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Thiophene-containing Schiff-base macrocycles: intermediate compounds between macroaromatics and azamacrocycles

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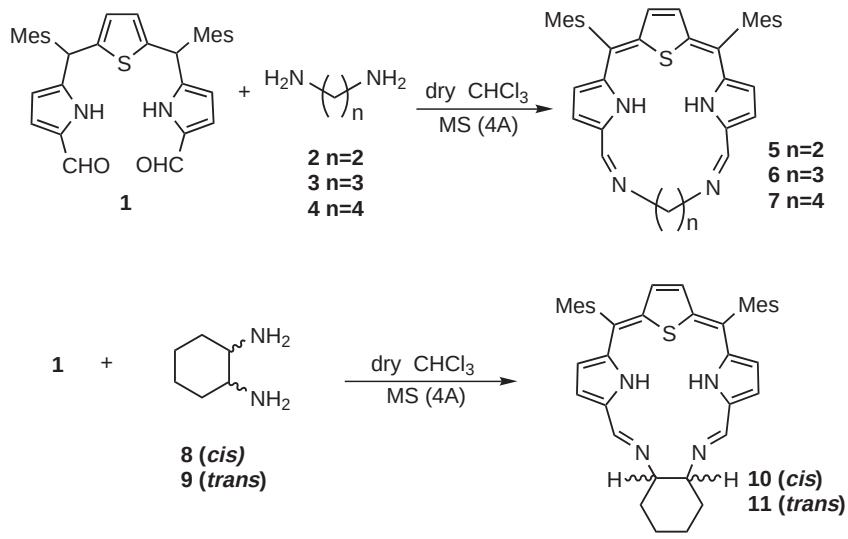
Abstract—Hybrid Schiff-base macrocycles were synthesized by acid-catalysed condensation of 1,14-bisformyl-16-thiatripyrromethane **1** with diamines. The condensation of aliphatic diamines with **1** resulted in the partially oxidized macrocycles **5**–**11**. On the other hand, the condensation of aromatic diamines with **1** gave simply cyclized Schiff-base **16**. Fully conjugated macrocycles were never formed and attempted oxidation of either macrocycles with various oxidants resulted in the extensive decomposition of the starting material. Hydride reduction of imine functions gave the new hybrid macrocycles.

Large porphyrin-like macrocycles and their metal complexes have shown considerable potential as diagnostic or treatment tools for various diseases.[1] The hybrid macrocycles composed of the combination of part of the porphyrin and part of the Schiff-base could be interesting compounds due to their ambient physical and spectroscopic properties. Since the first report of the synthesis of aromatic pentaaza-expanded porphyrins and their metal complexes by Sessler et al.,[2] many new macroaromatic compounds consisting of tripyrrin and imines have emerged and studied for potential biological applications.[3b] For example, some of the metal complexes of the expanded porphyrins have been used for enhancing images in MRI[3b] and also as selective anion binding agents.[4] We recently observed the new contractive cyclization and oxidation in the condensation of 1,14-bisformyl-16-oxatripyrromethane with 1,2-diphenylethylenediamines.[5,6] The amplified



Scheme 1.

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angle-strain was proposed for the differential reactivity of tripyrromethanes with different core-heteroatom.[5] In order to establish the scope and limitation of the reaction, we extended the reaction further and herein we report the formation of intermediate macrocycles between macroaromatic and azamacrocycle depending on the nature of the applied diamines.

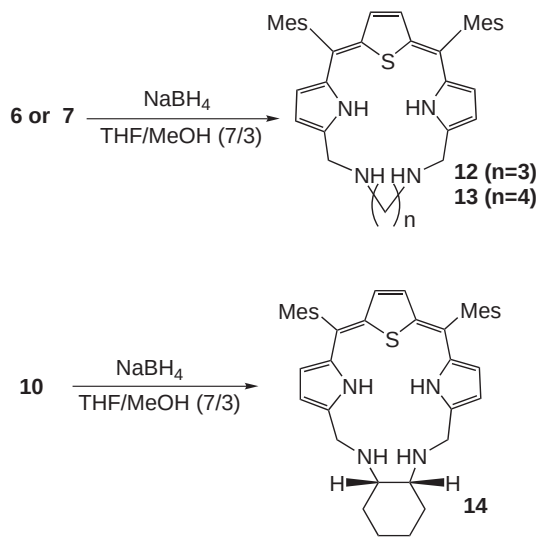
The crude diastereomeric mixture of **1** (vide infra) was used directly without further purification in the condensation because all the stereocenters disappear in the successive reaction sequences.[7] The reaction of **1** with appropriate diamines afforded Schiff-base macrocycles, as shown in Scheme 1. All the reactions proceeded smoothly in the presence of molecular sieves and concomitant oxidation of the two *meso*-positions was obvious according to the proton NMR spectra. This is somewhat in contrast to the case reported by Sessler et al.[1a,2a] All the macrocycles shown in Scheme 1 contain 18π electrons and they are not macroaromatics. Although oxidation of the two *meso*-positions and ethylene bridge could extend the conjugation, the fully conjugated compounds were not formed in these cases. The auto-oxidation of the two *meso*-positions may be related to the release of the steric strain between mesityl and β-pyrrolic hydrogens. Extensive hydrolysis observed during the column chromatographic separation is consistent with this observation.

The macrocycles **5**–**11** exhibit rather strong Soret-like bands at 360–380 nm in absorption spectra, which is characteristic of conjugated oligopyrrolic compounds.[8] The λ_{max} value was gradually shifted toward shorter wavelength by increasing the number of methylene units between the two imine functions. The thiophene and β-pyrrolic protons were also affected by the length of the bridge. For example, thiophene resonance in **7** appeared at 6.09 ppm, while that of **10** was observed at 6.47 ppm. The shortly bridged compound experiences more deshielding effect than that of the longer bridged one due to stronger ring current and the forced planarity. These are all consistent with the increased conjugation. Both of these azafulvene type structures could be generated by additional four electron oxidation and the resulting 20π anti-aromatic macrocycles must be less stable than **10**. Attempted oxidation of **10** or **11** with various oxidants (DDQ, proton sponge and *p*-chloranil) was not successful and only extensive decomposition was observed.

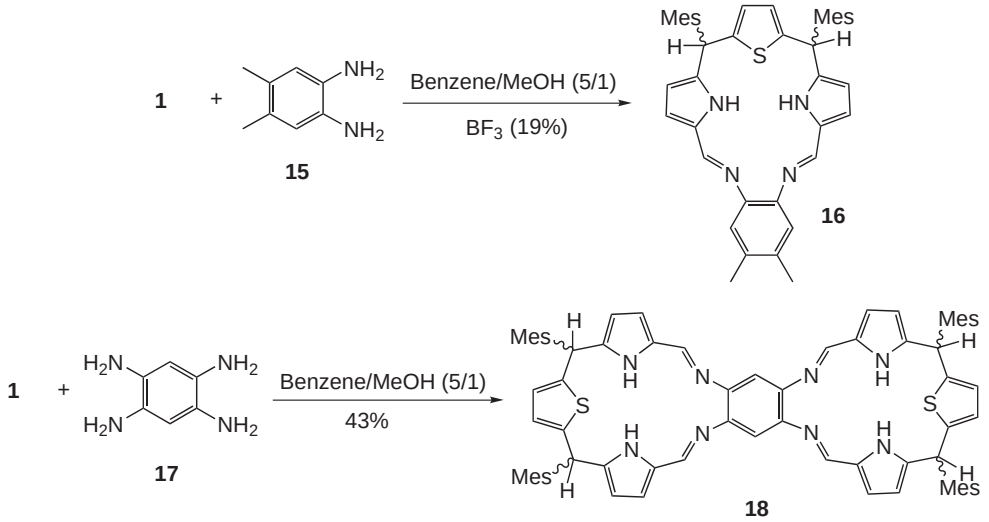
Observation of a single resonance line for the two imine *C–H*s in all the synthesized macrocycles indicated that the relative configuration must be *trans* to each other. The *trans*-configuration must be more stable and the resonance was observed in the range 8.26–8.36 ppm, depending on the number of methylene groups. The compounds **5**, **6** and **7** also showed single resonance lines for the two imine *C–H* protons.[9] Proton NMR spectra of **10** and **11** (chloroform-*d*) showed broadened resonance lines but clean separation of all the resonance lines was achieved upon adding a trace amount of acid. Reduction of macrocycles **6** or **7** with $NaBH_4$ afforded corresponding reduced compounds **12** and **13**. Only the imine function was reduced leading to the hybrid azamacrocycles. Attempted catalytic hydrogenation of *meso*-double bonds in **6** ended up with reduction of imines, while the *meso*-double bonds were not reduced. On the other hand, reduction of **10** under the same condition afforded a high yield (76%) of compound **14**. The methylene protons arising from the reduction of imines in **10** showed two sets of distinctive resonance, indicating the diastereotopic nature of the geminal protons. These observations indicate the asymmetric nature of the molecule resulting from severe distortion.

The pyrrolic N–H resonance was not observed for all the compounds shown in Schemes 1 and 2. This is due to fast exchange and slow tumbling of the molecule within the NMR time scale. It has been well known that the shapes of resonance lines are closely related to the exchange rates and conformational fluctuation of the compounds.

The condensation of **1** with aromatic 1,2-diamine **15** also afforded the Schiff-base compound **16** (Scheme 3). The *meso*-positions were not oxidized in this case. Attempted oxidation of **16** employing various oxidants to the full aromatic macrocycle was not successful either. This is because the complete oxidation of *meso*-positions results in the anti-aromatic 24π macrocyclic system. The formation of the azafulvene type structure is much more unlikely. Proton NMR spectra of compound **16** showed two sets of signals for all protons, indicating the formation of diastereomeric mixture. The ratio of the two diastereomers was found to be 1/0.9 based on proton NMR. The crude compound obtained from simple column chromatography (methylene chloride/ethyl acetate, 4/1) contains almost equal amounts of each diastereomer. Recrystallization in methylene chloride/methanol enriched one of the two diastereomers in the ratio of 5/2.



Scheme 2.



Scheme 3.

Condensation of **1** with aromatic tetramine **17** also afforded bis cyclic compound **18** in 43% yield. Due to the electron rich nature of **17**, the condensation proceeded smoothly without any acid catalysts. Careful analysis of resonance lines for individual protons indicated the existence of three different diastereomers. Three distinctive methine signals were observed in proton NMR spectra. The attempted isolation of each diastereomer was not successful due to poor resolution combined with extensive hydrolysis of the imines. The individual resonance lines in compound **18** exactly matched with those of compound **16** as is expected. The compounds synthesized here were resistant to full oxidation and thereby exist as partially conjugated macrocycles. This may be the inherent characteristic of the compound.

In conclusion, the synthetic methodology described here could be applied in creating new asymmetric expanded porphyrinoids. The synthetic approaches presented could also be applicable in designing unique macrocyclic systems with intrinsic chirality, which could serve as potential receptors for various guest molecules. Currently, efforts are underway to isolate each diastereomers from the mixture and to prepare metal complexes.

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References

1. (a) Sessler, J. L.; Hemmi, G.; Mody, T. D.; Murai, T.; Burrell, A. K.; Young, S. W. *Acc. Chem. Res.* **1994**, *27*, 43; (b) Sessler, J. L.; Burrell, A. K. *Top. Curr. Chem.* **1991**, *161*, 177; (c) Sessler, J. L.; Miler, R. A. *Biochem. Pharm.* **2000**, *59*, 733.
2. (a) Sessler, J. L.; Johnson, M. R.; Lynch, V. *J. Org. Chem.* **1987**, *52*, 4394; (b) Sessler, J. L.; Murai, T.; Lynch, V.; Cyr, M. *J. Am. Chem. Soc.* **1988**, *110*, 5586; (c) Sessler, J. L.; Murai, T.; Lynch, V. *Inorg. Chem.* **1989**, *28*, 1333.
3. (a) Sessler, J. L.; Miller, R. A. *Biochem. Pharmacol.* **2000**, *59*, 733; (b) Sessler, J. L.; Mody, D. M.; Hemmi, G. W.; Lynch, V.; Young, S. W.; Miller, R. A. *J. Am. Chem. Soc.* **1993**, *115*, 10368; (c) Acholla, F. V.; Takusagawa, F.; Mertes, K. B. *J. Am. Chem. Soc.* **1985**, *107*, 6902.
4. (a) Iverson, B. L.; Shreder, K.; Kral, V.; Sessler, J. L. *J. Am. Chem. Soc.* **1993**, *115*, 11022; (b) Furuta, H.; Cyr, M. J.; Sessler, J. L. *J. Am. Chem. Soc.* **1991**, *113*, 6677; (c) Kral, V.; Furuta, H.; Shreder, K.; Lynch, V.; Sessler, J. L. *J. Am. Chem. Soc.* **1996**, *118*, 1595; (d) Mizutani, T.; Ema, T.; Tomita, T.; Kuroda, Y.; Ogoshi, H. *J. Am. Chem. Soc.* **1994**, *116*, 4240.
5. Lee, C. H.; Ka, J. W.; Won, D. H. *Tetrahedron Lett.* **1999**, *40*, 6799.
6. Lee, C. H.; Oh, K. T. *Tetrahedron Lett.* **1999**, *40*, 1921.
7. *Organic Reactions*; Pquette, L. A., Ed.; John Wiley & Sons: New York, 1997; Vol. 49, p. 1.
8. Meyer, S.; Andrioletti, B.; Sessler, J. L.; Lynch, V. *J. Org. Chem.* **1998**, *63*, 6752.
9. Spectroscopic data for **10**: ^{1}H NMR ($CDCl_3$+TFA-*d*): δ 8.36 (s, 2H, imine-H), 7.35 (d, 2H, $J=4.2$ Hz, pyrrole-H), 6.98 (d, 4H, $J=9.0$ Hz, Ar-H), 6.73 (s, 2H, thiophene-H), 6.23 (d, 2H, $J=4.2$ Hz, pyrrole-H), 4.42 (s, 2H, cyclohexyl-H), 2.34 (s, 6H, Ar-CH_3), 2.22–2.16 (m, 4H, cyclohexyl-H), 2.09 (s, 6H, Ar-CH_3), 2.04 (s, 6H, Ar-CH_3), 1.79–1.67 (m, 4H, cyclohexyl-H); UV–vis λ_{max} 378 nm; FAB MS calcd for $C_{40}H_{42}N_4S$ 610.31. Found 611.37. For **11**: ^{1}H NMR ($CDCl_3$+D_2O+TFA-*d*): δ 8.27 (s, 2H, imine-H), 7.24 (d, 2H, $J=4.4$ Hz pyrrole-H), 6.96 (d, 4H, $J=8.0$ Hz, Ar-H), 6.62 (s, 2H, thiophene-H), 6.19 (d, 2H, $J=4.4$ Hz, pyrrole-H), 3.52–3.50 (m, 2H, cyclohexyl-H), 2.43–2.40 (m, 2H, cyclohexyl-H), 2.34 (s, 6H, Ar-CH_3) 2.16–2.14 (m, 2H, cyclohexyl-H), 2.06 (s, 6H, Ar-CH_3), 2.03 (s, 6H, Ar-CH_3), 1.63 (m, 2H, cyclohexyl-H), 0.88 (m, 2H, cyclohexyl-H); UV–vis λ_{max} 376 nm. For **16** and its

diastereomer: ratio = 1.0/0.9; major isomer; ^{1}H NMR ($CDCl_3$): δ 8.32 (s, 2H, imine-H), 7.09 (s, 2H, Ar-H), 6.84 (s, 4H, Ar-H), 6.60–6.58 (m, 2H pyrrole-H), 6.27 (s, 2H, thiophene-H), 6.11 (s, 2H, pyrrole-H), 5.91 (d, 2H, J = 3.6 Hz, *meso*-H), 2.29 (s, 6H, Ar-CH_3), 2.26 (s, 12H, Ar-CH_3), 2.10 (br s, 6H, Ar-CH_3). Minor isomer; δ 8.30 (s, 2H, imine-H), 7.08 (s, 2H, Ar-H), 6.85 (s, 4H, Ar-H), 6.60–6.58 (m, 4H pyrrole-H and thiophene-H), 6.14 (s, 2H, pyrrole-H), 5.85 (d, 2H, J = 3.5 Hz, *meso*-H), 2.29 (s, 6H, Ar-CH_3), 2.23 (br s, 6H, Ar-CH_3), 2.16 (br s, 12H, Ar-CH_3); FAB MS calcd for $C_{42}H_{42}N_4S$ 634.31. Found 635.22. For **18** and its diastereomer: ratio = 1.1/1), major isomer; ^{1}H NMR ($CDCl_3$): δ 8.37 (s, 4H, imine-H), 7.25 (s, 2H, Ar-H), 6.84 (s, 8H, Ar-H), 6.66–6.61 (m, 4H pyrrole-H), 6.29 (s, 4H, thiophene-H), 6.13 (s, 4H, pyrrole-H), 5.94 (d, 4H, J = 3.6 Hz, *meso*-H), 2.26–2.24 (m, 18H, Ar-CH_3). Minor isomer; δ 8.39 (s, 4H, imine-H), 7.25 (s, 2H, Ar-H), 6.85 (s, 8H, Ar-H), 6.66–6.61 (m, 8H pyrrole-H and thiophene-H), 6.16 (s, 4H, pyrrole-H), 5.88 (d, 4H, J = 3.4 Hz, *meso*-H), 2.17–2.02 (m, 18H, Ar-CH_3); FAB MS calcd for $C_{74}H_{70}N_8S_2$ 1134.52. Found 1135.34. For **14**: ^{1}H NMR ($CDCl_3$): δ 9.92 (br s, 2H, N-H), 6.89 (s, 4H, Ar-H), 5.97 (s, 2H, thiophene-H), 5.90–5.89 (m, 2H, pyrrole-H), 5.64 (t, 2H, J = 3.1 Hz, pyrrole-H), 4.07 and 3.80 (two doublets, 4H, J = 14.5 Hz, CH_2), 3.02 (m, 2H, cyclohexyl-H), 2.31 (s, 6H, Ar-CH_3), 2.11 (s, 6H, Ar-CH_3), 2.09 (s, 6H, Ar-CH_3), 1.76–1.60 (m, 8H, cyclohexyl-H); FAB MS calcd for $C_{40}H_{46}N_4S$ 614.34. Found 613.35.