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Mild and Selective Reduction of Imines: Formation of an Unsymmetrical Macrocycle

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During investigations of **5**, a [3 + 3] Schiff-base macrocycle with six imines, a partially reduced Schiff-base macrocycle, **6**, possessing one CH_2NH and five imine groups was obtained. Control experiments and deuterium labeling indicate that the macrocycle is reduced by a benzimidazoline generated during the reaction. Benzimidazolines may be convenient reagents for the mild and selective reduction of imines.

Conjugated macrocycles are a rapidly growing area of interest because they may form the basis of catalytic,[1] magnetic,[2] liquid crystalline,[3] pharmaceutical,[4] and supramolecular materials.[5] Schiff-base condensation is a convenient route for the construction of conjugated macrocycles such as expanded porphyrins (e.g., Texaphyrin) and Robson-type macrocycles (e.g., **1**).[6,7] Indeed, many examples of macrocycles that form by [2 + 2] and [3 + 3] Schiff-base condensation reactions are now known.[8] We have recently reported on new giant metallomacrocycles that form by [3 + 3] condensation reactions.[9]

Macrocycle **1** is an attractive ligand to form new magnetic and catalytic materials as it may bind to two metals.[10] These metal complexes can be prepared directly by condensation of a 2,6-diformylphenol with a diamine in the presence of a transition metal template or by reaction of the preformed macrocycle with a metal salt.[2,11] Unfortunately, the synthesis of these fully conjugated organic macrocycles is usually complicated by in situ reduction.[12−14] For example, the reaction to form **1** yields

(1) (a) Vigato, P. A.; Tamburini, S.; Fenton, D. E. *Coord. Chem. Rev.* **1990**, *106*, 25−170. (b) Schmidt, J. A. R.; Mahadevan, V.; Getzler, Y. D. Y. L.; Coates, G. W. *Org. Lett.* **2004**, *6*, 373−376. (c) Nestler, O.; Severin, K. *Org. Lett.* **2001**, *3*, 3907−3909. (d) Nelson, A. P.; DiMagno, S. G. *J. Am. Chem. Soc.* **2000**, *122*, 8569−8570.

(2) Dziembowska, T.; Guskos, N.; Typek, J.; Szymczak, R.; Likodimos, V.; Glenis, S.; Lin, C. L.; Wabia, M.; Jagodzinska, E.; Fabrycy, E. *Mater. Res. Bull.* **1999**, *34*, 943−954.

(3) Sessler, J. L.; Callaway, W.; Dudek, S. P.; Date, R. W.; Lynch, V.; Bruce, D. W. *Chem. Commun.* **2003**, 2422−2423.

(4) (a) Pandey, S. K.; Gryshuk, A. L.; Graham, A.; Ohkubo, K.; Fukuzumi, S.; Dobhal, M. P.; Zheng, G.; Ou, Z.; Zhan, R.; Kadish, K. M.; Oseroff, A.; Ramaprasad, S.; Pandey, R. K. *Tetrahedron* **2003**, *59*, 10059−10073. (b) Dairou, J.; Vever-Bizet, C.; Brault, D. *Antiviral Res.* **2004**, *61*, 37−47. (c) Lottner, C.; Knuechel, R.; Bernhardt, G.; Brunner, H. *Cancer Lett.* **2004**, *203*, 171−180.

(5) (a) Campbell, K.; Kuehl, C. J.; Ferguson, M. J.; Stang, P. J.; Tykwinski, R. R. *J. Am. Chem. Soc.* **2002**, *124*, 7266−7267. (b) Zhao, D.; Moore, J. S. *Chem. Commun.* **2003**, 807−818. (c) Höger, S.; Bonrad, K.; Mourran, A.; Beginn, U.; Möller, M. *J. Am. Chem. Soc.* **2001**, *123*, 5651−5659.

(6) Sessler, J. L.; Seidel, D. *Angew. Chem., Int. Ed*. **2003**, *42*, 5134−5175.

(7) Pilkington, N. H.; Robson, R. *Aust. J. Chem.* **1970**, *23*, 2225−2236.

(8) For examples of macrocycles formed by Schiff-base condensation, see: (a) Gawroński, J.; Kołbon, H.; Kwit, M.; Katrusiak, A. *J. Org. Chem*. **2000**, *65*, 5768−5773. (b) Kuhnert, N.; Rossignolo, G. M.; Lopez-Periago, A. *Org. Biomol. Chem*. **2003**, *1*, 1157−1170. (c) Jazwinski, J.; Lehn, J.-M.; Méric, R.; Vigneron, J.-P.; Cesario, M.; Guilhem, J.; Pascard, C. *Tetrahedron Lett.* **1987**, *28*, 3489−3492. (d) Shimakoshi, H.; Kai, T.; Aritome, I.; Hisaeda, Y. *Tetrahedron Lett*. **2002**, *43*, 8261−8264. (e) Menif, R.; Martell, A. E. *J. Chem. Soc., Chem. Commun*. **1989**, 1521−1523. (f) Kwit, M.; Gawroński, J. *Tetrahedron: Asymmetry* **2003**, *14*, 1303−1308. (g) Gao, J.; Martell, A. E. *Org. Biomol. Chem.* **2003**, *1*, 2795−2800. (h) Zhao, D.; Moore, J. S. *J. Org. Chem*. **2002**, *67*, 3548−3554. (i) Depree, C. V.; Beckmann, U.; Heslop, K.; Brooker, S. *Dalton Trans*. **2003**, 3071−3081. (j) Chadim, M.; Buděšinský, M.; Hodačová, J.; Závada, J.; Junk, P. C. *Tetrahedron: Asymmetry* **2001**, *12*, 127−133. (k) Sessler, J. L.; An, D.; Cho, W.-S.; Lynch, V. *J. Am. Chem. Soc*. **2003**, *125*, 13646−13647.

(9) Ma, C.; Lo, A.; Abdolmaleki, A.; MacLachlan, M. J. *Org. Lett*. **2004**, *6*, 3841−3844.

(10) (a) Okawa, H.; Furutachi, H.; Fenton, D. E. *Coord. Chem. Rev*. **1998**, *174*, 51−75. (b) Bosnich, B. *Inorg. Chem*. **1999**, *38*, 2554−2562. (c) Brooker, S. *Coord. Chem. Rev*. **2001**, *222*, 33−56. (d) Gavrilova, A. L.; Bosnich, B. *Chem. Rev*. **2004**, *104*, 349−383.

(11) For examples of metal complexes of Robson-type macrocycles, see: (a) Huang, W.; Gou, S.; Hu, D.; Chantrapromma, S.; Fun, H.-K.; Meng, Q. *Inorg. Chem*. **2002**, *41*, 864−868. (b) Adams, H.; Bailey, N. A.; Bertrand, P.; Rodriguez de Barbarin, C. O.; Fenton, D. E.; Gou, S. *J. Chem. Soc., Dalton Trans*. **1995**, 275−279. (c) Lacroix, P.; Kahn, O.; Theobald, F.; Leroy, J.; Wakselman, C. *Inorg. Chim. Acta* **1988**, *142*, 129−134. (d) Diril, H.; Chang, H. R.; Zhang, X.; Larsen, S. K.; Potenza, J. A.; Pierpont, C. G.; Schugar, H. J.; Isied, S. S.; Hendrickson, D. N. *J. Am. Chem. Soc*. **1987**, *109*, 6207−6208. (e) Atkins, A. J.; Black, D.; Finn, R. L.; Marin-Becerra, A.; Blake, A. J.; Ruiz-Ramirez, L.; Li, W.-S.; Schroeder, M. *Dalton Trans*. **2003**, 1730−1737. (f) Thompson, L. K.; Mandal, S. K.; Tandon, S. S.; Bridson, J. N.; Park, M. K. *Inorg. Chem.* **1996**, *35*, 3117−3125. (g) Handa, M.; Farida, A.; Thompson, L. K.; Hayashibara, C.; Sugimori, T.; Hiromitsu, I.; Kasuga, K. *Mol. Cryst. Liq. Cryst. Sci. Technol., Sect. A* **2000**, *342*, 75−80. (h) Brooker, S.; Croucher, P. D.; Davidson, T. C.; Smith, P. D. *Polyhedron* **2000**, *19*, 1887−1894.

(12) (a) Ustynyuk, Y. A.; Borisova, N. E.; Nosova, V. M.; Reshetova, M. D.; Talismanov, S. S.; Nefedov, S. E.; Aleksandrov, G. A.; Eremenko, I. L.; Moiseev, I. I. *Russ. Chem. Bull., Int. Ed.* **2002**, *51*, 488−498. (b) Borisova, N. E.; Reshetova, M. D.; Ustynyuk, Y. A. *Russ. Chem. Bull., Int. Ed.* **2004**, *53*, 181−188.

(13) (a) Aguiari, A.; Bullita, E.; Casellato, U.; Guerriero, P.; Tamburini, S.; Vigato, P. A. *Inorg. Chim. Acta* **1992**, *202*, 157−171. (b) Brychcy, K.; Dräger, K.; Jens, K.-J.; Tilset, M.; Behrens, U. *Chem. Ber.* **1994**, *127*, 1817−1826. (c) Kumar, D. S.; Alexander, V. *Inorg. Chim. Acta* **1995**, *238*, 63−71. (d) Bowden, F. L.; Ferguson, D. *J. Chem. Soc., Dalton Trans.* **1974**, 460−462.

(14) (a) Atwood, D. A.; Jegier, J. A.; Lindholm, N. F.; Martin, K. J.; Rutherford, D. *J. Coord. Chem.* **1996**, *38*, 305−318. (b) Singer, A. L.; Atwood, D. A. *Inorg. Chim. Acta* **1998**, *277*, 157−162. (c) Chiu, S.-M.; Wong, T.-W.; Man, W.-L.; Wong, W.-T.; Peng, S.-M.; Lau, T.-C. *J. Am. Chem. Soc.* **2001**, *123*, 12720−12721.

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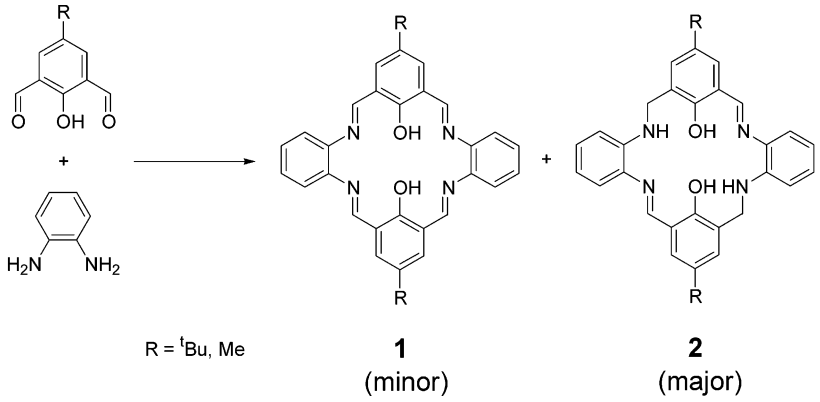
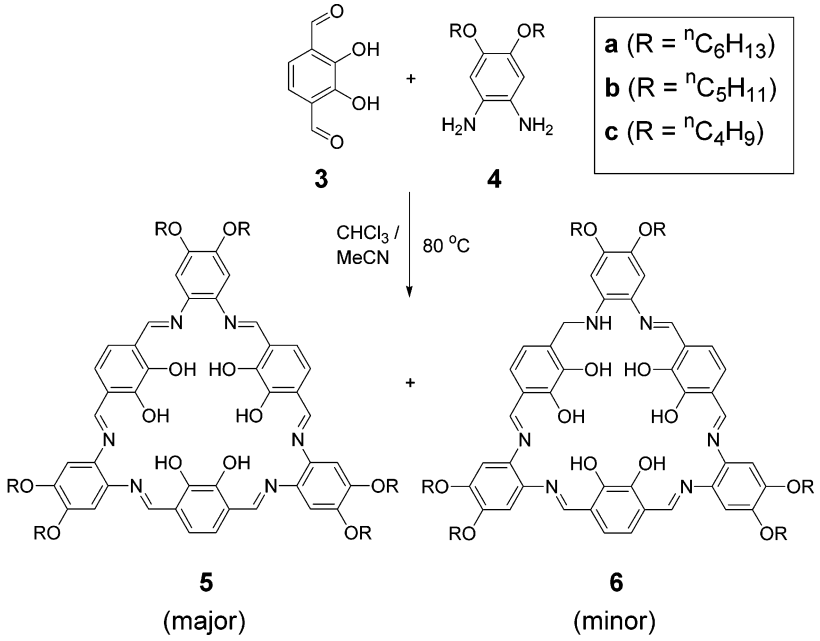
SCHEME 1. Synthesis of Robson-Type Macrocycle 1



SCHEME 2. Synthesis of Macrocycles 5 and 6



mostly the partially reduced macrocycle **2**, Scheme 1. A few research groups have studied these reduced products, but the reducing agent in these reactions is still disputed.[12−15]

We are interested in the supramolecular chemistry of macrocycles, such as **5a**, which aggregate into tubular assemblies in solution when combined with small cations.[16,17] These red, crystalline compounds are conveniently prepared in high yield by reacting 3,6-diformylcatechol **3** with substituted *o*-phenylenediamine **4** in $CHCl_3$/MeCN at 80 °C, Scheme 2.[17]

During our investigations of macrocycle **5a**, we isolated a deep red crystalline byproduct (ca. 10−20% by mass) by fractional crystallization of the crude reaction mixture. The ^{1}H NMR spectrum of this compound showed five imine (8−8.5 ppm) and six hydrogen-bonded phenol (11−15 ppm) resonances, as well as numerous aromatic protons (6.2−7.2 ppm). This is in contrast to macrocycle **5a**, which shows only one imine resonance (8.54 ppm), one phenol OH (13.23 ppm), and two aromatic protons as a result of its average D_{3h} symmetry. The ^{1}H and ^{13}C NMR spectra show new peaks at 4.4 and 48.5 ppm, respectively, consistent with a CH_2NH group. The IR spectrum of this byproduct was very similar to that of **5a**, showing an intense C=N stretch (1609 cm^{-1}) and no carbonyl group. In addition, a new peak at 3605 cm^{-1} was observed and is characteristic of the N−H stretch for a secondary amine. ESI-MS revealed the mass of this byproduct to be greater than that of macrocycle **5a** by exactly 2 amu, Figure S1. Single-crystal X-ray diffraction confirmed that the byproduct was indeed a macrocycle and not an oligomeric compound, Figure 1. Together, the structural and spectroscopic data indicate the byproduct to be monoreduced macrocycle **6a**.

The crystal structure of **6a** confirms that this byproduct is cyclic and shows that the compound is nonplanar with a single molecule of water hydrogen-bonded to the center of the macrocycle. A plane of symmetry runs through the molecule, reflecting one-half of the macrocycle onto the other.[18] The six hydroxyl groups of the

(15) Tian, Y.; Tong, J.; Frenzen, G.; Sun, J.-Y. *J. Org. Chem.* **1999**, *64*, 1442−1446.
(16) (a) Huck, W. T. S.; van Veggel, F. C. J. M.; Reinhoudt, D. N. *Recl. Trav. Chim. Pays-Bas* **1995**, *114*, 273−276. (b) Akine, S.; Taniguchi, T.; Nabeshima, T. *Tetrahedron Lett.* **2001**, *42*, 8861−8864.
(17) Gallant, A. J.; MacLachlan, M. J. *Angew. Chem., Int. Ed.* **2003**, *42*, 5307−5310.

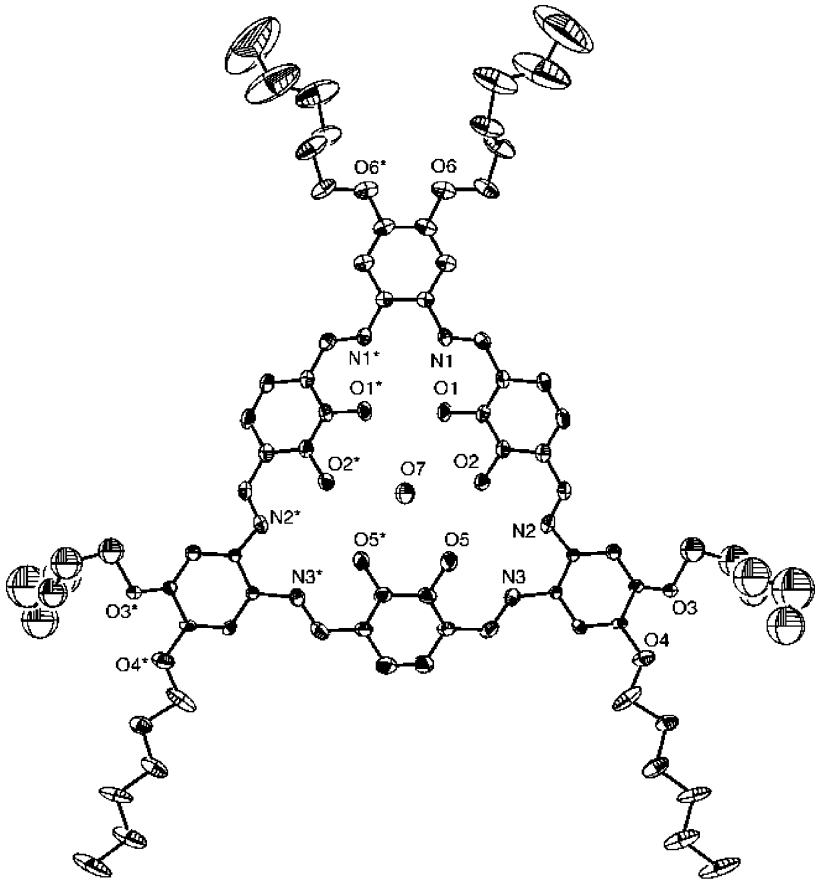


FIGURE 1. Molecular structure (from single-crystal X-ray diffraction) of monoreduced macrocycle **6a** with H_2O coordinated in the center (thermal ellipsoids shown at 33% probability).

macrocycle are tilted out of planarity with two of the diol moieties oriented upward and the third downward relative to the center of the macrocycle. Within the unit cell, the macrocycles are organized into planes, but the pores of the macrocycles are not aligned into channels.

It is not surprising that this macrocycle is nonplanar. Even the fully conjugated macrocycle (with no or different alkoxy groups) is nonplanar as deduced by single-crystal X-ray diffraction.[16b,19] These macrocycles likely twist to relieve interatomic interactions within the macrocycle, but there may also be an electronic or solvent effect (i.e., due to the water molecule hydrogen-bonded in the center).

Mechanistic Studies

As imines are usually reduced using considerable pressures of hydrogen or in the presence of a metal catalyst,[20] it was surprising to isolate the unsymmetrical monoreduced macrocycle **6a** without the addition of any formal reducing agent or catalyst. We therefore conducted experiments to identify the in situ reducing agent and to investigate the reduction process itself. Initially, we postulated that either starting material **3** or **4** could serve as reducing agent, forming a quinone or diimine, respectively. Others have postulated that the amine may be responsible for in situ reduction in the synthesis of related macrocycle **1**, forming direduced macrocycle **2**.[15] The combination of equimolar concentrations of compound **3** and macrocycle **5a** in acid-free $CHCl_3$ (dried with K_2CO_3) produced no reaction. However, using commercial $CHCl_3$, which contains residual acid, results varied but usually a mixture of products was obtained by ^{1}H NMR spectroscopy, including monoreduced macrocycle **6a** and the 1:1 condensation product **7a** (Scheme 3). The reaction of diamine **4a** with macrocycle **5a** showed only a 1:2 condensation product **8a** (and unreacted **5a**) with no evidence (^{1}H NMR) of monoreduced macrocycle **6a** in both commercial and acid-free $CHCl_3$ (even after reflux for 24 h), as shown in Scheme 3. Compounds **7** and **8**, which are possible intermediates in the macrocycle formation and may also form via hydrolytic fission of the macrocycle, could be independently prepared by the controlled reaction of **3** and **4** in the appropriate stoichiometry.[21] These results suggest that neither **3** nor **4** is independently responsible for the reduction of **5**.

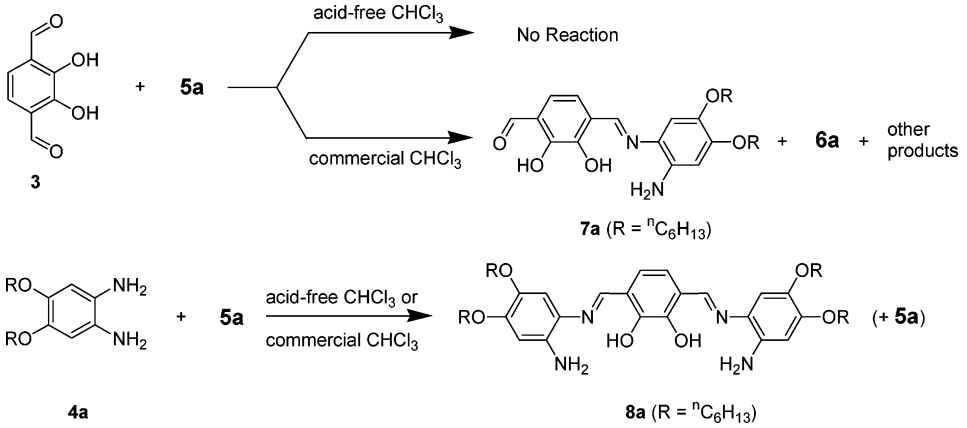
(18) It was impossible to identify exactly which imine was reduced because of disorder. The macrocycle appears to pack equally well with the imine or amine in any position, as there is a crystallographic mirror plane through the middle of the macrocycle (i.e., it appears more symmetrical as a result of disorder).

(19) Gallant, A. J.; Hui, J.-K.; Zahariev, F. E.; Wang, A.; MacLachlan, M. J. Manuscript in preparation.

(20) Adams, J. P. *J. Chem. Soc., Perkin Trans. 1* **2000**, 125−139.

(21) The 1:1 condensation product **7** containing both an amine and an aldehyde is quite reactive, readily undergoing condensation. Attempts to purify this compound with short alkoxy chains failed; **7** with short alkoxy chains (4, 5, and 6 carbon atoms) could be observed by ^{1}H NMR spectroscopy but could only be isolated with long alkoxy chains (∼12 or 14 carbon atoms). As well, it always contained an impurity of ∼10% of compound **8** (confirmed by ^{1}H NMR spectroscopy and MS).

SCHEME 3. Reactions of 3 and 4a with Macrocycle 5a



Reaction of equimolar quantities of diol **3** and diamine **4a** in commercial $CHCl_3$ at 50 °C afforded mostly monoreduced macrocycle **6a**. In the presence of added macrocycle **5a**, the major product was still monoreduced species **6a**. As these reactions may involve formation of the 1:1 adduct, we combined compound **7**[22] with **5a** at 50 °C, and after 7 h the ^1H NMR spectrum showed that **5a** was consumed (>80%) with monoreduced macrocycle as the major product. When the same three experiments were performed using acid-free $CHCl_3$, no monoreduced product was observed. These results indicate that residual acid must be present in the reaction solvent for macrocycle reduction. Moreover, an intermediate condensation product (e.g., **7**) needs to be present to permit the reduction.

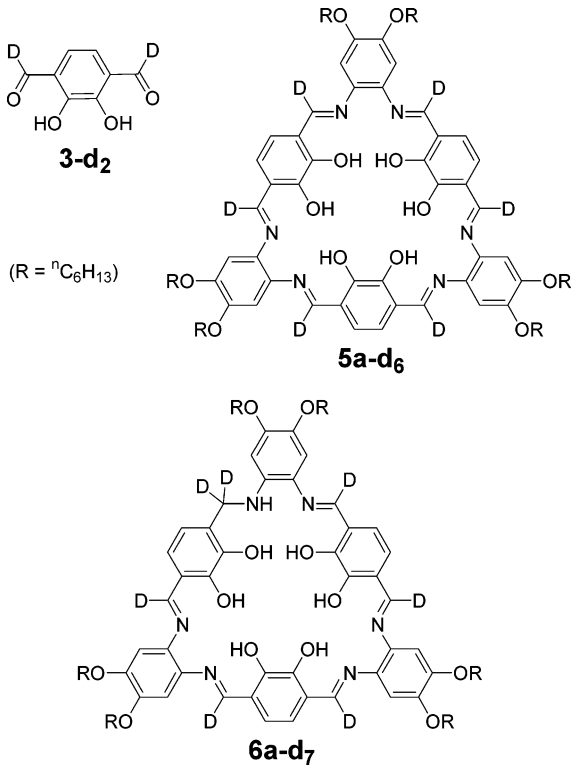
The formation of **6** proceeds slowly (days) in commercial $CHCl_3$ from diol **3** and diamine **4** but noticeably faster (hours) when acid is added. As macrocycle **5** forms quickly in solution, the acid may catalyze the hydrolysis of **5** to yield significant amounts of **7** that would not otherwise be present to allow for reduction. Unsymmetrical macrocycle **6a** could be prepared in 53% yield by the addition of less than 5% *p*-toluenesulfonic acid to **3** and **4a** in $CHCl_3$, keeping the reaction mixture at approximately 50 °C. Monoreduced macrocycles with different alkoxy substituents (e.g., **6b,c**) could also be prepared by the same procedure, demonstrating the generality of this reaction. Alternatively, monoreduced macrocycle **6a** could be obtained by the addition of less than 5% *p*-toluenesulfonic acid to macrocycle **5a** in $CHCl_3$. In this case, however, the reaction leads to a mixture of products and a lower yield of **6a**.

Ustynyuk et al. have postulated that a benzimidazoline may be involved in the formation of **2**.[12] They did not believe that macrocycle **1** was being reduced but rather that **2** formed through recombination of reduced intermediates. It was reported that in the first step, the diformylphenol and *o*-phenylenediamine condense to form a 1:1 condensation product. This species then undergoes disproportionation in the second step to yield a benzimidazole and a reduced 1:1 condensation product. In the final step, two reduced 1:1 condensation products combine to form macrocycle **2**. Although this does rationalize the formation of **2**, it is not clear why a monoreduced macrocycle is not also obtained as a product.

We propose that a benzimidazole is also responsible for the reduction of macrocycle **5** but that the preformed macrocycle is being reduced directly. That is, macrocycle **6** is not assembled from reduced components. Benzimidazoline **9** formed from the 1:1 condensation product **7** is responsible for the in situ reduction of macrocycle **5** to afford compound **6**.

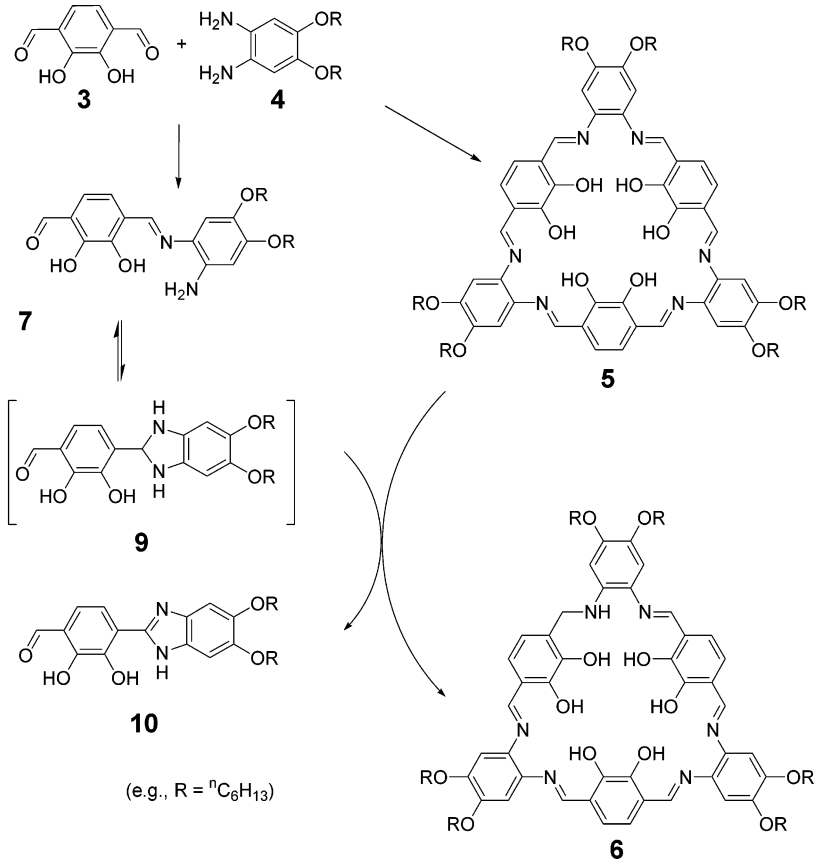
Benzimidazolines, generated in situ by the reaction of a diamine with an aldehyde, are known to be selective, mild reagents for reducing C=C bonds.[23] In our reaction, benzimidazoline **9** is likely generated from **7** and reacts with macrocycle **5** to afford **6**, yielding benzimidazole **10** as a byproduct, Scheme 4.

A deuterium labeling experiment was conducted to provide insight into the reaction mechanism. Diol **3-d$_2$** with deuterium-labeled formyl groups and macrocycle **5a-d$_6$** with deuterium-labeled imines were synthesized. When diol **3-d$_2$** and phenylenediamine **4a** were combined with a catalytic amount of acid and macrocycle **5a-d$_6$** in



(22) Because of the difficulty of purifying **7** with short alkoxy chains, **7** with tetradecyloxy chains was used for these experiments.

SCHEME 4. Proposed Mechanism for Formation of 6 by in Situ Reduction of Macrocycle 5



$CDCl_3$, compound **6a-d$_7$** was observed to be the major product within a few hours. The absence of a peak at 4.4 ppm in the ^{1}H NMR spectrum, where the characteristic CH_2NH resonance is observed in **6a**−**c**, indicated that only deuterium atoms were on the methylene carbon of the reduced imine in **6a-d$_7$**. This suggests that the reduction is selective and does not involve HD formation.

We also conducted an experiment in which the OH and NH_2 groups in **3** and **4a**, respectively, were deuterated (by exchange with D_2O). When treated with catalytic acid to generate **6a**, the product showed no significant deuterium incorporation into the methylene adjacent to the amine as determined by ^{1}H NMR spectroscopy. This further confirms that regioselective HD transfer occurs during the reaction.

Analogous to the reduction of C=C bonds,[23b] reduction may take place by either a stepwise mechanism with hydride (H^-) transfer from C−H of **9** followed by proton (H^+) transfer from NH of **9** or by the concerted addition of H^- and H^+ from benzimidazoline **9**. The acid catalyst may protonate the imine of **5**, thereby promoting H^- abstraction by the carbon adjacent to the iminium cation of **5**.[24]

Supporting the proposed mechanism, benzimidazole **10** has been isolated from the *p*-toluenesulfonic acid catalyzed reaction of **3** with **4a**. Its identity was verified by ESI-MS and NMR experiments. Presumably, this fluorescent product is formed as a byproduct in the reduction of macrocycle **5a** to afford **6a**. Efforts to isolate benzimidazoline **9** or benzimidazole **11** from the reaction mixtures have been unsuccessful. It has also not been possible to prepare **10** or **11** separately by oxidation (including the use of catalytic $FeCl_3$).[25]

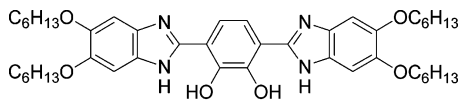
Although the isolation of benzimidazole **10** lends support to **9** being the reducing agent, it is possible that other condensation products are also responsible for the reduction. For example, a bis(benzimidazoline) formed from **8** may be involved. There may also be oligomeric species that are involved but could not be isolated. Their presence in reactions to form **6** is difficult to discern because of the complexity of the ^{1}H NMR spectrum of **6**, but ESI-MS analysis of a reaction mixture showed major peaks assigned to both benzimidazoles **10** and **11**, providing evidence for their involvement in the reaction. The same species (but with butyl substituents in the place of hexyl groups) were observed in the ESI-MS spectrum of the crude reaction mixture to form **6c**. The peak assigned to **11** in the MS is also observed as a fragment of both macrocycles **5a** and **6a**, but compound **10** is not.[26] The ESI-MS experiments indicated that **10** was present in

(23) (a) Chikashita, H.; Nishida, S.; Miyazaki, M.; Itoh, K. *Synth. Commun*. **1983**, *13*, 1033−1039. (b) Chikashita, H.; Nishida, S.; Miyazaki, M.; Morita, Y.; Itoh, K. *Bull. Chem. Soc. Jpn.* **1987**, *60*, 737−746. (c) Risitano, F.; Grassi, G.; Foti, F.; Bilardo, C. *Heterocycles* **2001**, *55*, 1311−1314. (d) Chikashita, H.; Morita, Y.; Itoh, K. *Synth. Commun.* **1985**, *15*, 527−533. (e) Itoh, K.; Ishida, H.; Chikashita, H. *Chem. Lett.* **1982**, 1117−1118.

(24) Lewis acids such as $[CpFe(CO)_2(THF)]^+$ coordinate to imines to generate electrophilic iminium ions that react with nucleophiles. For example, see: Mayer, M. F.; Hossain, M. M. *J. Org. Chem.* **1998**, *63*, 6839−6844.

(25) (a) Coville, N. J.; Neuse, E. W. *J. Org. Chem*. **1977**, *42*, 3485−3491. (b) Mackman, R. L.; Hui, H. C.; Breitenbucher, J. G.; Katz, B. A.; Luong, C.; Martelli, A.; McGee, D.; Radika, K.; Sendzik, M.; Spencer, J. R.; Sprengeler, P. A.; Tario, J.; Verner, E.; Wang, J. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 2019−2022.

the crude reaction mixture and did not form during the isolation procedure.



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Benzimidazole **10** is presumably formed from benzimidazoline **9**, which is in equilibrium with **7**, during the in situ reduction of macrocycle **5**. Recent calculations indicate that the reaction to form the benzimidazoline from the 1:1 condensation compound (i.e., **7**) should be endothermic.[12b] High-temperature NMR experiments in $C_2D_2Cl_4$ and $C_2D_2Cl_4$/EtOH showed no evidence for a benzimidazoline. Similar experiments with the 1:2 condensation compound **8** failed to show any evidence for equilibrium with a bis(benzimidazoline). Either the equilibrium concentration of benzimidazoline is too low to detect by ^{1}H NMR spectroscopy or the equilibrium is acid-catalyzed (acid was not added to the reaction as this was shown previously to afford macrocycle **6a**).

Remarkably, the reaction is selective and stops after monoreduction of the macrocycle. No polyreduced macrocycles were observed (^{1}H NMR) even after several days or under a variety of conditions. ESI-MS of the reaction mixture after nearly complete monoreduction (by ^{1}H NMR spectroscopy) showed only macrocycles **5a** and **6a** (plus benzimidazoles **10** and **11**), with no further reduced products present (Figure S2). We anticipated that the imines would be reduced nonselectively, especially those that are separated across the macrocycle, but this is not the case. After monoreduction, the macrocycle may be stabilized by additional hydrogen bonding from the amine, or there may be stabilization from hydrogen-bonding solvent molecules (e.g., H_2O) in the interior of the macrocycle. Interestingly, our attempts (and those of others) to synthesize macrocycle **1** usually afford the direduced macrocycle **2**, with no evidence of mono-, tri-, or fully reduced macrocycles (or other direduced isomers). This selectivity in the reduction of macrocyclic imines suggests that benzimidazolines may be mild and selective reducing agents for other imines.

The driving force for the reduction likely arises from the formation of a stable, aromatic benzimidazole and has been suggested in the formation of **2**. Macrocycle **5** with 48 π electrons is not aromatic, so the reduction does not break aromaticity. The reduction may also afford a relief of strain from interatomic repulsion or torsions within the macrocycle to lead to a stable monoreduced product. It is very likely that hydrogen bonding to solvent or water trapped within the macrocycle plays a role in stabilizing the monoreduced macrocycle relative to the fully conjugated precursor.

Conclusions

We have synthesized and characterized the unsymmetrical macrocycle **6**. On the basis of isolation of a benzimidazole byproduct and deuterium labeling experiments, we have shown that **6** is obtained by the reduction of **5** with a benzimidazoline intermediate generated in situ from diol **3** and diamine **4**. This discovery may shed light on the reduction of other Schiff-base macrocycles (such as **1**) and may lead to improved synthetic routes to these compounds. More generally, in situ generation of benzimidazolines may offer a convenient, purely organic reducing agent for mild and selective reduction of imines.

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Supporting Information Available: Crystallographic data for **6a** (in CIF format), experimental procedures, ^{13}C NMR data for **6a**, ESI-MS data (S2) for a reaction to form **6a**, and ^{1}H NMR spectra for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(26) We have used tandem mass spectrometry to verify the fragmentation pattern of macrocycles **5a** and **6a** by MS. By analyzing the mass spectra of macrocycles **5** with various chain lengths, the peaks are easily assigned. One fragment of $[\mathbf{5a} + H]^+$ and $[\mathbf{6a} + H]^+$ is a species with the same chemical composition as bis(benzimidazole) **11**. Compound **10** is never observed as a fragment of $[\mathbf{5a} + X]^+$ or $[\mathbf{6a} + X]^+$ (X = H, Na, K, Rb, Cs).