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Multifarenes: new modular cavitands†

Cite this: *Chem. Commun.*, 2014, 50, 2494

Received 29th October 2013,
Accepted 9th January 2014

DOI: 10.1039/c3cc48284g

www.rsc.org/chemcomm

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Multifarenes, a new class of macrocycles, which are constructed of alternating building blocks, are conveniently accessible by three complementary syntheses that provide modularity and scalability. In addition to metal-ion coordination, these cavitands show increased flexibility with increasing ring size, offering opportunities for induced fit to guest molecules.

Macrocyclic molecules, which often serve as cavitands,[1] offer a broad spectrum of useful applications in many areas,[2] including supramolecular architecture, nanotechnology, catalysis, surface chemistry, environmental sciences, analytical and medicinal chemistry. Each macrocycle exhibits unique traits that offer specific uses. The most common species, such as calixarenes,[3] resorcinarene,[4] calixpyrroles,[5] pillararenes,[6] cucurbiturils[7] and cyclodextrins[8] (Fig. 1A), are formed by cyclooligomerization of a single monomeric building block, which dictates particular binding properties, substitution patterns, functionalization and solubility.

We reasoned that it would be beneficial to design modular cavitands from multiple building blocks. Here we demonstrate this notion by the synthesis of several members of a new class of macrocycles, for which we propose the name *multifarene*[9] (Fig. 1B). We show that multifarene[*m*,*n*], where *m* and *n* are the number of various subunits, can be practically synthesized by three different methods.

We aimed at macrocycles with a rim of alternating functional groups, including a less common thiourea group,[10] which could offer unique binding opportunities to metal ions and surfaces. The two building blocks chosen for connection by methylene bridges were 4-*t*-butylphenol, **4**, and 2-imidazolidinethione, **5**. Exploring synthetic strategies that would be general and scalable, we first examined the basic conditions commonly used for synthesis of calixarenes.[3] Unfortunately, these conditions were found to be inadequate for the reaction between **4** and **5** with paraformaldehyde, leading to complex mixtures of various linear oligomers and uncharacterized products. Apparently, in a basic environment formaldehyde condenses with the sulfur atom of **5** rather than with its nitrogen atoms.[11] Nevertheless, by using acid catalysis we were able to invert this chemoselectivity. Thus, the reaction of **4** and **5** (at a 4 : 1 ratio) with paraformaldehyde in toluene containing *p*-toluenesulfonic acid (PTSA) (30 mol%) at 65 °C afforded compound **6** in 86% isolated yield (Scheme 1). The 4 : 1 ratio was required in order to minimize the formation of longer oligomers and balance the greater reactivity of **5** over **4**.

Higher linear co-oligomers could be obtained by adjusting the molar ratio of the reactants. For example, the use of **4** and **5** at a 2 : 3 ratio followed by chromatographic separation afforded **6**, **7** and **8** in 28, 24 and 10% yields, respectively. We expected that using **4** and **5** at a ratio of 1 : 1 would result in a mixture of multifarenes of various ring sizes. Surprisingly, this ratio resulted in the selective formation of multifarene[4,4], **3**, in 67%. The thermodynamic preference of **3** over its homologs could be explained by minimal molecular dipole moment (*vide infra* crystal structure) and molecular strain. Other multifarenes, linear oligomers and cooligomers were observed as side products.

We attempted to control the multifarene ring size by fragment condensation[12] of the appropriate linear oligomer **6**, **7** or **8** through a

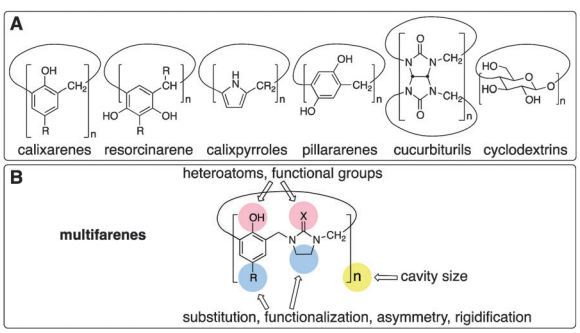

Fig. 1 (A) Representative families of cyclooligomeric cavitands. (B) General design elements of the multifarenes.

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† Electronic supplementary information (ESI) available. CCDC 952889 (**3**), 952890 (**2**) and 952891 (**1**). For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c3cc48284g

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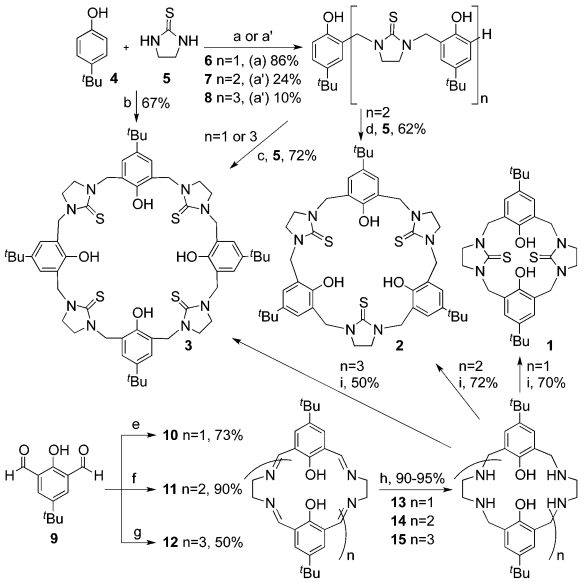

Scheme 1 Synthesis of multifarenes **1**, **2** and **3**. (a) **4** (1 eq.), **5** (4 eq.), $(CH_2O)_n$ (3 eq.), PTSA·H_2O (30 mol%), toluene, 65 °C, 2d; (a′) same as (a) but with 1.5 eq. of **4** and 1 eq. of **5**; (b) **4** (1 eq.), **5** (1 eq.), $(CH_2O)_n$ (10 eq.), PTSA·H_2O (30 mol%), toluene, 55 °C, 6d; (c) **6** (1 eq.), **5** (1 eq.), $(CH_2O)_n$ (4 eq.), PTSA·H_2O (50 mol%), toluene, 60 °C, 2d; (d) **7** (1 eq.), **5** (1 eq.), $(CH_2O)_n$ (5 eq.), PTSA·H_2O (2 eq.), toluene, 60 °C, 2d; (e) 1,2-diaminoethane (DAE, 1 eq.), $NaClO_4$ (4 eq.), AcOH–MeOH, reflux, 24 h; (f) DAE (1 eq.), CH_3CN–MeOH, −10 °C, 8 h; (g) DAE (1 eq.), Mg $(OAc)_2{\cdot}4H_2O$ (0.5 eq.), $Mg(NO_3)_2{\cdot}6H_2O$ (0.5 eq.), CH_3OH, reflux, 8 h; (h) $NaBH_4$, MeOH, 0 °C to rt, 2 h; (i) TCDI, dry THF, rt, 3 h.

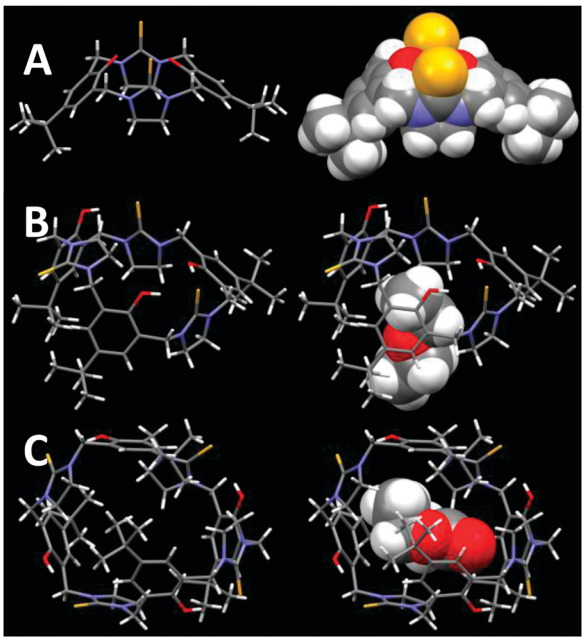

Fig. 2 Capped sticks representation of solid-state molecular structures. (A) Multifarene[2,2], **1**, also shown in space-fill representation (right). (B) Multifarene[3,3], **2**, with and without diethyl ether guest. (C) Multifarene[4,4], **3**, with and without ethyl acetate guest. Color codes: red – oxygen, blue – nitrogen, yellow – sulfur, grey – carbon.

reaction with **5**. Indeed, the reaction between **7** and **5** (path d in Scheme 1) afforded multifarene[3,3], **2**, in 62% yield. Similarly, the reaction between **8** and **5** under the same conditions afforded **3**. However, the reaction between **6** and **5** under identical conditions resulted in **3** rather than multifarene[2,2], **1**.

The inability to obtain **1** by the above approaches and the need for non-trivial chromatographic separations led to the pursuit of a third synthetic strategy. To that end we adopted the principles of Robson's macrocyclization strategy[13] to prepare imino-phenol macrocycles, **10–12**. Previous studies revealed that 2,6-diformylphenols react with diaminoalkanes to form cyclic poly-imines whose size can be controlled by cation templates.

Thus, the reaction between 4-*t*-butyl-2,6-diformylphenol, **9** and diaminoethane (DAE, 1 eq.) in a mixture of methanol and acetic acid in the presence of $NaClO_4$ (4 eq.) afforded the [2,2] macrocyclic polyimine, **10**, in 73% yield (Scheme 1).[14] In contrast, performing the same reaction in the absence of a template under conditions of kinetic control (acetonitrile, −10 °C) afforded the [3,3] macrocyclic polyimine, **11**, in 90% yield.[15] Alternatively, carrying out the same cyclocondensation reaction in the presence of a Mg(II) template afforded the [4,4] macrocyclic polyimine, **12**, in 50% yield.[16]

Reduction of polyimines **10**, **11** and **12** with $NaBH_4$ in methanol at 0 °C afforded the corresponding polyamines, **13**, **14** and **15**, in essentially quantitative yields. Finally, treatment of the latter macrocycles with 1,1′-thiocarbonyldiimidazole (TCDI) in THF at room temperature afforded all three multifarenes, **1**, **2**, and **3**, in 70%, 72% and 50% isolated yields, respectively.

The solid-state structure of **1** (Fig. 2A) exhibits a highly polar conformation with all functional groups pointing in the same direction along its *C*-2 axis of symmetry. The thiourea and phenol groups are all hydrogen-bonded with O–S distances of 3.3, 3.3, 3.5 and 3.5 Å. The thiourea rings are essentially planar and nearly parallel at a distance of 5.1–5.4 Å. In contrast, the phenol groups are tilted towards one another at an angle of ∼100° with a distance of 7.23 Å between the centroids of the aromatic rings. This arrangement forms a small hydrophobic cavity. As can be concluded from its ^{1}H NMR spectrum, multifarene **1** is locked in this conformation not only in the solid state but also in solution, exhibiting a very large chemical shift difference of over 2.2 ppm between the two doublets assigned to the methylene bridge protons. The protons of the imidazolidinethione ring are less affected by the different chemical environment, showing a chemical shift difference of only 0.5 ppm.

The solid-state structure of **2** features a larger cavity than that of **1**, accommodating diethyl ether. The host exhibits a polar conformation with most of the functional groups being hydrogen bonded (O–S distances of 3.1, 3.3 and 3.2 Å). Yet, one thiocarbonyl group points away from the polar portal, representing a possible case of induced fit.[17] The loss of hydrogen bonding stabilization energy due to this distortion is probably compensated by the tight hydrophobic interactions with the guest, with the distances between the centroids of the three aromatic rings being 7.21, 8.36 and 8.39 Å (Fig. 2B). This solid-state structure is very different from the solution structure at room temperature, which seems to average many conformations of similar energy, as indicated by the peak broadening in the ^{1}H NMR spectrum.

The solid-state structure of **3** (Fig. 2C) reveals a unique conformation of a nearly tetrahedral symmetry. Featuring

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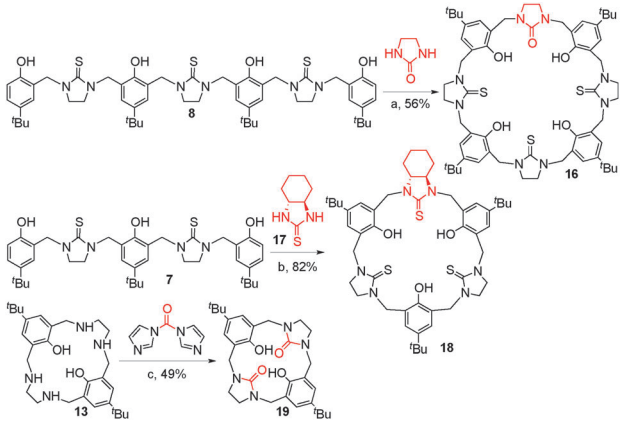

Scheme 2 Synthesis of multifarenes **16**, **18** and **19**. (a) **8** (1 eq.), 2-imidazolidinone (1 eq.), $(CH_2O)_n$ (5 eq.), PTSA·H_2O (50 mol%), toluene, 60 °C, 2d. (b) **7** (1 eq.), **17** (1 eq.), $(CH_2O)_n$ (2.1 eq.), PTSA·H_2O (50 mol%), toluene, 70 °C, 3d. (c) **13** (1 eq.), CDI (3.3 eq.), dry THF, RT, 2.5 h.

another interesting case of induced fit, the molecule is folded around its guest molecule, ethyl acetate. The guest itself adopts a less favored *syn-gauche* conformation, fitting into the host cavity. This conformation is dictated by the four pairs of hydrogen-bonded thiocarbonyl and phenol groups with S–O distances of 3.15, 3.26, 3.19, and 3.26 Å, and minimization of the molecular dipole moment. The centroids of the four aromatic rings are positioned at the vertices of a distorted tetrahedron with the six edges being 7.36, 7.96, 7.66, 7.30, 7.93 and 9.20 Å. The elongation of the latter edge corresponds to the presence of a methyl group of the host at that specific edge. Another distorted tetrahedron is defined by the centroids of the pentagonal imidazolidinethione rings with measured edges of 7.64, 7.21, 7.20, 7.56, 8.05 and 9.95 Å, again with the ethyl group of the guest corresponding to the main distortion. As is the case for **2**, the ^{1}H NMR data suggest that the solution structure of **3** at room temperature averages multiple conformations of similar energy.

All three of the above-described synthetic approaches to multifarenes offer three significant advantages. First, the ability to construct them either *via* single-step or multi-step synthesis allows for easy diversification and heterogeneity, a task that is non-trivial for the common cavitands, which are usually made in a single step. Second, the mild synthetic conditions are compatible with a broad variety of functional groups. Finally, these synthetic approaches are simple, inexpensive and scalable.

We demonstrated these advantages by the convenient synthesis of heterogeneous multifarenes (Scheme 2). For example multifarene-[4,3$_S$,1$_O$], **16**, was prepared in 56% yield by the reaction of precursor **8** with 2-imidazolidinone. Alternatively, an element of chirality could be incorporated into the multifarene skeleton by using an enantiomerically pure unit. For example, the chiral multifarene[3,3], **18**, was prepared in 82% yield by the reaction of oligomer **7** with (*R*,*R*)-**17**. Furthermore, the synthesis of multifarene[2,2$_O$], **19**, was accomplished in 49% yield simply by using 1,1′-carbonyldiimidazole (CDI) in the reaction with polyamine **13**.

Expectedly, multifarenes bind metal ions, as evidenced by NMR, UV and LCMS. For example, LCMS showed that **1** and $Pd(OAc)_2$ in CH_3CN–water formed various complexes, including **1**·Pd (*m*/*z* 657). In the presence of excess of **1**, we also observed **1**$_2$·Pd (*m*/*z* 1209) whereas with $Pb(NO_3)_2$ **1**·Pb (*m*/*z* 759) was formed. Titration of $Pd(OAc)_2$ with **1** in chloroform (by UV-vis) afforded a binding constant of $(1.3 \pm 0.8)10^7$. Titration of $HgCl_2$ with **1** in chloroform (using ^{1}H NMR) revealed a weaker binding constant of $(1.2 \pm 0.3)10^3$ (see ESI†). The multiple binding stoichiometries and different metal affinities suggest that the multifarenes offer non-trivial binding geometries, which could arise from the tangential rather than diametrical orientation of the sulfur lone pairs.

In conclusion, the multifarenes presented here are synthetic macrocycles constructed of alternating building blocks. These new molecules are conveniently accessible by three alternative synthetic approaches that provide modularity, generality and scalability. With increasing ring size, multifarenes exhibit increased flexibility, adopting multiple conformations with induced fit to their guest molecules. Expectedly, these new cavitands can bind metals at their heteroatom portals. Work is currently underway in our labs to explore their host–guest chemistry and unique metal binding properties, which can find useful applications, including catalysis, metal ion extraction, surface chemistry and nanoparticle coating.

EK is the incumbent of the Benno Gitter & Ilana Ben-Ami Chair of Biotechnology. GP acknowledges the Schulich Scholarship program and the Israel Ministry of Science and Technology for the Eshkol scholarship.

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