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An inverted porphyrin with a pendant pyrrole—identification of a tetraphenylsapphyrin isomer in the Rothemund synthesis

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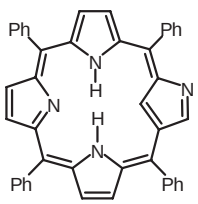
Abstract—2-Aza-3-(2′-pyrrolyl)-5,10,15,20-tetraphenyl-21-carbaporphyrin was identified among the products of a Rothemund synthesis and characterized. An alternative convenient method of its synthesis starting from 2-aza-5,10,15,20-tetraphenyl-21-carbaporphyrin was proposed.

The Rothemund synthesis, i.e. the acid catalyzed condensation of pyrrole and an aryl aldehyde, has long been used as an efficient source of tetraaryl porphyrins. Only recently has it been shown that apart from the porphyrin, other tetra-[1,2] and pentapyrrolic[3] aromatic macrocycles can be isolated from the reaction mixture, although in only minute yields.



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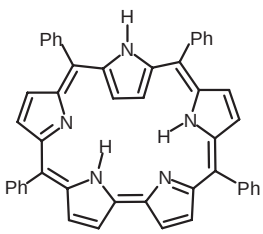
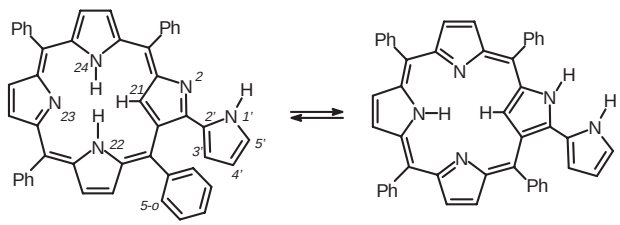


2

The appropriate modifications of conditions can alter the reaction pathway in such a way that one of these compounds, i.e. 2-aza-5,10,15,20-tetraphenyl-21-carbaporphyrin,[4] an inverted porphyrin, an *N*-confused porphyrin **1**, becomes the major product of condensation. On the other hand, the yield of the only pentapyrrolic macrocycle isolated to date from the Rothemund reaction mixture, i.e. tetraphenyl sapphyrin, **2** has never exceeded one percent despite optimization efforts.[5]

Here we report on the isolation, spectroscopic characterization and tautomeric equilibrium of another pentapyrrolic product of the Rothemund condensation, namely 2-aza-3-(2′-pyrrolyl)-5,10,15,20-tetraphenyl-21-carbaporphyrin **3**, which, being an isomer of **2**, belongs to the newly emerging class of macrocycles identified by the presence of a CH motif in the inner macrocyclic perimeter.



3 3a

Scheme 1.

Compound **3** has been identified among the products of the condensation that had been carried out according to the Lindsey protocol, although with an excess of pyrrole with respect to benzaldehyde. In a typical synthesis, condensation was carried out in degassed dichloromethane with a pyrrole/benzaldehyde molar ratio of 1.5:1 and with pyrrole and BF_3 etherate concentrations of 80 and 0.8 mM, respectively. After 1 h of stirring at room temperature, *p*-chloranil (20 mM) was added and the reaction mixture was refluxed for 1 h. Chromatographic work-up and precipitation with hexane gave a red–brown powder of **3** (yield 1.5%).[6] Faster moving bands contained mainly tetraphenylporphyrin (ca. 10%), **1** (5%) and **2** (ca. 1%). It seems that application of an excess of pyrrole is crucial for the formation

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of **3** since no traces of this compound have been observed when stoichiometric ratios of pyrrole and benzaldehyde were used.

The ^{1}H NMR spectrum of **3** (Fig. 1) shows a pattern typical of inverted porphyrins[1] with three upfield signals (21-CH, 22-NH, 24-NH) and three low-field AB systems assigned to the β protons of the three pyrrole rings. The most diagnostic spectral features of the compound comprise a relatively broad low-field NH peak and three signals in the region of 5.5–7 ppm assigned to the protons of extraneous pyrrole based on 2D COSY and NOESY techniques. The *ortho* protons of the *meso*-phenyl in position 5 are represented by only one ^{1}H NMR signal in the temperature range 213–293 K showing their magnetic equivalence. The degeneration of the phenyl protons indicates either a planar conformation of the pentapyrrolic system or porphyrin ring interconversion that is fast in the NMR time scale. Another dynamic factor leading to the averaging of chemical shifts of the *ortho* protons in non-planar porphyrin systems, i.e. rapid rotation of 5-phenyl, can be excluded in this case considering the steric overcrowding caused by closeness of the extraneous pyrrole. The effective planar conformation of the system can be combined with the internal hydrogen bond formation between the nitrogen atoms of the bipyrrolic fragment. The low-field position of the 1′-NH signal (about 10 ppm) supports formation of such a bond since the corresponding signal of free pyrrole appears at 7.70 ppm. The contribution from the porphyrin ring current on the low-field shift of this proton can be neglected because there is no analogous downfield shift observed for other protons of the pendant pyrrole.

The electronic spectrum of **3** in dichloromethane shows features typical of tetraphenyl sapphyrin[3] rather than an inverted porphyrin,[1] which include relatively broad bands located near 500 and 800 nm (Fig. 2). A similar spectrum is observed for a pyridine solution, but it

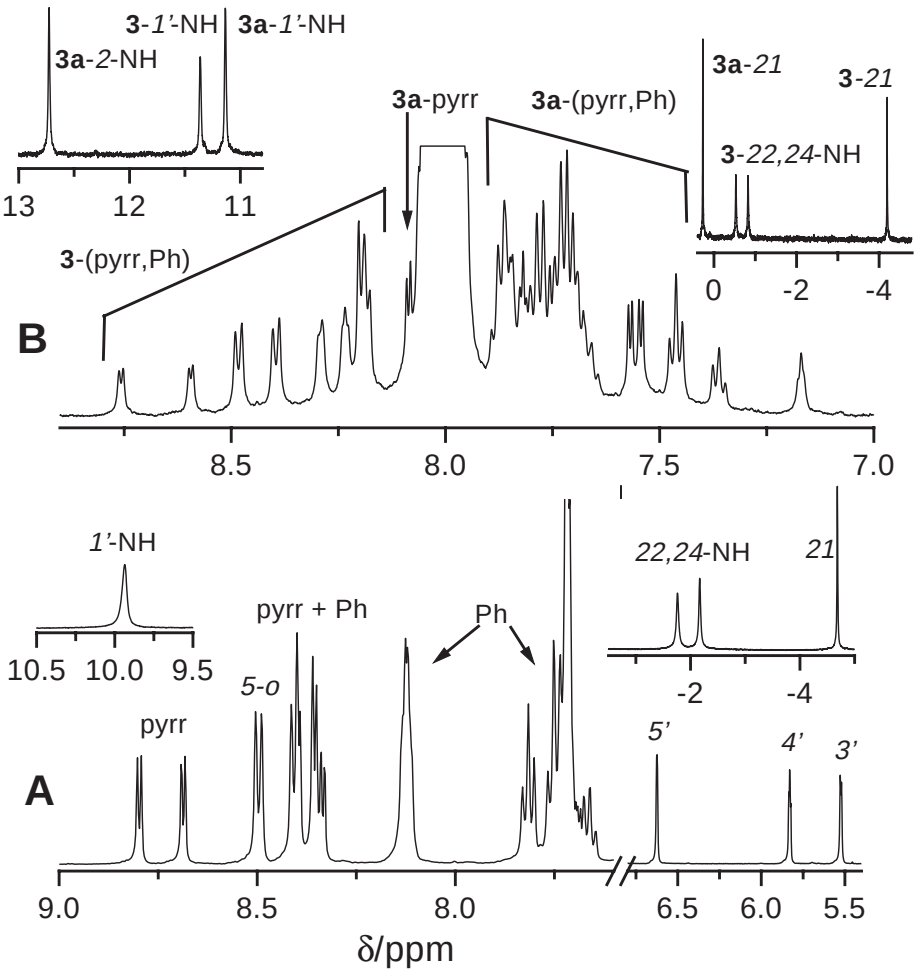


Figure 1. 500 MHz ^{1}H NMR spectrum of **3**: (A) pyrrole and phenyl part of the spectrum of **3** at 293 K in $CDCl_3$, insets show low- and high-field parts of the spectrum taken at 223 K in $CDCl_3$; (B) central part and low- and high-field parts (insets) of the spectrum at 253 K in DMF-d_7. Assignments: pyrr-β-pyrrole protons of porphyrin ring, Ph-*meso*-aryl protons. The other labels follow those of Scheme 1.

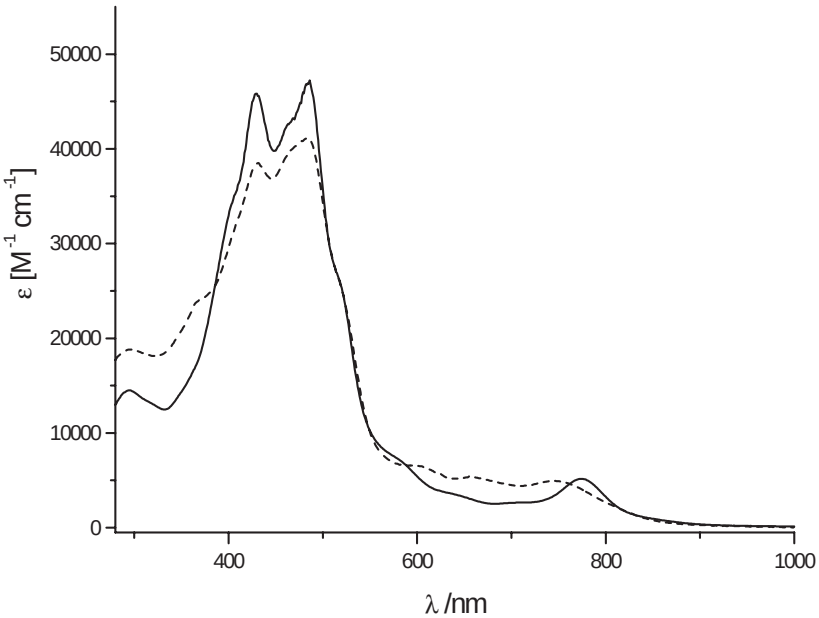


Figure 2. Electronic spectra of **3** in dichloromethane (solid line) and in DMF (dashed line).

differs in DMF. This alteration is due to an equilibrium between tautomers (Scheme 1). Similar tautomeric equilibria have been observed in polar solvents for **1** and inverted thia- and selenaporphyrins.[7]

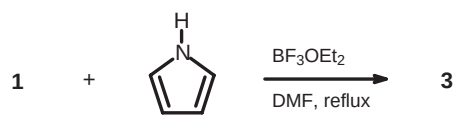
^{1}H NMR in DMF-d_7 confirms formation of **3a** (the **3**:**3a** molar ratio is about 1:1 at 293 K) showing an additional set of signals for which the most characteristic is the one at 12.73 ppm (253 K) assigned to the 2-NH being spin–spin coupled to the 21-CH proton at 0.27 ppm (Fig. 1(B)). We found about 90% equilibrium shift to the right at 293 K in the case of **1** based on ^{1}H NMR measurements in DMF-d_7. Likely, the hydrogen bond between the 1′ and 2 nitrogen atoms disfavors proton transfer from the inner to the outer perimeter of the inverted porphyrin ring in **3**.

As in the case of **1**,[1a] protonation of **3** with strong acids proceeds in two steps giving (**3**-H)$^+$ with the proton attached to the position 2 and (**3**-H_2)$^{2+}$ with all nitrogen atoms protonated.

The very limited effectiveness of the Rothemund synthesis with respect to **3** prompted us to look for an alternative synthetic path since this compound seems to be a very interesting macrocyclic/chelating ligand for coordination of transition metal ions. We found that **3** can be more effectively obtained from a reaction of inverted porphyrin **1** (50 mg, 0.08 mM) with a five-fold excess of pyrrole in refluxing DMF (20 ml) containing a catalytic amount of acid (0.01 mM BF_3OEt_2). No additional oxidant is required if the reaction is conducted in the presence of air. The full conversion of the porphyrin was observed after 1 h. The yield after basic alumina column chromatography (elution with CH_2Cl_2) and hexane crystallization is 60%. Since **1** is now readily obtainable even on a gram scale[4] the procedure described is a promising synthetic method for **3** (Scheme 2).

The reaction proceeds in DMF but not in chloroform, dichloromethane, toluene or benzonitrile. Thus, during the Rothemund condensation carried out in CH_2Cl_2, the macrocycle-pyrrole link must be formed prior to oxidation of the inverted porphyrinogen. A pentapyrrolic species containing a direct pyrrole–pyrrole bond may be a 'linear' precursor of **2**, **3** or **1** depending on the way in which ring closure is accomplished. In the latter case, however, a dissociation of the bipyrrolic fragment is necessary after macrocyclic ring closure but prior to oxidation.

In conclusion, we have shown formation of a new pentapyrrolic, aromatic product in the Rothemund synthesis. The internal and external donor systems of **3** make it attractive as a potentially bifunctional ligand possessing macrocyclic and chelating or hydrogen-bonding properties. The new type of reactivity of inverted pyrrole of the *N*-confused porphyrin is noteworthy.



Scheme 2.

Acknowledgements

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6. *Selected data for* **3**: λ_{max} (CH_2Cl_2)/nm (log ε) 294 (4.16), 405 sh, 430 (4.66), 463 sh, 485 (4.67), 519 sh, 582 sh, 642 sh, 773 (3.71); δ_H ($CDCl_3$, 293 K) 9.64 (1H, b, 1′-NH), 8.80 (1H, d, J_{AB}=4.88 Hz), 8.69 (1H, d, J_{AB}=4.88 Hz), 8.49 (2H, m, Hz, 5-*o*), 8.40 (2H, m), 8.39 (1H, d, J_{AB}=4.6 Hz), 8.36 (1H, d, J_{AB}=4.6 Hz), 8.35 (1H, d, J_{AB}=4.9 Hz), 8.33 (1H, d, J_{AB}=4.9 Hz), 8.12 (4H, m), 7.81 (2H, m), 7.72 (10H, multiplets), 6.62 (1H, dd, ^3J=3.5 Hz, ^4J=1.2 Hz, 5′), 5.83 (1H, dd, ^3J=3.5 Hz, ^3J=4.0 Hz, 4′), 5.55 (1H, dd, ^4J=1.2 Hz, ^3J=4.0 Hz, 3′), −1.46 (1H, b, NH), −1.90 (1H, b, NH), −4.52 (1H, s, 21); HRMS: calcd for $C_{48}H_{33}N_5$+H: 680.2809. Found: 680.2675.
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