[6 + 6] Schiff-base macrocycles with 12 imines: giant analogues of cyclohexane†

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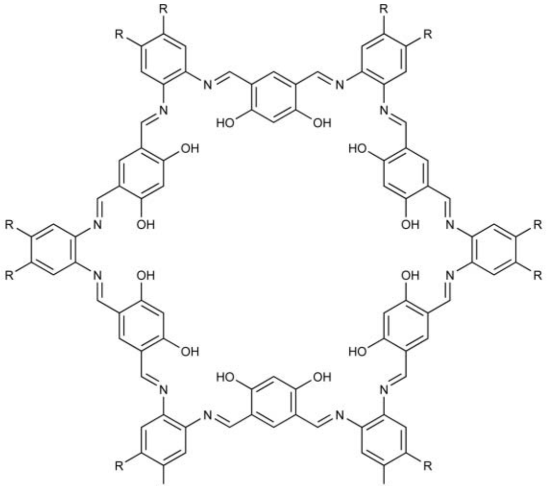
Hexagon-shaped [6 + 6] Schiff-base macrocycles with 12 imine bonds are reported. These giant macrocycles possess 6 N_2O_2 coordination environments and mass spectrometry evidence for hexametallation of one macrocycle is provided. Semi-empirical calculations reveal two stable conformations with boat and chair geometries for the macrocycles metallated with Ni(II), analogous to the conformations observed for cyclohexane.

Large shape-persistent macrocycles are challenging synthetic targets, attractive for their novel properties, including liquid crystallinity and self-assembly.[1–3] With a few exceptions, large organic macrocycles are prepared stepwise requiring sequences of protection, deprotection, reaction, and chromatographic separation, or requiring the elegant application of templates.[4,5]

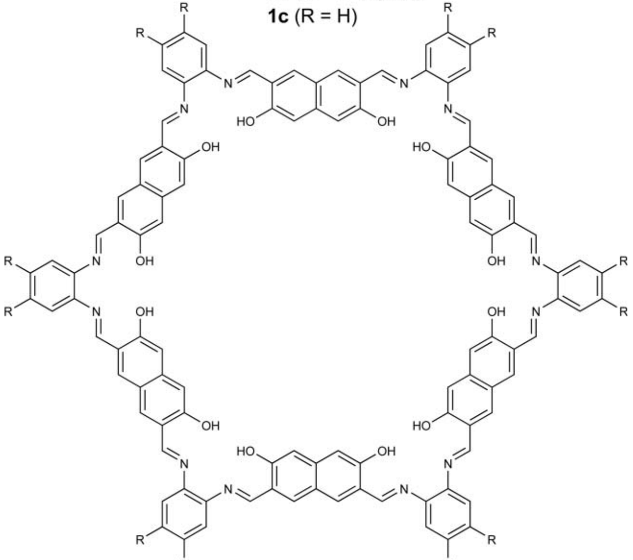
Reversible reactions may permit self-assembly of macrocycles.[6–8] The reversible condensation of an aldehyde and an amine to give an imine (Schiff-base condensation) is a convenient route to synthesize macrocycles, and has been used to make [2+2] and [3+3] Schiff-base macrocycles.[9–12] Using templates, even [4 + 4] Schiff-base macrocycles may be prepared.[13] To date, no examples of larger Schiff-base macrocycles have been reported. This is not surprising given the vast number of possible products, the difficulty of purification, and their tendency to hydrolyze or undergo other side reactions (*e.g.*, benzimidazole formation).[14] We have recently prepared large triangular [3 + 3] Schiff-base macrocycles by condensation of six components in solution.[15] Here we report the first examples of [6 + 6] Schiff-base macrocycles (**1** and **2**). Remarkably, the preparation of these organic macrocycles involves the reaction of 12 individual components in solution to form 12 new covalent bonds.

We believed that condensation of 4,6-diformylresorcinol **3**[16] with substituted phenylenediamine **4a** could give macrocycle **1a**. Recognizing that the reaction may be very sensitive to impurities, we prepared intermediate compound **5a** from the reaction of **3** with two equiv. of **4a**, Scheme 1. This air-stable intermediate is easily handled and avoids the need to use **4a** directly, advantageous since compound **4a** is very air-sensitive and difficult to purify.

Reaction of **3** with **5a** afforded a mixture of oligomers as determined by MALDI-TOF MS, Fig. 1(a). Significantly, the dominant species is the desired macrocycle **1a**. Shorter oligomers are also observed, but they are open-chain oligomers rather than closed cycles.[17] This reaction was repeated several times to ensure that macrocycle **1a** was the principal component.



1a (R = $O^nC_6H_{13}$)
1b (R = $O^nC_5H_{11}$)
1c (R = H)



2a (R = $O^nC_6H_{13}$)

Attempts to separate macrocycle **1a** from the oligomeric by-products by silica gel, alumina, or size-exclusion chromatography failed to give pure macrocycle **1a** (these compounds do not elute from silica). However, we discovered that macrocycle **1a** could be purified by trituration with hot CH_2Cl_2, taking advantage of the lower solubility of the macrocycle relative to oligomers. Fig. 1(b) shows the MALDI-TOF spectrum of a sample of macrocycle after purification. Pure macrocycle **1a**, which possesses 54 atoms in the

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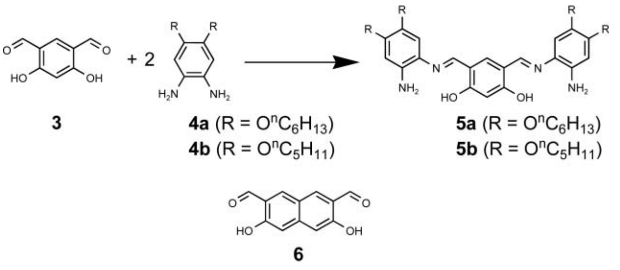

Scheme 1 Synthesis of air-stable intermediates **5a** and **5b**.

smallest closed ring, was isolated in *ca.* 19% yield by this route. Although low, this yield is *substantially* higher than a statistical mixture of oligomers and cycles.

Macrocycle **1a** gave satisfactory analysis. The IR spectrum of the deep red product showed $\nu_{C=N}$ at 1631 cm^{-1}, and confirmed that no aldehyde was present. The ^{1}H NMR spectrum of macrocycle **1a** was very broad, as we have seen with other macrocycles due to aggregation, but only broad features were observed, indicating the absence of starting materials and small oligomers. In particular, a broad imine resonance near 8.5 ppm, broad aromatic resonances, and no aldehyde resonance are consistent with the macrocycle.

Reaction of **3** with other phenylenediamines showed the [6 + 6] macrocycle as the major product (MALDI-TOF), with open-chain oligomers as the by-products. Macrocycle **1b** with pentyloxy chains could be isolated in *ca.* 25% yield by a similar procedure to that for **1a**. When longer substituents were employed (*e.g.*, O^{n}C$_{10}$H$_{21}$ or O^{n}C$_{12}$H$_{25}$), the major product was the [6 + 6] macrocycle, but we have not found suitable conditions to separate these macrocycles from oligomers due to their similar solubilities.

It may seem that our route to macrocycle **1** is not technically a [6 + 6] cyclization, but rather a [3 + 3] cyclization since we begin by pre-assembling **5**. Under the reaction conditions, we know that the imine bonds are formed and broken, so it does not matter that the larger component was used. In fact, the MALDI-TOF spectrum of the crude reaction mixture shows substantial quantities of oligomers with odd numbers of diamines (C, D, E, H, I, and J in Fig. 1(a)) that must arise from imine hydrolysis and recondensation. To demonstrate that the same macrocycle can truly be prepared by a [6 + 6] Schiff-base condensation, we reacted **3** with **4a** in CHCl$_3$–MeCN for 3 d. The MALDI-TOF spectrum of the crude product was similar to the product prepared using **5a**, showing oligomers and **1a**. After purification, macrocycle **1a** was obtained in very low yield (<2%). The lower yield may be attributed to the difficulty of accurately obtaining the 1 : 1 stoichiometry of compounds **3** and **4a** required for the formation of the [6 + 6] Schiff-base macrocycle.

To further verify that macrocycle **1a** was prepared, we reacted a small sample of macrocycle **1a** with excess VO(acac)$_2$ in THF. MALDI-TOF MS of this product (Fig. 1(c)) showed that the metal-free macrocycle was no longer present and that the major product was the compound with 6 VO^{2+} groups (m/z = 3020). The incorporation of six metals into the product is consistent with the structure of macrocycle **1a**, since each tetradentate N$_2$O$_2$ environment is expected to coordinate one metal ion.

As the Schiff-base condensation is reversible, thermodynamic products are obtained. By utilizing rigid precursors that are predisposed to a particular geometry, we can favour certain macrocycles to form. In the preparation of **1a**, we have observed ring-opened oligomers, but only the [6 + 6] product[17] is ring-closed. Once the oligomers have reached this length, they condense to form a stable macrocycle that maximizes hydrogen-bonding, has minimal strain, and precipitates from solution. These results suggest that by varying the geometry of the precursor, we may be able to access very large macrocycles, even beyond macrocycles **1**.

To prove this hypothesis, we reacted naphthalene precursor **6**[18] with phenylenediamine **4a**. The [6 + 6] Schiff-base macrocycle **2a** was obtained in 78% yield after trituration with hot CH$_2$Cl$_2$. Elemental analysis, IR spectroscopy, and MALDI-TOF MS verified that the [6 + 6] macrocycle was the major product. In this case, a higher yield was obtained due to the insolubility of the [6 + 6] macrocycle, causing it to precipitate from solution during the reaction. This insolubility prevented us from obtaining a ^{1}H NMR spectrum of **2a**. The macrocycle could also be prepared from a 1 : 2 compound analogous to **5**.

Semi-empirical calculations on macrocycle **1c** metallated with Ni^{2+} were performed to determine the geometry and intramolecular distances of the [6 + 6] metallomacrocycles.[19] Calculations show that the Ni$_6$ metallomacrocycles will not be flat, but instead have two stable conformations that are similar to those of cyclohexane (Fig. 2). The minimum energy conformation will be a boat (C_{2v} symmetry) conformation, with the chair (D_{3d} symmetry)

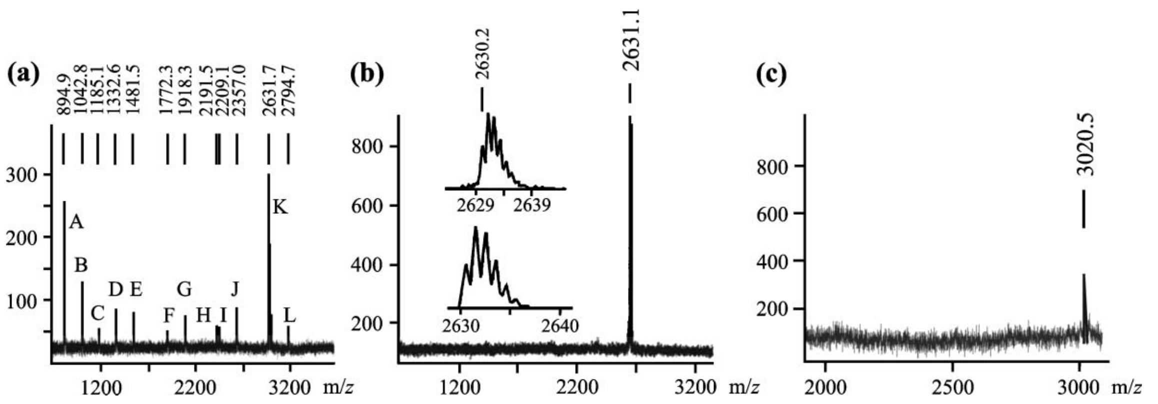

Fig. 1 MALDI-TOF spectra of (a) crude reaction mixture from the preparation of macrocycle **1a**; (b) purified macrocycle **1a**, and (c) macrocycle **1a** reacted with VO(acac)$_2$. Insets: top: isotope distribution obtained for macrocycle **1a**; bottom: isotope distribution calculated for [**1a** + H]$^+$.

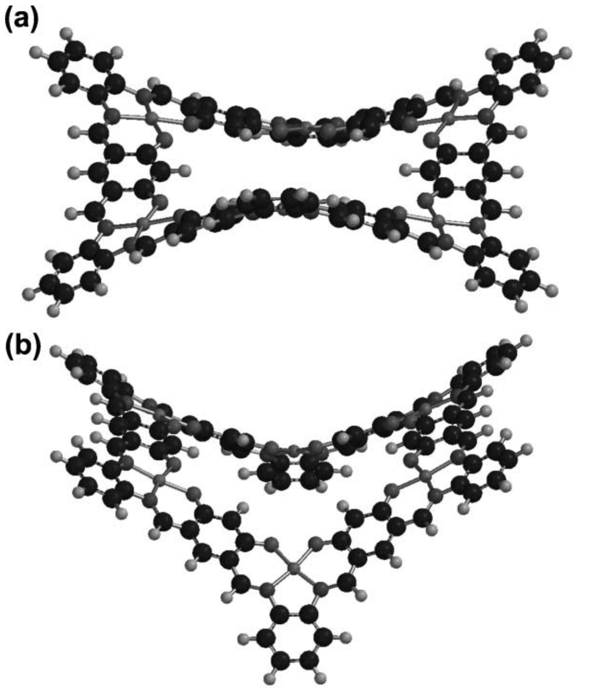

Fig. 2 Calculated structure of macrocycle **1c** metallated with 6 Ni^{2+} ions (PM3): (a) view of chair (D_{3d}) conformation; (b) view of boat (C_{2v}) conformation.

conformation only *ca.* 3 kcal mol^{-1} higher in energy. The pore diameter of the giant metallomacrocycle is *ca.* 10.5 Å (cross-interior CH···HC distance for flat conformation). Semi-empirical calculations of the macrocycle metallated with six Pd^{2+} centers indicate that the larger metal will lead to more planar geometries.

In summary, we report the first [6 + 6] Schiff-base macrocycles. This one-pot assembly illustrates the utility of Schiff-base condensation to prepare large macrocycles. We have also reported an improved synthesis of the macrocycles using new air-stable, isolable intermediate **5** in the preparation. Further studies of these large macrocycles and their metallated products are underway.

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