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Tautomerization in Naphthalenediimines: A Keto-Enamine Schiff Base Macrocycle

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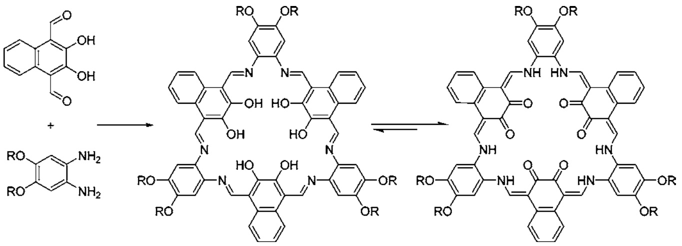
ABSTRACT



A new [3 + 3] Schiff base macrocycle incorporating naphthalene groups has been prepared. By examination of its properties, X-ray crystallography of model compounds, and calculations, it has been determined that the macrocycle exists predominantly as the keto-enamine tautomer. This unexpected tautomerization presents an unusual hexaketo interior in the macrocycle.

Conjugated macrocycles, such as porphyrins and phthalocyanines, may be extended using polyaromatic components to modify their electronic and optical properties.[1,2] Macrocycles with free volume, such as cyclodextrins,[3] calixarenes,[4] and resorcinarenes,[5] have long been investigated as hosts for supramolecular chemistry. The size, shape, and chemical properties of the cavity within these molecules influences the guests to which they bind. Extending the cavity of the macrocycles may enhance the binding affinity or selectivity of the macrocycle. For example, attaching a second row of linked aromatic moeities to the upper rim of the resorcinarene scaffold produces compounds with even deeper cavities.[6] These macrocycles can be used as templates for the formation of large crown ethers, as well as enzyme mimics, and have been shown to self-assemble into molecular capsules.[7]

We have recently synthesized a conjugated Schiff base macrocycle **1** (Figure 1) with a crown-ether-like interior.[8,9]

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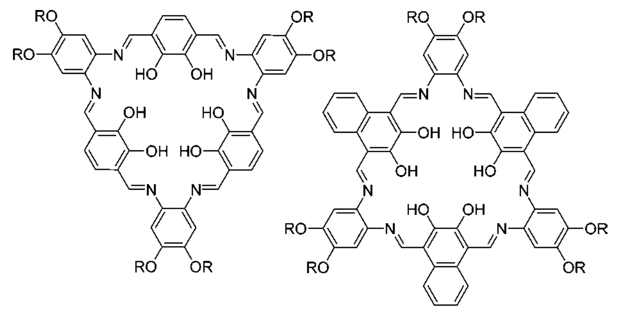


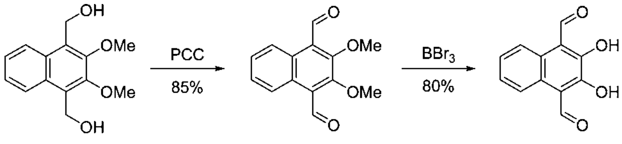
1 (R = n-alkyl) **2** (R = C_3H_7)

Figure 1. Structures of macrocycles **1** and **2**.

Upon addition of small cations (e.g., Na^+, NH_4^+), **1** assembles into tubular structures.[8] The crystal structure and calculations of this rigid macrocycle reveal that it is nonplanar, with the macrocycle adopting an open-cavity structure similar to classical calixarenes.[10] In an effort to expand these macrocycles and to modify their properties, we sought to simply replace the dihydroxybenzene rings in **1** with dihydroxynaphthalene rings to generate macrocycle **2** with increased aromatic exposure, retaining the hydroxyimine groups in the center. Reinhoudt et al. previously investigated the incorporation of naphthalene rings into Schiff base macrocycles related to **2**.[11] They required the use of Ba^{2+} as a template, and the template was not removed. Moreover, the structural aspects of the macrocycle were not investigated.

We found it was necessary to improve the synthesis of 1,4-diformyl-2,3-dihydroxynaphthalene **5**.[11] With the recent report of 1,4-bis(hydroxymethyl)-2,3-dimethoxy-naphthalene (**3**),[12] we developed a simple route to **5** that can be scaled to multigram quantities (Scheme 1). Oxidation of **3** with pyridinium chlorochromate (PCC) yielded the diformylnaphthalene species **4** (85%), which afforded compound **5** in 80% yield after deprotection with BBr_3. These steps provided product that was ca. 99% pure (^1H NMR) without chromatography. The structure of **5** was verified by single-crystal X-ray diffraction (SCXRD). Notably, the molecules assemble into a 1-D π-stacked assembly with a pitch of 1/3 and an average separation between the molecules of 3.356 Å (Figure 2).

Scheme 1. Synthesis of Diformyl Precursor **5**



3 **4** **5**

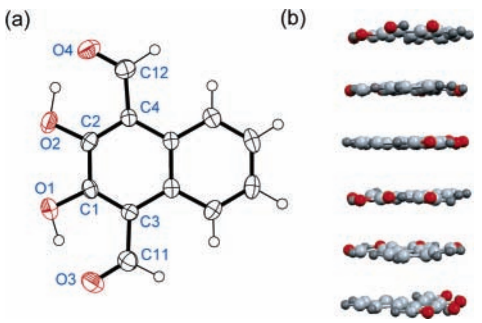
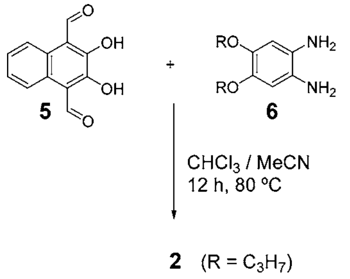


Figure 2. (a) Crystal structure of **5**. (b) 1-D π-stacked assembly of **5** showing the 1/3 pitch.

Reaction of compound **5** with phenylenediamine **6** afforded macrocycle **2** in 46% yield as shown in Scheme 2.

Scheme 2. Synthesis of Macrocycle **2**



The reversibility of the Schiff base condensation allows the reaction to achieve the thermodynamically stable [3 + 3] macrocycle rather than expected kinetic intermediates of oligomer and polymer. This macrocycle is unstrained and maximizes intramolecular hydrogen bonding. Initially, we tried to prepare macrocycle **2** with longer alkoxy chains (e.g., hexyloxy), but we found that the product was more soluble than macrocycle **1** and difficult to crystallize. We had anticipated that the additional aromatic rings of **2** would render the macrocycle less soluble than **1**. The ^1H NMR spectrum of **2** shows the expected resonances for the extended macrocycle. However, the resonances assigned to the hydroxyl (15.6 ppm) and imine (9.6 ppm) groups are considerably shifted downfield relative to where they are observed in the spectrum for **1** (13.3 and 8.5 ppm, respectively). The naphthalene *C*O and imine *C* resonances (^{13}C NMR spectroscopy) are observed in **2** at 162.0 and 155.6 ppm, respectively. For comparison, the imine *C* is observed at 161 ppm in the ^{13}C NMR spectrum of macrocycle **1**.

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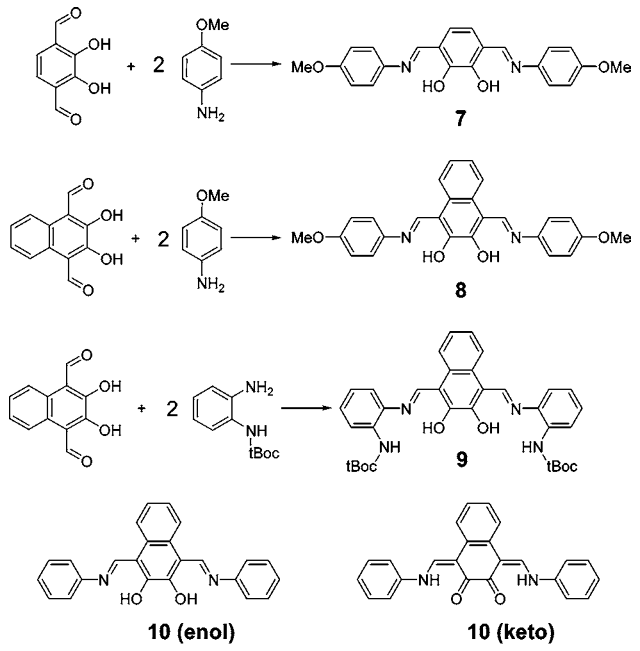
The mass spectrum of macrocycle **2** shows the expected mass for the [3 + 3] Schiff base macrocycle. However, the IR and UV−vis spectra are substantially different for this new extended macrocycle as compared to macrocycle **1**, suggesting a fundamental difference between these two systems.

To improve our understanding of macrocycle **2**, we synthesized model compounds **7**−**9** (Scheme 3). The imine and hydroxyl resonances in the ^{1}H NMR spectrum of **7** are comparable to those of macrocycle **1**. Both the macrocycle and the model compound are unequivocally present as the enol-imine tautomer. The *C*OH resonance is observed at 150.7 and 150.3 ppm in the ^{13}C NMR spectra of **1** and **7**, respectively.

Scheme 3. Synthesis of Model Compounds **7**−**9** and the Tautomers of Compound **10** Used for Calculations



The imine and hydroxyl resonances observed for compounds **8** and **9** are similar to those observed for macrocycle **2**, suggesting that the naphthalene unit is responsible for the structural differences. The ^{13}C NMR spectrum of the model compounds **8** and **9** revealed the naphthalene *C*O resonance at 168.7 and 158.5 ppm, respectively. Although these resonances are shifted downfield relative to the typical position of a phenol (e.g., 154.9 ppm in **5**), the assignment of enol-imine vs keto-enamine tautomer was ambiguous. To obtain more accurate structural information, SCXRD was performed on both **8** and **9**.

The single-crystal structure of **8** (Figure 3) revealed that the model compound is in the keto-enamine form in the solid state at −100 °C. The naphthalene C−O bond lengths observed in the structure are characteristic of ketones rather than phenols, and the C−N bond is elongated relative to that of a typical imine. Moreover, the hydrogen atoms involved in hydrogen bonding were located on the nitrogen atoms rather than on the oxygen atoms. The structure of **9** (Figure 4) is also in agreement with the keto-enamine form.

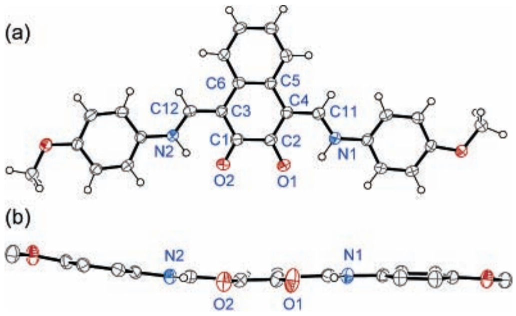


Figure 3. Structure of compound **8** as determined by SCXRD. (a) View perpendicular to the naphthalene ring. (b) View parallel to the naphthalene ring reveals O═C−C−CH torsions (dihedral angles of 0.7° and 4.8°). H atoms removed for clarity in (b). Thermal ellipsoids are shown at 50% probability.

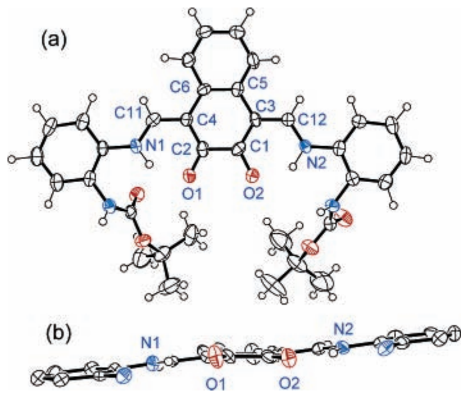


Figure 4. Structure of compound **9** as determined by SCXRD. (a) View perpendicular to the naphthalene ring. (b) View parallel to the naphthalene ring reveals O═C−C−CH torsions (dihedral angles of 5.9° and 7.3°). ^{t}Boc groups and H atoms removed for clarity in (b). Thermal ellipsoids are shown at 50% probability.

To confirm that **8** and **9** were keto-enamine tautomers in the solid state, ab initio DFT calculations were performed using compound **10** as an analogue of **8** and **9**. Energy-minimized structures were determined using B3LYP with a 6-31G(d,p) basis set.[13] DFT calculations of compound **10** (**keto**) predict the bond lengths and overall structure of the model compounds very well. Table 1 compares key bond lengths obtained from the crystal structures and calculations. Most of the bonds affected by the tautomerization agree with the calculated bond lengths for the keto isomer within error. These data show that the model compounds **8** and **9**, which are structurally analogous to one side of the [3 + 3] Schiff base macrocycle **2**, are present mostly in the keto-enamine tautomer at −100 °C.[14] Moreover, the DFT calculations

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(13) *Spartan '04*; Wavefunction: Irvine, CA.

Table 1. Calculated and Measured Lengths (Å) of Selected Bonds

bond[a]	**8**[b]	**9**[b]	**10** (**keto**)[c]	**10** (**enol**)[c]
C2−O1	1.275(3)	1.261(7)	1.247	1.328
C11−N1	1.324(4)	1.33(1)	1.341	1.298
C4−C11	1.399(3)	1.39(1)	1.392	1.449
C1−C2	1.494(3)	1.510(6)	1.519	1.438
C2−C4	1.427(3)	1.428(9)	1.401	1.450

[a] Labeling as in Figures 3 and 4; averaged assuming mirror symmetry through the naphthalene ring. [b] SCXRD (−100 °C). [c] Calculated at B3LYP/6-31G(d,p).

predicted that the keto tautomer **10** (**keto**) would be ca. 0.7 kcal/mol more stable than the enol tautomer **10** (**enol**) (0 K, vacuum).

On the basis of these results, we can conclude that the [3 + 3] Schiff base macrocycle **2** is a mixture of tautomers, but predominantly the keto-enamine isomer, Figure 5. This tautomerization breaks the conjugation in the macrocycle and renders it more flexible and thus more soluble. The formation of stable keto-enamines must be a sufficient driving force to overcome the aromatic stabilization of the second ring in naphthalene.[15]

These compounds are the first naphthalene-based 1,4-diimines to be structurally characterized. Studies of tautomerization in these molecules are relevant to understanding photochromism and thermochromism in *N*-salicylaldimines and their naphthyl analogues.[16]

In conclusion, we have studied new naphthalenediimine model compounds that tautomerize to the keto-enamine form. We have used the reversible Schiff base condensation reaction to prepare a new [3 + 3] macrocycle incorporating naphthalene groups and established that it is present mostly in the keto-enamine tautomer, thus exposing a hexaketo interior.[17] Investigations are underway to study the host−guest and coordination chemistry of these new extended Schiff base macrocycles.

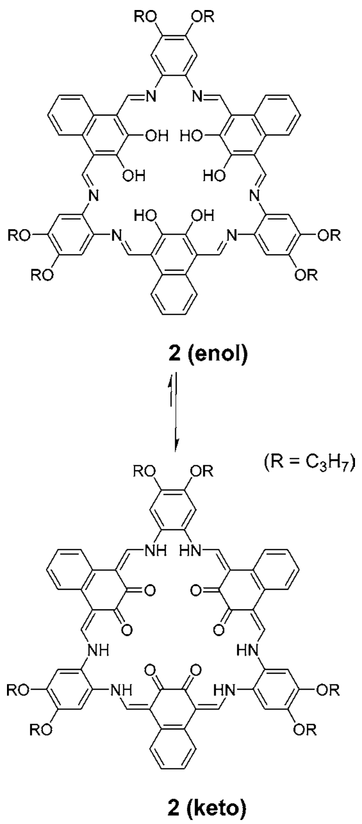

Figure 5. Tautomerization of macrocycle **2** between the enol-imine and keto-enamine tautomers. The latter is more stable in the case of this naphthalene-based macrocycle.

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Supporting Information Available: Experimental procedures and spectroscopic data; ^{1}H and ^{13}C NMR spectra for new compounds; CIF files for **5**, **8**, and **9**; and coordinates of calculated structures. This material is available free of charge via the Internet at http://pubs.acs.org.

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(14) In solution at room temperature, the model compounds exist as a mixture of tautomers; on the basis of calculation and VT ^{13}C NMR studies, we estimate that the ratio of keto to enol is ca. 4:1 for **8**. In the solid state at −100 °C, we estimate that the model compounds are present as ∼99% keto-enamine tautomer. Details are provided in Supporting Information.

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