 d at room temperature. The orange precipitate was collected on a Buchner funnel, washed with THF (3 × 4 mL) and dried *in vacuo* to give 160 mg (58%) of cage compound **3** as an orange solid with mp >410 °C, IR (KBr): $\tilde{\nu}$ = 1625 cm^{-1}, UV–Vis (THF): λ (nm) = 228, 336, 349, 377. MALDI-TOF (dithranol): m/z = 2217.9, 2218.9, 2219.9, 2220.9, 2221.9, 2222.9, 2223.9. Elemental analysis calcd for $C_{152}H_{128}N_{12}O_6$ (M = 2218.76 g mol^{-1}): C 82.28, H 5.81, N 7.58; found: C 82.05, H 5.80, N 7.30%.
Synthesis of **6**: To a suspension of **3** (56 mg, 0.025 mmol) in 4 mL of dry methanol $NaBH_4$ (88 mg, 2.3 mmol) was added and the mixture was stirred for one day at room temperature. Another portion of $NaBH_4$ (80 mg, 2.1 mmol) was added and the mixture was stirred for an additional two days. 4 mL dichloromethane and 4 mL water were added. The layers were separated and the aqueous phase was extracted with dichloromethane. The combined organic extract was dried with sodium sulfate and solvent was removed to give 42 mg (76%) of **6** as an off-white solid with mp >410 °C (dec.).
^{1}H NMR (THF-d8, 278 K, 400 MHz): δ = 1.18 ppm (s, 54 H, *t*Bu-H), 4.27 (d, J = 5.2 Hz, 24H, Ar–CH_2NH–Ar′), 4.95 (s, 4 H, bridgehead-H), 5.03 (s, 4H, bridgehead-H), 5.10 ("t", 12H, Ar–CH_2N*H*–Ar′), 6.37 (dd, J = 8.0 Hz, 2.0 Hz, 12H, triptycenyl-H), 6.73 (d, J = 2.0 Hz, 12H, triptycenyl-H), 7.04 (d, J = 8.0 Hz, 12H, triptycenyl-H), 7.10 (s, 12H, salicyl-H), 8.79 (s, 6H, Ar–O*H*). ^{13}C NMR (THF-d8, 100 MHz): δ = 32.1 ppm (q, –C(CH_3)$_3$), 34.7 (s, –*C*(CH_3)$_3$), 47.0 (t, –CH_2–NH–), 52.7, 56.2 (both d, both bridgehead-*C*), 110.0 (s), 111.7 (s), 123.7 (s), 125.6 (d, two superimposed signals), 138.1 (s), 142.0 (s), 146.7 (d), 147.5 (d), 153.8 (s, Ar*C*–OH). MS (ESI, methanol, acetonitrile, formic acid): m/z = 2243 $[M+H]^+$, 1122 $[M+2H]^{2+}$. Elemental analysis calcd. for $C_{152}H_{152}N_{12}O_6{\cdot}5H_2O$: C 78.25, H 6.99, N 7.20; found: C 78.19, H 6.81, N 6.92%.

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