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# Reversible–Irreversible Approach to Schiff Base Macrocycles: Access to Isomeric Macrocycles with Multiple Salphen Pockets

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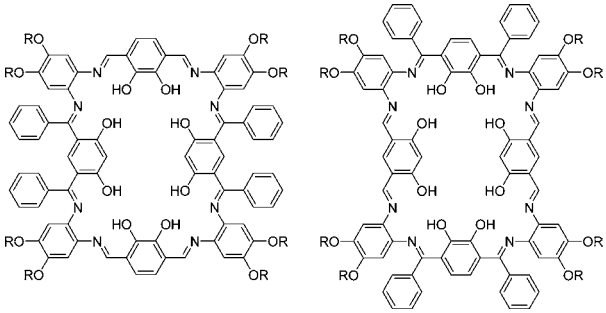
## ABSTRACT



**We have developed methodology for the formation of a new family of metal-free Schiff base macrocycles utilizing the differential exchange rates of aldimines and ketimines. The more robust ketimine bond is kinetically inert under the milder conditions used for aldimine bond formation. In particular, this route enables access to the first conjugated macrocycles with four unsymmetrical $N_2O_2$ salphen-like pockets.**

Over the past 30 years, many Schiff base macrocycles have been synthesized, often with the ultimate goal of metal complexation.[1,2] The polydentate nature of Schiff base macrocycles makes them excellent scaffolds for the coordination of multiple metal ions. These multimetallic complexes frequently exhibit intriguing magnetic,[3] catalytic,[4] or supramolecular[5] behavior.

We have been especially interested in conjugated macrocycles with multiple salphen-type $N_2O_2$ pockets. These macrocycles have proven to be useful precursors to molecular metal clusters[5a,6] and nanotubular assemblies.[7] The Schiff base condensation of geometrically programmed dialdehydes

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and diamines is a very convenient route to these macrocycles, as the reversibility of the reaction enables the preparation of macrocycles in high yield and purity without formation of oligomer and polymer.

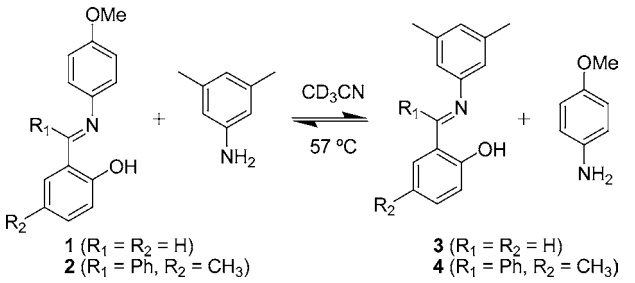
Although the reversibility of Schiff base condensation is convenient for preparing macrocycles, it leads to one significant drawback—this route is usually limited to highly symmetrical macrocycles. For example, we have reported facile routes to conjugated [3 + 3] Schiff base macrocycles with average $D_{3h}$ symmetry,[8] but template-free routes to larger cycles are virtually unknown.[9] Schiff base condensation is not generally useful for obtaining fully conjugated macrocycles with more than one type of imine. Attempts to make macrocycles with chemically distinct imines often leads to a mixture of products unless imines are reduced or coordinated to metals to prevent exchange.

Salphens and salens have been synthesized with two different aldimines or one ketimine and one aldimine by stepwise condensation.[10] This low symmetry in a single $N_2O_2$ pocket is useful for developing chirality in metal complexes[11] which might in turn influence the products of catalysis. Despite the appeal of unsymmetric $N_2O_2$ pockets, methodology to make Schiff base macrocycles possessing them is lacking.

Here we report a new route to Schiff base macrocycles with multiple salphen pockets, each having two distinct imines. The synthesis is achieved by taking advantage of the differential exchange rates of aldimines and ketimines with primary amines. This route has enabled us to prepare a new family of [2 + 2] Schiff base macrocycles, each possessing four unsymmetrical $N_2O_2$ pockets.

The synthesis of ketimine macrocycles from the condensation of diketones and diamines results in a mixture of products, each in low yield, due to the kinetic stability of the ketimine bond.[12] We expected that aldimines and ketimines should exhibit very different rates of exchange when reacted with another amine. To test our hypothesis, model substrates, aldimine **1** and ketimine **2**, were synthesized by condensing *p*-anisidine with salicylaldehyde and 2-benzoyl-4-methylphenol,[13] respectively. Solutions of **1** and **2** were prepared in $CD_3CN$ and combined with 2 equiv of 3,5-dimethylaniline, Scheme 1. At equilibrium a mixture of

**Scheme 1.** Aldimine and Ketimine Exchange

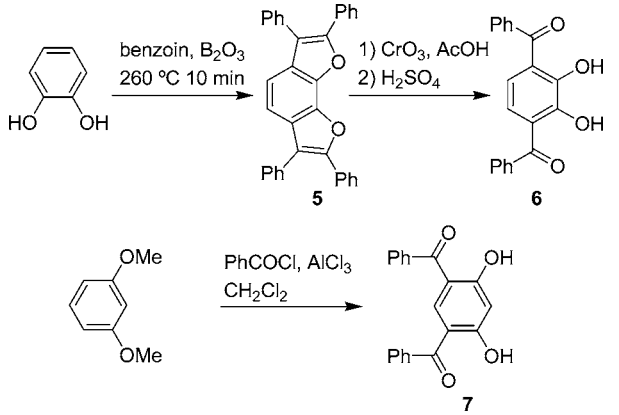



both aldimines or both ketimines should exist due to the similar electron-donating properties of *p*-anisidine and 3,5-dimethylaniline.[14]

At 20 °C, no exchange was observed by $^1$H NMR spectroscopy for either **1** or **2**. When a solution of **1** in $CD_3CN$ was heated to 57 °C (330 K), resonances assigned to free *p*-anisidine appeared indicating formation of **3** through imine exchange (measured rate of exchange: $1 \times 10^{-6}$ mol $L^{-1}$ $s^{-1}$). Conversely, when ketimine **2** was subjected to the same conditions for 36 h, no exchange was observed.[15] These results show that in hot acetonitrile aldimine bonds are labile but ketimines are kinetically inert.

We applied this knowledge to the synthesis of Schiff base macrocycles through a cascade of ketimine condensation followed by aldimine condensation. Dihydroxydibenzoylbenzenes **6**[16] and **7**[17] were prepared as shown in Scheme 2.

**Scheme 2.** Synthesis of Dihydroxydibenzoyl Compounds




Condensation of benzoin with catechol at 260 °C afforded tetraphenyl-*o*-benzodifuran **5** in 25% yield. Oxidation with $CrO_3$ followed by hydrolysis of the benzoate ester gave **6**.

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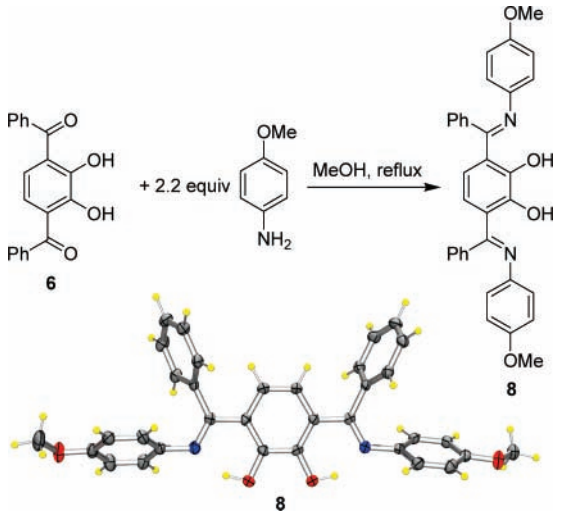
Compound **7** was obtained from the Friedel−Crafts acylation/demethylation of 1,3-dimethoxybenzene.

To examine the reactivity of **6**, we reacted **6** with 2 equiv of *p*-anisidine in refluxing MeOH, Scheme 3. Compound **8**

**Scheme 3.** Synthesis and Thermal Ellipsoid Plot of Model Compound **8**[a]




[a] Ellipsoids are at 50% probability (C = gray, N = blue, O = red, H = yellow).

was obtained in 82% yield and characterized by common spectroscopic techniques. Notably, a 3.6 ppm downfield shift is observed in the $^1$H NMR spectrum for the phenoxy resonance after condensing **6** to **8**, indicating strong intramolecular H-bonding between the imine and the phenoxy proton. A single-crystal X-ray diffraction study of **8** further supports our structural assignment and confirms that both ketimines are in the *E* configuration.

It is known that the condensation of a diphenyl ketone with phenylenediamine stops after only one of the amines has reacted unless harsh conditions are utilized.[18] Thus, condensation of **6** and **7** with dialkoxyphenylenediamines, **9a**,**b**, afforded diketimine macrocycle precursors **10** and **11a**,**b**, respectively (Scheme 4). These are air stable, bright red, crystalline compounds that are easily handled.

To demonstrate the reversible-irreversible Schiff base condensation approach to macrocycles with unsymmetrical $N_2O_2$ pockets, diketimine **10** was reacted with 1 equiv of 4,6-diformylresorcinol in refluxing $CH_3CN/CHCl_3$, Scheme 5. We anticipated this reaction to give the rectangular [2 + 2] Schiff base macrocycle **12**, and this was indeed obtained.

(15) To confirm that this was a kinetic effect and not a thermodynamic equilibrium, a solution of ketimine **4** and 2 equiv of *p*-anisidine in $CH_3CN$ was heated at 57 °C for 1.5 h. No exchange was observed under these conditions.

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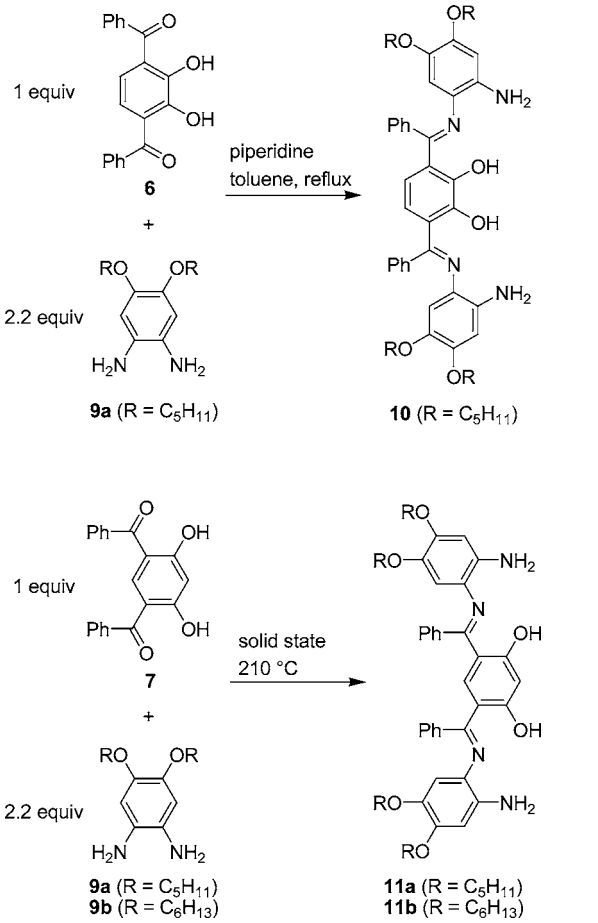
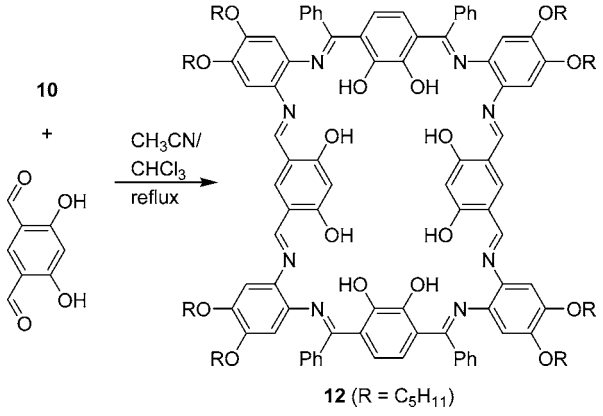
**Scheme 4.** Synthesis of **10** and **11a**,**b**




This macrocycle contains four equivalent $N_2O_2$ pockets, each incorporating one aldimine and one ketimine. Two downfield phenoxy resonances and one imine resonance are observed in the $^1$H NMR spectrum of macrocycle **12**. The molecular ion, found at *m*/*z* 1946.4, dominated the matrix assisted laser desorption ionization time-of-flight (MALDI-TOF) mass spectrum providing further support for the structural assignment. Macrocycle **12** was isolated in 41% yield via the

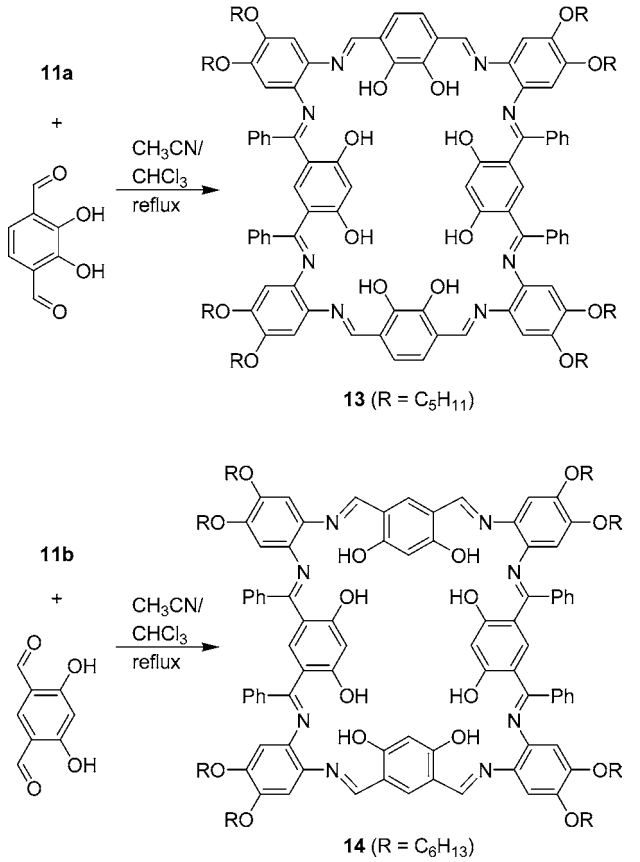
**Scheme 5.** Synthesis of Macrocycle **12**



formation of four aldimine bonds with no evidence for scrambling of the ketimines.

To further illustrate this approach, we synthesized macrocycle **13** by condensing **11a** with 3,6-diformylcatechol in $CH_3CN/CHCl_3$ as shown in Scheme 6. The $^1H$ NMR

**Scheme 6.** Synthesis of Macrocycles **13** and **14**




spectrum of **13** was very similar to that for **12** and the structure was confirmed by mass spectrometry, elemental analysis, and spectroscopy. Macrocycles **12** and **13** are isomers, with the ketimine phenyl groups and imine protons interchanged. Besides enantiomers and diastereomers, it is not usually possible to make isomeric forms of Schiff base macrocycles since the reversible condensation most often yields the high-symmetry, thermodynamic product.

Based on our previous studies of [6 + 6] Schiff base macrocycles made from the reaction of 4,6-diformylresorcinol with 1,2-dialkoxy-4,5-diaminobenzenes, the condensation of 4,6-diformylresorcinol with **11b** was anticipated to lead to a hexagon-shaped macrocycle, with the two reagents reacting in a 3:3 ratio.[9] Surprisingly, however, 4,6-diformylresorcinol and **11b** react to give exclusively a [2 + 2] Schiff base macrocycle, **14**, in 26% yield. MALDI-TOF mass spectrometry clearly indicated the [2 + 2] macrocycle was selectively formed, with no evidence of the anticipated [3 + 3] macrocycle.[19]

Macrocycle **14** appears highly strained and must adopt a nonplanar geometry. Semiempirical calculations indicate that it will have a bowl shape, but we have not yet been able to obtain single crystals of this macrocycle.

In conclusion, we have developed a strategy for making Schiff base macrocycles that have two inequivalent C═N bonds using a reversible−irreversible aldimine−ketimine condensation approach. This method gives access to the first conjugated Schiff base macrocycles containing eight imines and multiple unsymmetrical $N_2O_2$ salphen-like pockets. We are now exploring the scope of this versatile route and the incorporation of metals into these new macrocycles. In addition, we are studying the conformational dynamics of these macrocycles, including the role of the peripheral phenyl groups.

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**Supporting Information Available:** Synthetic procedures, full characterization, kinetic data, and crystallographic information. This material is available free of charge via the Internet at http://pubs.acs.org.

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(19) MALDI-TOF MS of the filtrate confirmed that no larger cyclization products were present.