

Unsymmetrical Triangular Schiff Base
Macrocycles with Cone Conformations

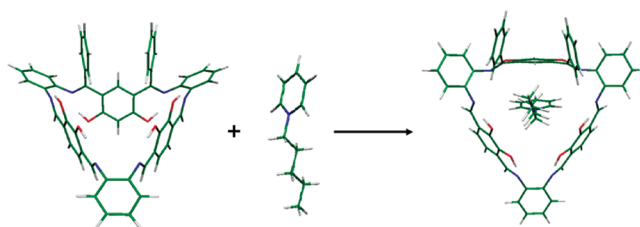
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ABSTRACT



Two new unsymmetrical Schiff base macrocycles with isosceles triangle shapes have been prepared. The macrocycles adopt cone-shaped conformations that rapidly interconvert at high temperature. Dynamic NMR studies show that the macrocycle that is tautomerized to the keto–enamine isomer is slower to flip than is the one in the enol–imine state. These macrocycles are good hosts for binding organic cations in their interiors.

Elegant control of molecular architectures and their self-assembly plays a central role in modern chemistry.^{1,2} The design and synthesis of discrete macrocyclic polygons and polyhedra have been under significant development for more than a decade,³ many assembled by metal coordination chemistry.⁴ Using reversible reactions, such as metal binding, an impressive assortment of high-symmetry structures have been assembled.⁵

Schiff base condensation offers a convenient route to self-assemble large macrocycles⁶ and polyhedra.⁷ Triangular macrocycles, in particular, are easily obtained by the condensation of a dialdehyde and diamine with the appropriate structure.⁸ We have been exploring the coordination chemistry and self-assembly of triangular Schiff base mac-

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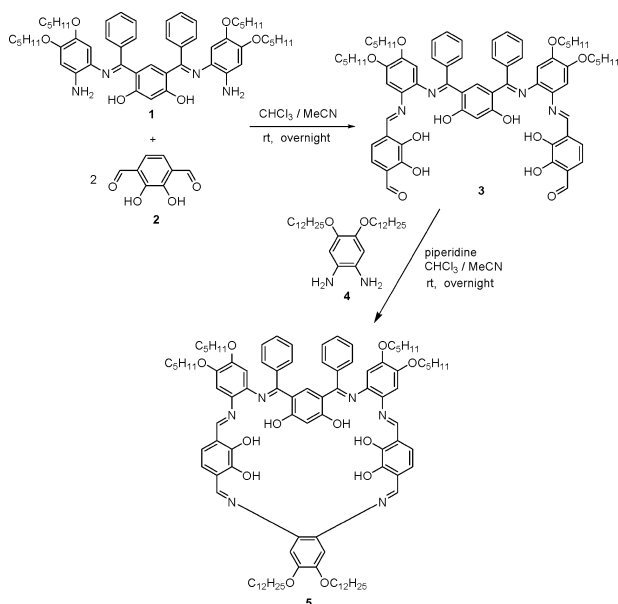
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rocycles, but our studies have been limited to cycles with high symmetry.⁹ We have found it very difficult to prepare macrocycles with different components. While the advantage of this self-assembly method lies in the reversibility of the imine condensation that enables preparation of thermodynamically stable macrocycles, reducing the symmetry by incorporating different components generally leads to a mixture of inseparable products unless metal templation is utilized.¹⁰ Facile routes to triangular macrocycles where one side is chemically different than the others may open avenues to making macrocycles that have different functional groups on the periphery (e.g., hydrophobic on one side, hydrophilic on the other). Surprisingly, there are few examples of macrocycles with isosceles triangular shapes. Only recently has the development of “isosceles macrocycles”, where two sides are chemically and geometrically distinct from the third, been met with success in the case of metal-coordination macrocycles.¹¹

Scheme 1. Synthesis of Macrocycle 5



Here we report the preparation of novel covalently linked molecular isosceles triangles using Schiff base chemistry. The new macrocycles adopt cone-like conformations in solution that enable them to bind organic cations in their interiors to form 1:1 host–guest complexes. Scheme 1 shows the synthetic route to macrocycle **5** with an isosceles shape. Compound **1** with two ketimine bonds¹² was first reacted with 1,4-diformylcatechol **2** to give dialdehyde compound

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3. Macrocycle **5** was prepared by the condensation of **3** with substituted *o*-phenylenediamine **4**. The mass spectrum of the product clearly showed the $[5 + H]^+$ ion at m/z 1581.3 Da.

At first we were surprised by this result. We expected to obtain a larger macrocycle or even a polymer since the macrocycle appears highly strained. However, semiempirical calculations showed that the macrocycle will adopt a cone shape analogous to that of a calixarene, Figure 1. In macrocycle **5**, the resorcinol moiety can be regarded as the base of an isosceles triangle, the two catechol parts are sides, and the three diamine components are vertices. Thus, the macrocycle has 3 N_2O_2 pockets, one flanked by two imines and the other two by one ketimine and one aldimine.

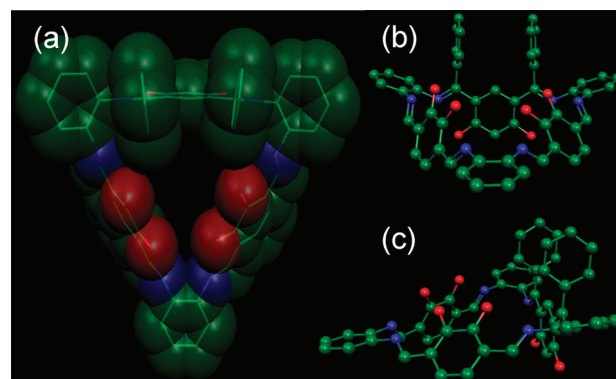


Figure 1. Semiempirical (PM3) calculated model of macrocycle **5**: (a) space-filling model showing the interior cavity; (b, c) views of the macrocycle in the cone conformation. Alkoxy chains were not included in the model.

There has been considerable interest in expanding calixarene-based molecules with use of naphthalenes in order to modify binding and other properties.¹³ Applying a similar strategy to that employed in the synthesis of **5**, we reacted diamine **6** (prepared from the condensation of 2 equiv of **4** with 3,6-dibenzoylresorcinol) with naphthalenedialdehyde **7**

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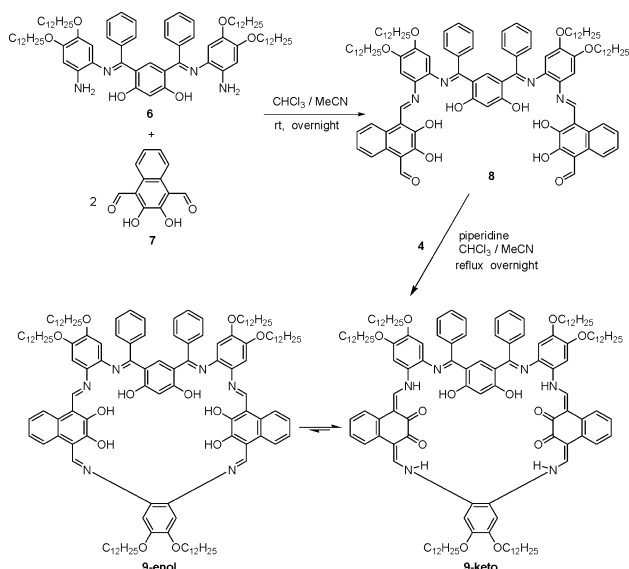
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Scheme 2. Synthesis of Macrocycle 9



to prepare an isosceles-shaped triangular macrocycle (**9**) that incorporates two naphthalenediimines (Scheme 2). In the ^1H NMR spectrum of **9** (Figure 2), the OH resonances (a, b, and e in Figure 2) appear as two doublets and a singlet. ^1H – ^1H COSY NMR spectroscopy revealed that the doublets near 15 ppm arise from coupling to the imine protons near 9 ppm.

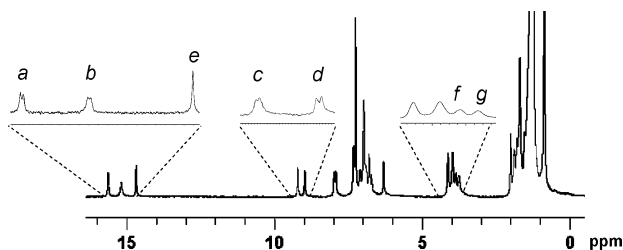


Figure 2. ^1H NMR spectrum of macrocycle **9** (400 MHz, CDCl_3 , 298 K). The peaks are labeled for reference in the text.

As this coupling is only observed in the keto–enamine form and not the enol–imine form of salicylaldimines, we conclude that macrocycle **9** is predominantly the keto–enamine form (**9-keto**). Tautomerization of naphthalenediimines is known,¹⁴ and it is also known that tautomerization of resorcinoldiimines is too high in energy to observe in the ground state.¹⁵ We have previously observed keto–enol tautomerism in a Schiff base macrocycle.¹⁴ Macrocycle **9** is the first to have both keto–enamine and enol–imine tautomers in the same cycle.

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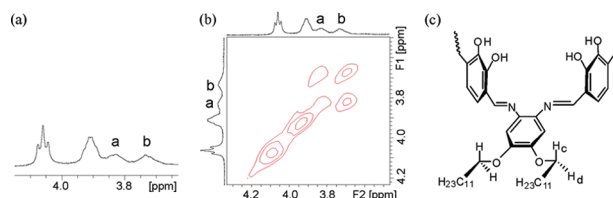


Figure 3. (a) Partial ^1H NMR spectrum of macrocycle **5** from 3.7 to 4.1 ppm. (b) Partial 2-D ^1H – ^1H COSY NMR spectrum of **5** from 3.5 to 4.2 ppm (400 MHz, CDCl_3 , 298 K). (c) Assignments of the protons of **5** discussed in the text.

The ^1H NMR spectrum of **5** showed two distinct resonances for the OCH_2 (H_c and H_d in Figure 3c) of the $\text{OC}_{12}\text{H}_{25}$ chain. The peaks a and b are located at 3.83 and 3.73 ppm, respectively (shown in Figure 3a). A ^1H – ^1H COSY NMR spectrum confirmed that peaks a and b couple with each other (Figure 3b) and are assigned to these two protons. In **5**, these two protons are therefore diastereotopic, indicating that there is no plane of symmetry that interchanges them—the macrocycle is not planar. Upon heating, these peaks coalesce, indicating that the macrocycle is interconverting between cone conformations on the NMR time scale (Figure 4). The observation of a stationary conformation at room temperature in these Schiff base macrocycles is interesting and potentially important for generating chiral cycles and other supramolecular structures.

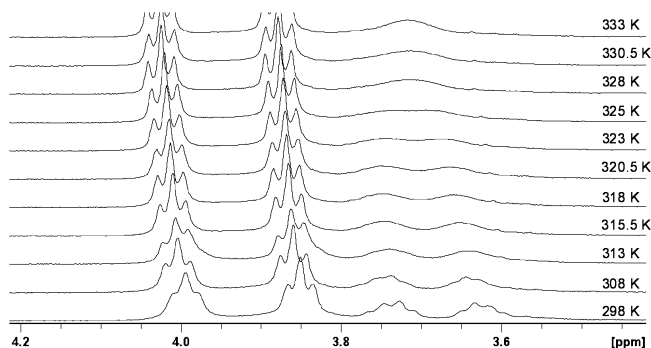


Figure 4. Stacked ^1H NMR spectra of **5** in the region 3.5–4.2 ppm at the temperatures indicated (400 MHz, 1,1,2,2-tetrachloroethane- d_2).

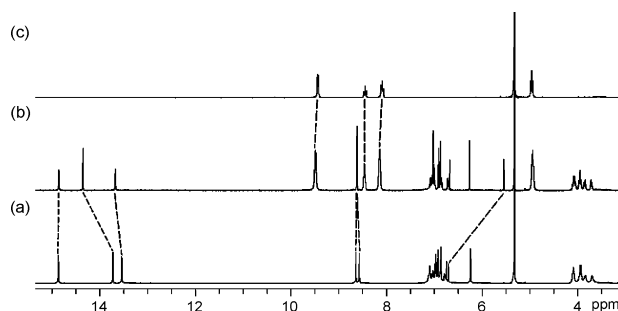
To explore the possibility that the tautomerization of the macrocycle, as observed in **9**, affects the kinetics of cone inversion, we conducted VT-NMR studies of both **5** and **9** at high temperature. Qualitatively, macrocycle **9** with naphthalene rings shows a higher barrier to inversion (coalescence of the methylene $\text{OCH}_2\text{C}_{11}\text{H}_{23}$ protons at 65 °C) than **5** (55 °C). The dynamic NMR line shapes at high temperature were fit with use of TopSpin 2.1 (see the SI). From the line shape analysis, we determined that the inversion barrier for macrocycle **9** is ca. 37 kJ mol^{-1} higher than that of macrocycle **5**, Table 1. From molecular modeling, we found

Table 1. Kinetic Parameters for High-Temperature Cone Conformation Interconversion from ^1H NMR Spectroscopy

macrocycle	E_a , kJ mol^{-1}	$\Delta H^\ddagger$, kJ mol^{-1}	$\Delta S^\ddagger$, $\text{J K}^{-1} \text{mol}^{-1}$
5	110 ± 4	107 ± 4	119 ± 12
9	147 ± 13	143 ± 13	190 ± 40

inversion of macrocycle **9** will change the orientation of the N–H bond. The intramolecular N–H $\cdots$ O=C hydrogen bonding is expected to reduce the mobility of the naphthalene-containing rings.

The cone shape adopted by the macrocycles, resembling calixarenes, suggested that these cycles could bind cationic guests. Indeed, both macrocycles **5** and **9** are supramolecular hosts for organic cations, such as pyridinium and ammonium derivatives. Figure 5 shows a representative NMR spectrum

**Figure 5.** (a) Partial ^1H NMR spectrum of macrocycle **5** from 3.5 to 15 ppm (400 MHz, CD_2Cl_2 , 298 K). (b) Partial ^1H NMR spectrum of a mixture of 10^+Cl^- and macrocycle **5** (400 MHz, CD_2Cl_2 , 298 K, $[10^+]:[5] = 3:1$). (c) Partial ^1H NMR spectrum of pyridinium chloride 10^+Cl^- (400 MHz, CD_2Cl_2 , 298 K).

of the changes observed when cetylpyridinium chloride (10^+Cl^-) was added to **5**. The formation of a complex formed by macrocycle **5** and cetylpyridinium chloride ($10^+\text{C}5$) was also verified by a 2-D ROESY spectrum, a MALDI-TOF mass spectrum, and a Job plot, and the UV–vis spectrum showed small changes (see the SI). Other organic cations (e.g., cetyltrimethylammonium bromide (11^+Br^-), tetraethylammonium bromide (12^+Br^-), and tetrabutylammonium bromide (13^+Br^-)) also bind inside of macrocycles **5** and **9**

Table 2. Binding Constants (K_{assoc}) for the Complexes Formed between Macrocycle **5** or **9** and Guests^a

macrocycle	K_{assoc} (M^{-1}) for guests $10^+ - 13^+$			
	10^+	11^+	12^+	13^+
5	19000 ± 6000	2900 ± 200	420 ± 10	50 ± 9
9	6300 ± 800	760 ± 70	– ^b	– ^b

^a Determined by ^1H NMR spectroscopy at 300 K in CDCl_3 . ^b Binding was too small to determine by NMR spectroscopy.

to form 1:1 complexes, Table 2. Neutral molecules tested and PPh_4Br , which is too large to fit in the macrocycles, do not bind.

There are a few interesting conclusions to draw from the binding studies (Table 2). First, the binding constants are largest for 10^+Cl^- , which has a pyridyl ring, indicating that π – π interactions probably play a role in stabilizing the host–guest complexes. Second, the binding constants for macrocycle **5** are about four times larger than those for macrocycle **9**, and we could not measure the binding of two of the guests to **9**. Even though **9** has more aromatic rings to potentially interact with a guest, it has weaker interactions. We attribute this difference to the keto–enamine tautomerization of the naphthalenediimine moieties, which should render the carbonyl groups less electronegative than the hydroxyl groups in **5**, and thus yield weaker electrostatic interactions with a cationic guest.

In summary, we have described a simple synthesis of novel unsymmetrical, isosceles triangle-shaped Schiff base macrocycles. These macrocycles adopt static cone-shaped conformations at low temperature, but can rapidly interconvert at high temperature. Differences in the inversion rate and the guest-binding constants of these new macrocycles indicate that keto–enol tautomerization plays a role in modifying their properties.

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Supporting Information Available: Synthetic procedures, full characterization of new compounds, kinetic data, and host–guest binding data. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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