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Rational design of a nanometre-sized covalent octahedron†

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The thermodynamically controlled reaction of six tetraformyl-cavitands with twelve rigid, linear diamines yields quantitatively polyimine octahedrons with diameters of up to 5 nm. The cavitands are optimized to match the ideal geometry of a 60° tetratopic vertex unit and are connected along the octahedron edges with the diamines through 24 newly formed imine bonds.

In recent years, nanocapsules have received much attention of the chemical community owing to their potential as nanoreactors,[1] in which reactive intermediates gain longevity, reaction rates, regiochemistry, and selectivity are altered, or as delivery, storage and separation devices.[2] Well-defined, nanometre-sized capsules are best synthesized using self-assembly processes involving primarily hydrogen bonding,[3] metal-coordination[2a,4] or dynamic covalent chemistry.[5] These syntheses are under thermodynamic control and either require a suitable template or judicious choice of building blocks with the correct geometry and reduced conformational flexibility in order to direct the assembly process towards the desired capsule. Several directional design strategies have been developed for the multi-component assembly of metal coordination polyhedrons.[4a–e] In these strategies, the particular coordination polyhedron is programmed into the metal/polytopic ligand combination by means of the ligand field of the metal component and the ligand geometry. An advantage of directional approaches is the ease of expanding structures by changing the dimension of the organic ligand, *e.g.* by inserting linear spacers, whereby maintaining the ligand's basic geometry. Similar reliable, modular design strategies for the multi-component synthesis of dynamic covalent polyhedrons are rare, in part, due to the difficulty of designing suitable polytopic organic building blocks that yield strain-free capsules.[5a,c–g,i,k]

Recently, we discovered the multi-component synthesis of octahedral [6 + 12] polyimine nanocapsule $C^d_6L^a_{12}$ that formed in close to 80% yield upon reacting six cavitands C^d with twelve ethylene diamines L^a (Chart 1).[5b] Unfortunately, this approach could not be extended to other 1,*n*-alkanediamines, which yielded octaimine hemicarcerands, or to rigid linear aryldiamines L^x ($x = a$–c), which quantitatively afforded tetrahedral [4 + 8]-polyimine capsules $C^d_4L^x_8$ ($x = a$–c).[5d,6] We rationalized these observations with the geometry of cavitand C^d, in which opposite

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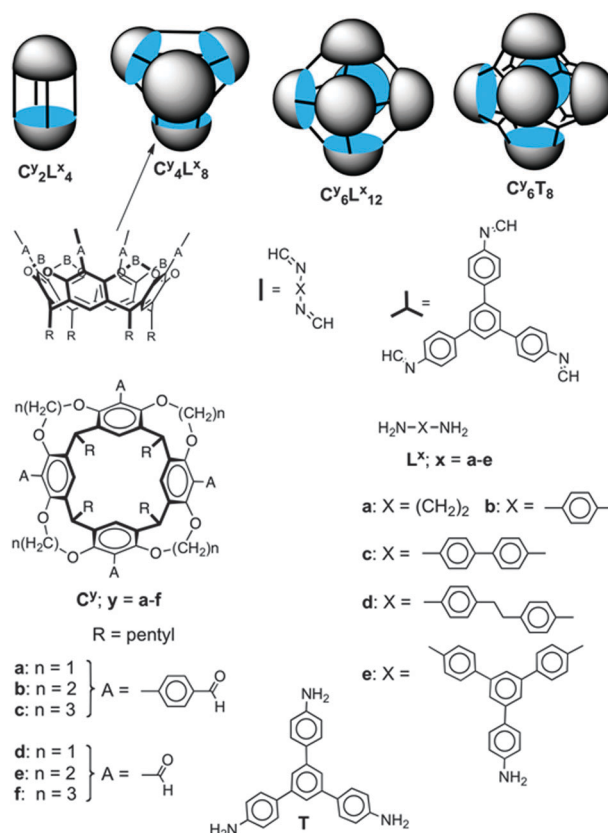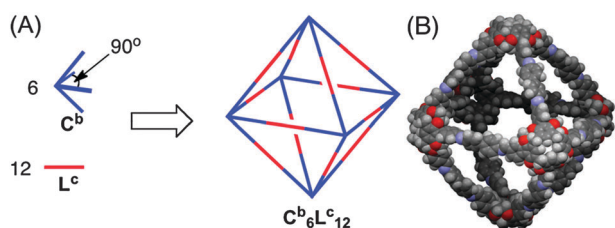
Chart 1 Hemicarcerands $C^y_2L^x_4$, polyimine capsules $C^y_2L^x_4$, $C^y_4L^x_8$, $C^y_6L^x_{12}$ and $C^y_6T_8$, cavitand C^y, and di- (L^x) and triamines **T**.

aryl units form angles of 65.4°, which is better suited for [4 + 8]-capsules $C^y_4L^x_8$ than for octahedral [6 + 12]-capsules $C^y_6L^x_{12}$. Herein, we describe the development of a rational approach towards the assembly of covalent Schiff base octahedrons based on an optimized cavitand-vertex geometry. To be an ideal octahedron vertex, the vectors connecting aryl-C1 and C4 in opposite aryl units of the cavitand should be orthogonal to each other (Fig. 1). This geometry can be achieved by increasing the O–(CH₂)ₙ–O spanner length, which flattens out the cavitand.

In modelling studies, the angles are 85.4° in the C_4 symmetric conformations of C^b and C^e and 93.7° in C^c and C^f, which are close to ideal (Fig. 2). Nevertheless, the condensation of C^e with two equivalents of ethylene-1,2-diamine (L^a) gave a complex mixture composed of multiple capsules with 2–6 cavitands. A similar condensation reaction of C^f yielded not the expected octahedral capsule, but the tetrahedral [4 + 8]-assembly $C^f_4L^a_8$,[5l]

Fig. 1 (A) Edge-directed synthesis of octahedron $\mathbf{C^b_6L^c_{12}}$ from 6 cavitands $\mathbf{C^b}$ and 12 benzidines $\mathbf{L^c}$. (B) Space-filling model of $\mathbf{C^b_6L^c_{12}}$ (Amber*, pentyl groups are omitted).
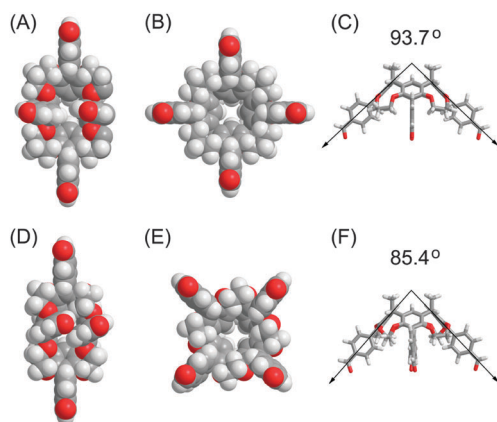
Fig. 2 Energy minimized structures of cavitand $\mathbf{C^c}$ (A–C) and $\mathbf{C^b}$ (D–F) with R = CH₃. Lowest energy C_{2v} symmetric conformations (A) and (D) and C_{4d} symmetric conformations (B), (C), (E) and (F).

in which the cavitands adopt a rectangular C_2 symmetric conformation similar to X-ray structures of related cavitands.[7] We rationalize these observations with the high energy penalty to adopt the required C_4 conformation. In the condensed phase, sandwiching a solvent molecule in between the nearly cofacial arenes of $\mathbf{C^e}$ or $\mathbf{C^f}$ in their C_2 conformation will further stabilize this conformation relative to the C_4 conformation, in which cavity–solvent size complementarity is expected to be less optimal. However, we realized that inserting a phenyl unit into the C_{aryl}–C(H)O bond creates a small pocket inside cavitand $\mathbf{C^b}$ and $\mathbf{C^c}$ in their C_2-conformation, which is too small to be filled with a solvent molecule (Fig. 2). Even though, gas phase force field calculations predict an 8.8 kcal mol⁻¹ and 1.9 kcal mol⁻¹ lower energy for the C_2 symmetric conformations of $\mathbf{C^b}$ and $\mathbf{C^c}$ than the desired C_4 symmetric conformations, respectively, we speculated that the energetic preference would be reversed in solution.

Indeed, TFA-catalyzed condensation of six equivalents of cavitand $\mathbf{C^b}$ with 12 equivalents of phenylene-1,4-diamine ($\mathbf{L^b}$) quantitatively afforded the desired octahedral [6 + 12]-polyimine nanocapsule $\mathbf{C^b_6L^b_{12}}$ within three hours.[8] The assignment of this product to octahedral $\mathbf{C^b_6L^b_{12}}$ is based on its MALDI-TOF mass spectrum, which shows an isotopic cluster at the expected mass-to-charge ratio $m/z = 8603.10$ ($m/z = 8603.36$ calculated for $[\mathbf{C^b_6L^b_{12}} + \mathrm{H}]^+$), its gel permeation chromatogram (GPC) and ^{1}H and ^{13}C NMR spectra (Fig. 3A, D, and F). The ^{1}H NMR spectrum of $\mathbf{C^b_6L^b_{12}}$ shows one multiplet each for the imine protons, H$_{im}$, the aryl protons H$_{a2}$, H$_{a3}$, H$_{a1}$ and H$_{a4}$, the benzylic protons H$_m$ and the ethylene protons H$_o$, H$_i$ at δ 8.53, 7.93, 7.67, 7.31, 7.26, 5.30, 3.89 and 3.46, respectively, in a
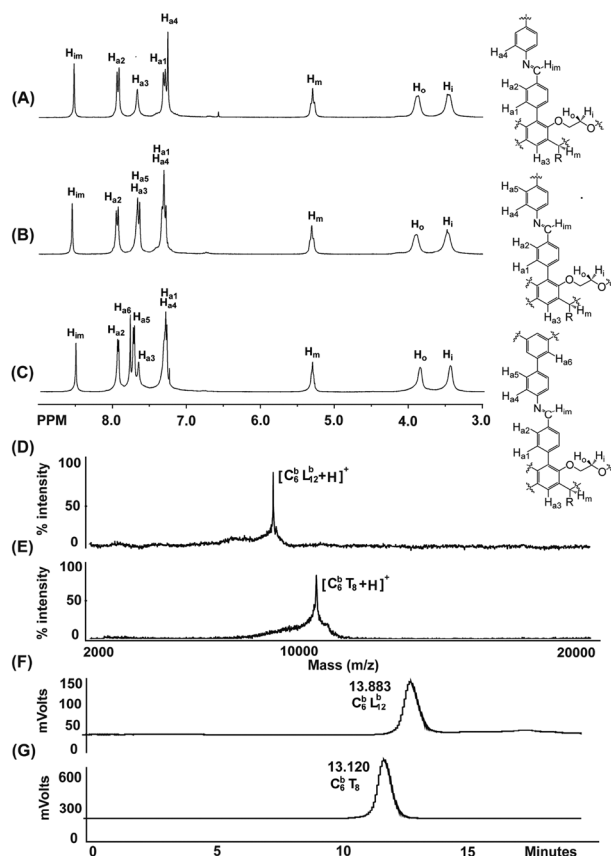
Fig. 3 ^{1}H NMR spectrum (300 MHz, CDCl₃, 25 °C) of $\mathbf{C^b_6L^b_{12}}$ (A), $\mathbf{C^b_6L^c_{12}}$ (B) and $\mathbf{C^b_6T_8}$ (C). MALDI-TOF MS of $\mathbf{C^b_6L^b_{12}}$ (D) and $\mathbf{C^b_6T_8}$. (E). GPC trace of products formed in the TFA-catalyzed reaction of 6$\mathbf{C^b}$ with 12$\mathbf{L^b}$ (F) or with 8$\mathbf{T}$ (G).

ratio 24 : 48 : 24 : 48 : 96 : 24 : 48 : 48, which is consistent with an octahedron. The modularity of this synthesis was demonstrated by replacing phenylene-1,4-diamine with benzidine ($\mathbf{L^c}$), which quantitatively produced the larger octahedron $\mathbf{C^b_6L^c_{12}}$. Again, MALDI-TOF MS, GPC, and ^{1}H and ^{13}C NMR of $\mathbf{C^b_6L^c_{12}}$ are fully consistent with its assigned structure (Fig. 3B and ESI†). The DOSY spectra of $\mathbf{C^b_6L^b_{12}}$ and $\mathbf{C^b_6L^c_{12}}$ provided diffusivities of $D(\mathbf{C^b_6L^b_{12}}) = 2.11 \times 10^{-10}$ m² s⁻¹ and $D(\mathbf{C^b_6L^c_{12}}) = 1.73 \times 10^{-10}$ m² s⁻¹ in CDCl₃ at 25 °C, from which we estimated solvodynamic diameters of 3.84 nm and 4.68 nm, respectively, which are comparable with force field calculations (Fig. 1). The latter provide octahedron edge and diagonal lengths, each measured as center-cavitand-to-center-cavitand distances, of $d_{edge} = 2.5$ nm and $d_{diagonal} = 3.6$ nm for $\mathbf{C^b_6L^b_{12}}$ and $d_{edge} = 3.0$ nm and $d_{diagonal} = 4.2$ nm for $\mathbf{C^b_6L^c_{12}}$, which is to the best of our knowledge the largest polyimine nanocapsule prepared to date.

Rigidity of the linker and the cavitand unit is essential for successful octahedron synthesis. For example, reaction of $\mathbf{C^b}$ with two equivalents of either $\mathbf{L^a}$ or $\mathbf{L^d}$ gave the entropically more favorable [2 + 4] octaimine hemicarcerands (Table 1). Presumably, adjustment of the central dihedral angle of each linker led to formation of [2 + 4] condensation products with little conformational strain. Likewise, the increased flexibility of cavitand $\mathbf{C^c}$ leads to complex mixtures despite that the C_4 symmetric conformation of $\mathbf{C^c}$ is slightly better suited as an

Table 1 Main capsular products in the TFA-catalyzed condensation of $n\mathbf{C^y}$ (y = a–c) with $2n\mathbf{L^x}$ (x = a–d) or $4/3n\mathbf{T}$ in CHCl$_3$

Reactants	$\mathbf{C^a}$	$\mathbf{C^b}$	$\mathbf{C^c}$
$\mathbf{L^a}$	Mixture	$\mathbf{C^b_2L^a_4}$ (>95%)[b]	Mixture
$\mathbf{L^b}$	$\mathbf{C^a_4L^b_8}$ (90%)[c]	$\mathbf{C^b_6L^b_{12}}$ (>95%)[b 8]	Mixture
$\mathbf{L^c}$	$\mathbf{C^a_4L^c_8}$ (80%)[c]	$\mathbf{C^b_6L^c_{12}}$ (>95%)[b]	Mixture
$\mathbf{L^d}$	$\mathbf{C^a_4L^d_8}$ (80%)[c]	$\mathbf{C^b_2L^d_4}$ (95%)[c]	Mixture
$\mathbf{T}$	$\mathbf{C^a_6T_8}$ (>95%)[c]	$\mathbf{C^b_6T_8}$ (>95%)[b]	N/A[a]

[a] No data available. [b] Based on ^{1}H NMR integration. [c] Based on GPC integration.

octahedron vertex than that of $\mathbf{C^b}$. The outcome of capsule synthesis using $\mathbf{C^b}$ contrasts that of $\mathbf{C^a}$, which gave tetrahedral [4 + 8] polyimine nanocapsules $\mathbf{C^a_4L^x_8}$ (x = b–d) as major products in its reaction with diamines $\mathbf{L^x}$ (x = b–d). The latter results are consistent with condensation reactions of $\mathbf{C^d}$,[5d] and support our earlier suggestion that cavitands with OCH$_2$O spanners intrinsically prefer formation of tetrahedral capsules, if reacted with a linear linker.

The extended cavitands $\mathbf{C^a}$ and $\mathbf{C^b}$ are highly versatile not only in the synthesis of tetrahedral and octahedral polyimine nanocapsules, but also in the synthesis of rhombicuboctahedral capsules. We recently reported the first example of a polyimine rhombicuboctahedron with the synthesis of $\mathbf{C^d_6T_8}$, which is formed in 60–70% yield in the TFA-catalyzed reaction of $\mathbf{C^d}$ with excess $\mathbf{T}$.[5c] Likewise, the TFA-catalyzed condensation of six equivalents of $\mathbf{C^a}$ or $\mathbf{C^b}$ with exactly eight equivalents of $\mathbf{T}$ quantitatively afforded rombicuboctahedrons $\mathbf{C^a_6T_8}$ and $\mathbf{C^b_6T_8}$, respectively, based on their MALDI-TOF MS, ^{1}H and ^{13}C NMR spectra, and the GPC traces of the equilibrated reaction mixtures (Fig. 3C, E, and G and ESI†). Both capsules have solvodynamic diameters of $d(\mathbf{C^a_6T_8})$ = 4.38 nm and $d(\mathbf{C^a_6T_8})$ = 4.50 nm, which we estimated from their diffusivities $D(\mathbf{C^a_6T_8})$ = 1.85 × 10^{-10} m^2 s^{-1} and $D(\mathbf{C^b_6T_8})$ = 1.80 × 10^{-10} m^2 s^{-1} in CDCl$_3$ at 25 °C, and which are in between those of octahedrons $\mathbf{C^b_6L^b_{12}}$ and $\mathbf{C^b_6L^c_{12}}$.

The use of aryl-extended cavitands $\mathbf{C^a}$ and $\mathbf{C^b}$ has major advantages in rhombicuboctahedron syntheses with respect to the kinetics of capsule formation and their acid-sensitivity. In the synthesis of $\mathbf{C^d_6T_8}$, a large excess of $\mathbf{T}$ was required as a transimination catalyst, in order to convert kinetic side products into desired $\mathbf{C^d_6T_8}$ within a reasonable reaction time (2 days).[5c] Due to the excess of $\mathbf{T}$, substantial amounts of hemicarcerand $\mathbf{C^d_2L^e_4}$ formed as a byproduct and became the sole product after an extended reaction time (5 1/2 days). Also, the long reaction time required careful optimization of the TFA concentration, in order to avoid partial cavitand–acetal cleavage, which is catalyzed intramolecularly, if an adjacent imine is protonated by TFA.[5c,d] On the other hand, the higher reactivity of cavitands $\mathbf{C^a}$ and $\mathbf{C^b}$, led to the complete assembly of $\mathbf{C^a_6T_8}$ and $\mathbf{C^b_6T_8}$ in less than three hours with stoichiometric amounts of $\mathbf{T}$. Furthermore, due to the impossibility of intramolecular iminium ion catalysis of acetal cleavage, $\mathbf{C^a_6T_8}$ proved to be completely acid-insensitive.

In summary, we have developed a rational approach for the multi-component synthesis of nanometre-sized Schiff base octahedrons, which complements earlier design strategies for the assembly of molecular tetrahedrons,[5d] adamantanoids,[2b,c,5g] rhombicuboctahedrons,[5c] and cubes.[5e] The octahedral capsule product is programmed into the specific combination of a 60° tetratopic cavitand unit and a rigid, linear diamino unit, the length of which is variable and allows tailoring of the capsule's diameter. Our work stresses (1) the importance of a high degree of conformational rigidity of the amino and cavitand building blocks in order to exclude other possible capsule products and to achieve maximum selectivity and (2) the advantages of using aryl-extended cavitands in polyhedron syntheses, which yield acid-stable capsules more efficiently.

The large cavity volumes of the described octahedrons and rhombicuboctahedrons, which range from 7400 Å^3 to approximately 13 000 Å^3, approach the sizes of smaller globular proteins or other biomacromolecules and suggest new and interesting applications in biomedical, biochemical and materials sciences, which is the subject of ongoing studies in this laboratory.

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8 In CDCl$_3$, the yield was >95%. In toluene[D$_8$], the reaction produced a mixture of nanocapsules.