

Cyclo[6]pyridine[6]pyrrole: A Dynamic, Twisted Macrocycle with No Meso Bridges

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S Supporting Information

ABSTRACT: A large porphyrin analogue, cyclo[6]-pyridine[6]pyrrole, containing no meso bridging atoms, has been synthesized through Suzuki coupling. In its neutral form, this macrocycle exists as a mixture of two figure-eight conformers that undergo fast exchange in less polar solvents. Upon protonation, the dynamic twist can be transformed into species that adopt a ruffled planar structure or a figure-eight shape depending on the extent of protonation and counteranions. Conversion to a bisboron difluoride complex via deprotonation with NaH and treatment with BF₃ acts to lock the macrocycle into a figure-eight conformation. The various forms of cyclo[6]-pyridine[6]pyrrole are characterized by distinct NMR, X-ray crystallographic, and spectroscopic features.

Conformation is an important feature of most molecules and can be intimately coupled with their specific properties and function. For instance, it has long been recognized that small conformational changes in a protein as in, e.g., the allosteric regulation of an enzyme, may lead to dramatic changes in, or complete loss of, activity. Conformational effects are no less important in small molecules. Calixpyrroles^{1–4} and foldmers,^{5,6} for example, must adopt a particular conformation to bind anions effectively. In recent years, the importance of the conformation–property relationship has been further underscored by studies involving expanded porphyrins. Certain representative systems that adopt a planar or figure-eight (double-sided) structure display Hückel-type aromaticity/antiaromaticity features. In contrast, conformers with a half-twisted (one-sided) topology can have Möbius aromatic/antiaromatic character.⁷ An attractive feature of expanded porphyrins is that high barriers between different conformers typical of most organic species are relaxed, allowing ready access to multiple conformations using the same basic system. To date, this control has been achieved in the case of hexa-, hepta-, and octapyrrolic systems through the use of temperature modulation,⁸ solvent effects,⁹ metalation,^{10,11} and protonation/deprotonation.^{12–14} Nevertheless, the basic determinants that favor one particular conformer or the factors that regulate the kinetics and thermodynamics of interconversion between various conformers are far from understood. New

expanded porphyrins having structures that differ dramatically from those studied to date could provide insights into these key aspects of conformational motion. With this view in mind, we detail here the synthesis of a new macrocyclic system, namely, cyclo[6]pyridine[6]pyrrole **1**. To our knowledge, macrocycle **1** is the largest expanded porphyrin analogue to be reported to date that contains no linking atoms between the individual heterocyclic subunits.¹⁵ This much larger ring, containing 12 heterocyclic subunits, stands in marked contrast to previous expanded porphyrins for which conformational features have been studied in that (1) it incorporates pyridine as well as pyrroles within the macrocyclic ring and (2) these subunits are directly linked to one another. As detailed below, this new system allows access to two different figure-eight conformations in less polar solvents. These conformations are “twist isomers” in that they are produced by a simple shifting of the crossing point that defines the nonplanar, figure-eight geometry of the overall system. Conversion to other forms, including ruffled planar geometries, may be achieved through protonation and control of the counteranion, whereas formation of the bis-BF₂ complex serves to stabilize a figure-eight conformation. The different geometrical forms of **1** are manifest in terms of distinct ground and excited state optical features.

We recently reported that palladium-catalyzed Suzuki coupling can be used to synthesize cyclo[*m*]pyridine[*n*]pyrroles and furan derivatives where *m* + *n* = 6.^{16,17} In the work to optimize the synthesis of the six-membered cyclo[3]-pyridine[3]pyrrole **4**, the formation of two relatively polar species was observed. Mass spectrometric analysis of the more polar product revealed a presumed molecular ion peak with an effective mass of 917; it also showed the isotope distribution characteristics of a bromine-containing compound. On this basis, it was tentatively assigned as being the linear [5]pyridine[4]pyrrole **5**. In contrast, the less polar species gave rise to a peak with a mass of 1077, corresponding to a molecular formula of C₇₀H₆₈N₁₂. Basically, this represents a doubling of what was observed in the case of cyclo[3]-pyridine[3]pyrrole **4**. This led us to consider that this new compound corresponds to a higher order cyclic congener. Support for the suggestion that the newly isolated fraction

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contained a total of 12 heterocyclic subunits came from an X-ray diffraction analysis of single crystals grown from chloroform/hexanes (Figure 1). On this basis, this species was

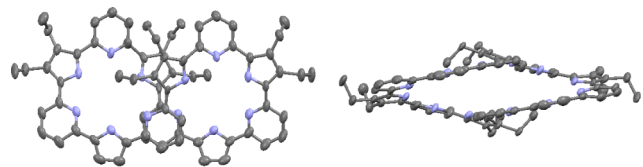
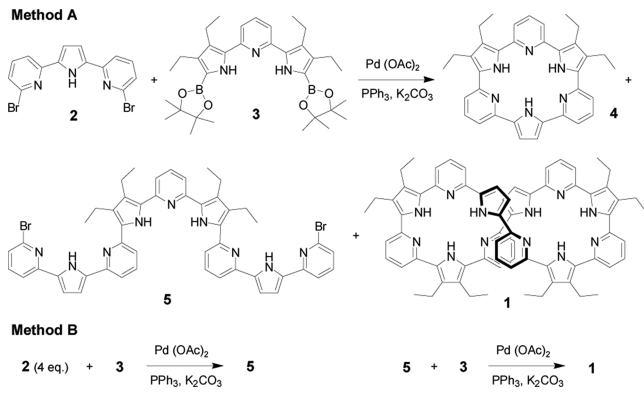


Figure 1. Single-crystal structure of cyclo[6]pyridine[6]pyrrole 1.

assigned to the cyclo[6]pyridine[6]pyrrole 1. In contrast to all other meso bridge-free expanded porphyrins reported to date (all of which contain nine or fewer heterocyclic subunits), compound 1 is found to adopt a figure-eight geometry in the solid state.

The 12 heterocycle-containing macrocycle 1 was isolated in yields of 1–2% when 2 was coupled directly with 3 (Scheme 1,

Scheme 1. Synthesis of Cyclo[6]pyridine[6]pyrrole 1



method A). This low yield is ascribed to the fact that formation of 1 requires coupling between four separate molecular species. We thus envisioned that the yield of 1 would be improved if the coupling step could be made to occur between only two reactants. In fact, when a Suzuki coupling between the linear polypyridine–pyrrole 5 and the bisboryl precursor 3 was carried out (method B), the yield of 1 increased to 15%. The key linear precursor 5 can be prepared in excellent yield if an excess of 2 is used in the cross coupling between 2 and 3.

The ^1H NMR spectrum of cyclo[6]pyridine[6]pyrrole 1 recorded in CD_2Cl_2 revealed two sets of signals. These signals share a similar resonance pattern and have a rough integration ratio of 3:1 (Figure 2). However, chromatography on either

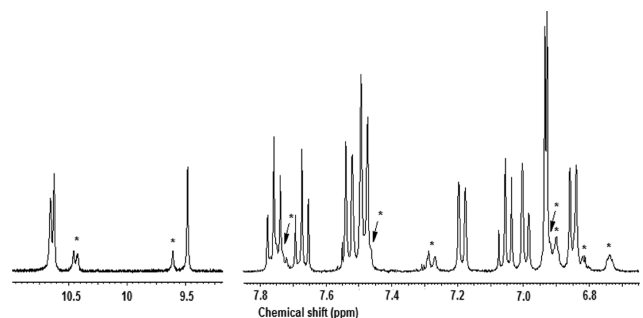


Figure 2. Partial ^1H NMR spectra of 1 in CD_2Cl_2 .

silica gel or biobeads gives rise to only one observable band, whereas an identical ^1H NMR spectral pattern is obtained when samples are made using crystals characterized as being a single compound by X-ray diffraction analysis. We thus conclude that the two sets of peaks correspond to two different conformers. Although the aromatic region peaks seen in the ^1H NMR spectrum are consistent with an approximate C_2 symmetry, both sets of signals are characterized by peak patterns in the alkyl region that reflect a lower level of symmetry. This mirrors what was seen for another figure-eight macrocycle.¹⁸

To obtain greater insights into the nature of these two putative conformers and their possible interconversion, variable-temperature (VT) ^1H NMR studies were carried out. When CD_2Cl_2 was used as the solvent, the percentage of the minor species decreased as the temperature was lowered. This observation provides support for the notion not only that observed peaks correspond to two conformers of the same molecule but also that they interconvert rapidly even at the low temperatures used for the study (i.e., $-80\text{ }^\circ\text{C}$). In toluene- d_8 an approximately constant ratio is observed (minor: major, 1:2) until the solution is warmed to $100\text{ }^\circ\text{C}$, whereupon coalescence between the two sets of signals begins to occur.

The ^1H NMR spectrum of 1 is solvent dependent. Whereas two sets of signals are observed in CD_2Cl_2 , CDCl_3 , and toluene- d_8 , only one set of severely broadened peaks is observed in $\text{DMSO}-d_6$ at room temperature. Rerecording the spectrum of the sample made in $\text{DMSO}-d_6$ as the temperature increased revealed increasingly sharp peaks. The ^1H NMR spectrum was also recorded in a mixture of toluene- d_8 and $\text{DMSO}-d_6$ (1:1). Either raising or lowering the temperature served to make the broad peaks at $60\text{ }^\circ\text{C}$ sharper; however, only one set of signals was observed. We propose that there are specific solvent-derived interactions, such as hydrogen bonding, which serve to stabilize a single conformer of 1 in the presence of DMSO . Consistent with this suggestion is the finding that the addition of methanol- d_4 , THF- d_8 , or acetone- d_6 into a CDCl_3 solution of 1 also gave rise to spectra with a single set of broad signals.

In macrocycle 1, there are two types of pyrrole subunits (substituted and unsubstituted, referred to as S and U, respectively, in Scheme 2). There are thus two limiting

Scheme 2. Three Plausible Conformers of Cyclo[6]pyridine[6]pyrrole 1

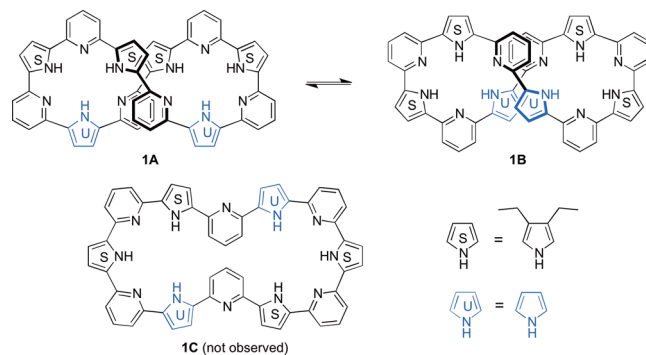


figure-eight conformations that are expected to be favorable. In one form, the substituted pyrrolic subunits overlap (conformer 1A, corresponding to the top view; cf. Figure 1), whereas in the other (conformer 1B) the unsubstituted pyrroles overlap. On the basis of their similarity in structure, these two conformers are expected to be close in energy and

thus capable of coexisting at room temperature in the absence of a specific stabilizing effect that would favor one conformer over the other.

The structures proposed for **1A** and **1B** are supported by both ^1H and 2D NMR studies. In CD_2Cl_2 , the two pyridine proton-derived doublets corresponding to the major species have a considerable upfield shift (<7.0 ppm), as would be expected for a structure wherein these protons are shielded as the result of an overall twisting of the macrocycle. Similarly, at least two pyridine proton signals corresponding to the minor species are also in a shielded environment. In contrast, all the pyridine protons of **4** resonate at ≥ 7.2 ppm. The rotating-frame Overhauser effect spectroscopy (ROESY) spectrum of **1** recorded in CD_2Cl_2 (Supporting Information) provides evidence for the NH protons (δ 9.5) of the two substituted pyrrole subunits in the major species being in close contact with three kinds of pyridine meta-protons. Because planar conformations, such as **1C**, can at most display two such signals and because other twisted geometries are likely to be much higher in energy, these observations are taken as evidence that **1** exists as in a figure-eight form under these experimental conditions. Given the specifics of the shifts involved, we further conclude that the major species in solution is conformer **1A**, as observed in the solid state. Signals consistent with close contacts were also observed between the major and minor species in the negative ROESY spectrum. This provides support for the conclusion based on the VT NMR spectral analysis that the two conformers undergo fast exchange at the NMR time scale in this less polar solvent.

Theoretical calculations support the conclusion that conformer **1A** is more stable than **1B** (Supporting Information). Energy estimates carried out at the B3LYP/6-31G** level reveal conformer **1A** to be ca. 2.3 kcal mol $^{-1}$ more stable than **1B** when account is taken of solvent effects (e.g., CHCl_3 , as modeled using the polarized continuum medium (PCM) method). The small energy gap between the conformers is consistent with the observed rapid interconversion seen at room temperature in less polar solvents. In contrast, the energy of the imaginary planar conformer (**1C**) is 12 – 13 kcal mol $^{-1}$ higher than that of **1B**.

The conformational features of **1** may be modulated by treatment with acids. For instance, the ^1H NMR spectrum of **1** recorded in CDCl_3 containing ≥ 6 equiv of methanesulfonic acid (MSA) consists of only one set of peaks. Moreover, in contrast to the complicated ROESY spectrum seen for the neutral form of **1** in CD_2Cl_2 , that of **1** in the presence of excess MSA is quite simple. In addition, a nuclear Overhauser effect (NOE) effect between the pyrrole β -protons and methylene/methyl groups was observed. Taken in concert, these findings are consistent with this protonated species existing in a time-averaged planar conformation (**1C** in Scheme 2) in CDCl_3 solution.

An X-ray diffraction analysis of **1·6MSA** revealed a ruffled planar conformation in the solid state (Figure 3). Two of the protonated pyridine rings (NH moieties) point out from the center of the ring and are bound to one MSA anion each. The other MSA anions are bound above and below the net macrocyclic plane via NH hydrogen bond interactions. Presumably, the specific conformation seen in the solid state is one that reduces steric hindrance between the peripheral substituents while facilitating interactions with the counteranion.

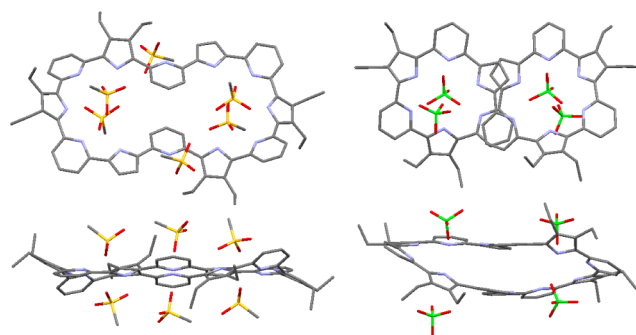


Figure 3. Top and side views of single-crystal X-ray diffraction structures of (left) **1·6MSA** and (right) **1·4HClO₄**.

The interactions with the counteranion appear important in terms of defining the conformation observed in the solid state. Support for this contention comes from the finding that when **1** was treated with $\text{Pb}(\text{ClO}_4)_2$ in acetonitrile and methylene chloride (neither solvent was subject to appreciable drying), a partially protonated species (**1·4HClO₄**) was obtained.¹⁹ X-ray diffraction analysis revealed a figure-eight conformation that is distinct from that seen in the case of the neutral form (Figure 3). Whereas **1** exists in the form of conformer **1A** in the solid state, **1·4HClO₄** is best described as being a type **1B** conformer. The ^1H NMR resonance pattern of **1·4HClO₄** is similar to that of the neutral form, except that only one set of signals is observed. Moreover, in contrast to what was seen in the case of **1·6MSA**, ^1H NMR spectroscopic analysis revealed that two of the pyrrole protons at the β position are shielded (δ 6.5). On this basis, we conclude that the extent of protonation and the nature of the counteranion may be used to control the conformation of **1**.

The steady-state absorption and fluorescence spectra of **1** were measured in various solvents (Supporting Information). Regardless of the solvent polarity, **1** displayed almost the same absorption and fluorescence features. The calculated vertical transition energies for the neutral electronic ground state of **1** are in a good agreement with the steady state absorption spectra (cf. Supporting Information). The fluorescence lifetimes of **1**, recorded in various solvents using time-correlated single photon counting (TCSPC), provided support for proposed structures **1A** and **1B**. In less polar solvents, such as toluene and CH_2Cl_2 , dual fluorescence decay processes were seen. When the highly viscous medium, paraffin oil, was used, the two time components appear in a ca. 3:1 ratio. These components were characterized by 5.5 and 2.5 ns lifetimes, respectively. In contrast, when measured in THF and DMSO, only a single decay was seen for **1**. The addition of excess MSA to a CH_2Cl_2 solution of **1** induces significant changes in the absorption and fluorescence spectra. A single fluorescence lifetime of 4.2 ns is observed under these conditions.

Macrocycle **1** may be converted to the corresponding binuclear BF_2 complex by treatment with NaH followed by BF_3 . The ^1H NMR spectrum of the bis- BF_2 complex (**1·2BF₂**) is characterized by only one set of peaks. This leads us to suggest that the conformation becomes locked in the form of a single conformer as the result of boron complexation. A single-crystal diffraction analysis reveals a figure-eight structure (Figure 4), wherein the unsubstituted pyrroles reside on top of one another. The B–N bond lengths are 1.65 (pyridine N–B) and 1.53 Å (pyrrole N–B), respectively, whereas the N–B–N angle is ca. 97° . These parameters are similar to those

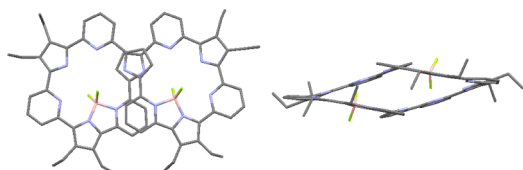


Figure 4. Two views of a single-crystal structure of $1 \cdot 2\text{BF}_2$.

observed in the only pyridine–pyrrole– BF_2 complex of which we are aware.²⁰ To our knowledge, this is the first time such a pyridine–pyrrole– BF_2 fragment has been incorporated into a macrocycle. The steady state absorption and fluorescence spectra of $1 \cdot 2\text{BF}_2$ were measured in CH_2Cl_2 . Compared to **1**, the boron complex of **1** is characterized by a new absorption band between 450 and 550 nm, as well as by red-shifted fluorescence. This more rigid species displays a single, relatively long-lived excited state lifetime of 6.3 ns.

In summary, we have synthesized a large, meso bridge-free expanded porphyrin analogue that exists as a dynamic mixture of two conformers in less polar solvents. The use of more polar media, protonation, or formation of a bis- BF_2 complex serves to stabilize the macrocycle in a particular conformation as inferred from NMR studies. This system is of interest because it shows that two “twist isomers”, obtained by shifting the location of the crossing point in a figure-eight system, may be obtained using a single expanded porphyrin framework.

■ ASSOCIATED CONTENT

📄 Supporting Information

Additional synthetic, spectroscopic, and structural information. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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Notes

The authors declare no competing financial interest.

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