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Mendeleev Commun., 2010, **20**, 192–194

Mendeleev Communications

Copper(II)-template synthesis of hexaphyrin *meso*-hexaaza analogues containing four thiadiazole moieties

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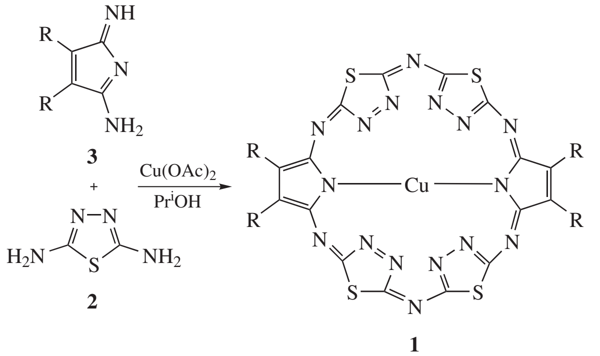
DOI: 10.1016/j.mencom.2010.06.002

The crossover condensation of 2,5-diamino-1,3,4-thiadiazole and isoindoline or pyrroline diimino derivatives in the presence of copper(II) affords a new 30π-electron hexamer with hemiporphyrazine-like character.

Expanded porphyrinoids constitute ideal models to explore the limits of the classical Hückel rule to define aromaticity.[1–3] Moreover, they possess exceptional coordination properties such as the ability to accommodate large cations (lanthanides and actinides)[4] or anions.[5] In addition, expanded macrocycles display red-shifted absorptions in the visible region,[1–3] presumably associated to their extended-conjugated π-systems, and this fact makes them potentially useful as therapeutic agents in photodynamic therapy (PDT),[6] non-linear optical materials[7] and in optical limiting.[8] In contrast with expanded porphyrins, expanded azaporphyrinoids have been hardly explored. Superphthalocyanines represent an exception.[9] In fact, these pentapyrrolic macrocycles were for many years the only reported expanded azaporphyrins.

We have performed different modifications of the tetraazaporphyrin structure in order to obtain other macrocycles structurally related to phthalocyanines and porphyrazines but exhibiting nonconventional physicochemical properties. One of the modifications is the incorporation of one or two 1,2,4-triazole moieties in the tetraazaporphyrin structure to afford cross-conjugated, 20π-electron hemiporphyrazine systems (THpz) with intrinsic ABAB symmetry.[10,11] Moreover, we have designed and reported for the first time the preparation and properties of 18π-electron A_3B-type triazoleazaporphyrin macrocycles. In this case, their aromatic and intrinsically unsymmetrical porphyrazinic character is evidenced by their spectroscopic features.[12]



Scheme 1 Synthesis of the [2 + 4] expanded hemiporphyrazines.

Currently, we are applying the methodology developed for the above intrinsically unsymmetrical azaporphyrins to the synthesis of expanded analogues. We have applied two main strategies based on the use of two azaporphyrin precursors. Hence, 28π-electron hexamers, which are able to accommodate two metal ions within their central cavity, have been obtained stepwise by the dimerization reaction of open trimeric intermediates.[13] Another approach to obtain azaporphyrin analogues other than tetramers relies on the use of 2,5-diamino-1,3,4-thiadiazole.[14] We report here on the synthesis of a new expanded [2 + 4] thiadiazole-derived azaporphyrin hexamer made up of four thiadiazole subunits and two face-to-face pyrrole rings.

Expanded azaporphyrins **1a**,**b** have been obtained in a 40–60% yield by the condensation of thiadiazole derivative **2** with diiminopyrroline or diiminoisoindoline derivatives **3a**,**b**, respectively, in a 2:1 stoichiometric ratio in isopropanol and in the presence of a Cu^{II} salt (Scheme 1).† Under these conditions, the corresponding [3 + 3] macrocycle was also obtained.[14]

The use of Cu^{II} as a template turned out to be essential to obtain [2 + 4] macrocycles **1a**,**b**, whereas other transition metals such as Ni^{II}, Zn^{II} and Co^{II} afforded only the related [3 + 3] macrocycles. Compounds **1a**,**b** were identified based on their spectroscopic characteristics. The MALDI-TOF MS spectra of **1a**,**b** displayed their corresponding molecular ions at *m/z* 1139–1145 and 823–827, respectively (Figure 1). Their UV-VIS spectra showed the lowest energy band appearing at 430–462 nm, indicating the presence of a non-aromatic macrocycle.

The first rationalization of this result seems inconsistent with the proposed structures for **1a**,**b**. As these compounds possess 30π-electrons in their most favourable π-conjugation pathway,

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† A mixture of the corresponding diimine **3** (0.25 mmol), 2,5-diamino-1,3,4-thiadiazole **2** (0.50 mmol) and $Cu(OAc)_2$ (0.30 mmol) was heated in isopropanol (20 ml) at reflux temperature for 24 h. After the solvent was rotary evaporated, the residue was sequentially washed with hexanes, toluene and methanol to give **1a**,**b** in addition to the corresponding [3 + 3] macrocycles.

1a: yield 59% ([3 + 3] compound was obtained in 15% yield). IR (KBr, ν/cm^{-1}): 2950, 2890, 2850, 1580, 1500, 1450, 1410, 1360, 1310, 1270, 1160, 810. UV-VIS ($CHCl_3$, λ_{max}/nm): 381, 462. MS (MALDI-TOF, dithranol), *m/z*: 1139–1145 $[M]^+$.

1b: yield 40% (the corresponding [3 + 3] macrocycle was obtained in 23% yield). IR (KBr, ν/cm^{-1}): 2960, 2920, 2850, 1580, 1510, 1490, 1420, 1390, 1340, 1250, 1200, 1110, 1090, 1040. UV-VIS ($CHCl_3$, λ_{max}/nm): 366, 392, 430. MS (MALDI-TOF, dithranol) *m/z*: 823–829 $[M]^+$.

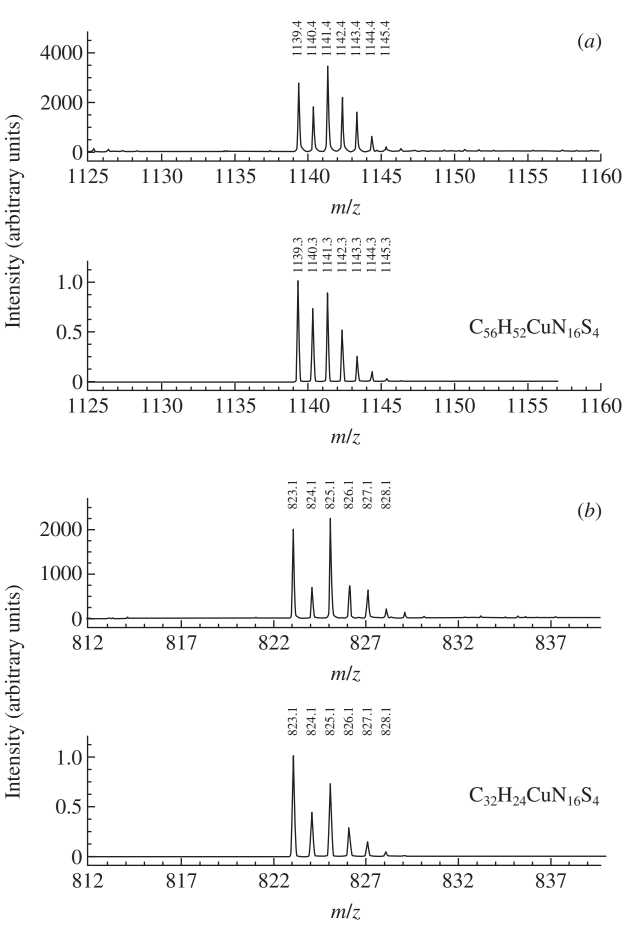
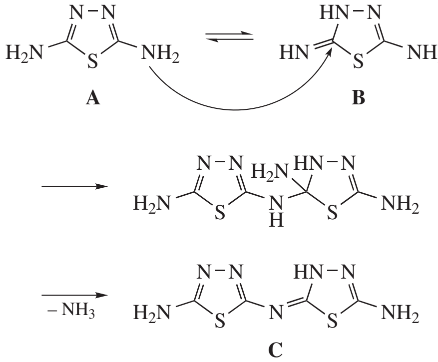


Figure 1 Isotopic patterns of molecular ions corresponding to (*a*) **1a** and (*b*) **1b**.

they should be classified as aromatic according to Hückel [$4n + 2$] rule. Their non-aromatic nature could arise from a strong deviation their planarity, thus preventing the effective delocalization of 30π-electrons. Alternatively, a supposed planar macrocycle **1a**,**b** could maintain the π-electrons localized within the corresponding thiadiazole and pyrroline circuits, respectively, so that each heterocyclic subunit preserves its own aromaticity against the overall delocalization.[15] Thus, aromaticity and anti-aromaticity are more important concepts in small rings than in large ones.[16,17]

The formation of compounds **1a**,**b** implies a condensation between two thiadiazole moieties, one of them as the amino, and the other as the imino tautomer, which can be rationalized by considering the tautomeric equilibrium between **A** and **B** (Scheme 2) and the condensation between the two tautomers to afford the dimeric species **C**. The existence of the imino tautomer in acidic medium has been proven before.[18] Further copper(II) template condensation reaction of dimer **C** with diiminopyrroline or iminoisoindoline, followed by spontaneous oxidation, should lead to isolated azaporphyrins **1a**,**b**.



Scheme 2 Condensation reaction of two thiadiazole subunits.

The role of the Cu^{II} salt is not clear, however its presence is essential for the formation of macrocycles **1a**,**b**. Since the use of other ions (Ni^{II}, Zn^{II} and Co^{II}) did not afford compounds **1**, the coordination sphere of the metal should be a key in the arrangement of macrocycles **1a**,**b**. Furthermore, the presence of the Cu^{II} salt could also shift the equilibrium towards imino thiadiazole form **B** (Scheme 2) in a similar fashion to a protic acid.

In conclusion, we have prepared expanded heteroazaporphyrinoids made up of two face-to-face pyrrole subunits and four thiadiazole rings.

This work was supported by the ESF-SOHYD Programme, COST Action D35, and the EU Project ROBUST DSC, FP7-Energy-2007-1-RTD no. 212792. Financial support by the MEC, Spain (CTQ2008-00418/BQU, CONSOLIDER-INGENIO 2010 CDS 2007-00010, PLE2009-0070, PSE-120000-2009-008 FOTOMOL) and CAM (MADRISOLAR-2, S2009/PPQ/1533) is gratefully acknowledged. M. S. R-M. acknowledges the MEC for a R&C contract.

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Received: 15th March 2010; Com. 10/3489