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Application of 2-ethylpyrrole for a direct synthesis of 3-substituted inverted porphyrins

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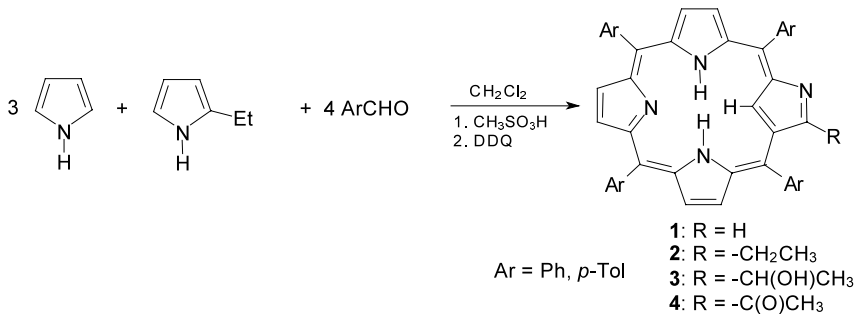
Abstract—3-Ethyl-5,10,15,20-tetraphenyl-2-aza-21-carbaporphyrin is the major macrocyclic product in the condensation of 2-ethylpyrrole, pyrrole, and benzaldehyde. Oxidation of the ethyl substituent leads to 3-(1′-hydroxyethyl)- and 3-acetyl-substituted inverted porphyrins.

Porphyrins, as well as their contracted or expanded analogues, attract much attention due to the interest of annulenic chemistry and many potential applications in coordination chemistry, catalysis, photochemistry, medicine etc.[1] The macrocycles identified by the presence of a CH motif in the inner macrocyclic perimeter constitute a special class of aromatic, porphyrin-related compounds. Among them are the carbaporphyrins with one[2] or two[3] pyrrole rings replaced by an all-carbon ring(s), so-called inverted or *N*-confused porphyrins that are isomers of porphyrins,[4,5] doubly *N*-confused porphyrins[6] and isomers of oxa-, thia-, and selenaporphyrins.[7] Owing to the inner core carbon and the outward pointing nitrogen the inverted porphyrins are particularly interesting as macrocyclic ligands having an additional external functionality that can act as a protonation/coordination site.

Recently, we have introduced an *N*-confused porphyrin with a pyrrolic moiety appended to the inverted pyrrole in its α-position that participates in the ring closure upon the formation of a regular porphyrinogen[8] in the Rothemund synthesis, i.e. the acid catalyzed condensation of pyrrole and arylaldehyde. In order to evaluate the influence of α-substitution on the formation of inverted porphyrins we have decided to use 2-ethylpyrrole as one of the building blocks of the porphyrin ring.

A typical reaction was carried out according to the Lindsey protocol[4d] i.e. in dichloromethane solution with stoichiometric ratios of components. Pyrrole (6 mM), 2-ethylpyrrole (2 mM), and benzaldehyde or *p*-tolylaldehyde (8 mM) with methanesulfonic acid (8 mM) as a catalyst were brought together in deaerated CH_2Cl_2 and mixed in darkness for 0.5 h (Scheme 1). After oxidation with DDQ (8 mM) the reaction yields the corresponding tetraarylporphyrin (2%), inverted porphyrin **1** (5%), and 3-ethyl-5,10,15,20-tetraaryl-2-aza-21-carbaporphyrin **2** (10%).[9]



Scheme 1.

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The attempts to isolate the 3-ethyl-substituted inverted porphyrin **2** by means of alumina or silica-gel column chromatography resulted in the formation of new products containing a 3-substituted inverted pyrrole. One of them was formulated as 3-(1′-hydroxyethyl)-5,10,15,20-tetraphenyl-2-aza-21-carbaporphyrin **3** (yield 8%).[10] Its molecular mass clearly shows the presence of an oxygen atom in addition to the ethyl group. Apparently, the oxygenation of the α-carbon of the 3-ethyl substituent is facilitated by the vicinity of the imine-like moiety of the inverted porphyrin. This finding is surprising considering that no such reactivity was reported for heptaalkyl inverted porphyrins.[5]

The most diagnostic feature in the ^{1}H NMR spectrum of **3** is a complex signal at 4.84 ppm ($CDCl_3$, 298 K) that resolves at 233 K (Fig. 1A) into a doublet (5.08 ppm) and a quasi-quintet (4.86 ppm). These signals are scalar coupled. The former disappears after shaking the sample with D_2O and thus is assigned to an OH, while the latter correlates with the doublet at 0.69 ppm in the COSY map. The three types of proton were assigned to the 1′-hydroxyethyl group. In a ^{13}C, ^{1}H HMBC spectrum all three are coupled with a carbon signal at 165.8 ppm that is assigned to the quaternary carbon in the position 3 of the porphyrin skeleton i.e. in the vicinity of the external nitrogen. The proton in position 21, i.e. the internal CH of the inverted pyrrole, which is distinguished by its high-field signal in the ^{1}H NMR spectrum (–4.96 ppm, $CDCl_3$, 233 K), also correlates with the signal of carbon 3 in the long-range heteronuclear correlation experiment. The optical spectrum of **3** in dichloromethane is similar to that of **1**[4a] with Soret and Q-bands only slightly shifted to the longer wavelengths (4–7 nm).

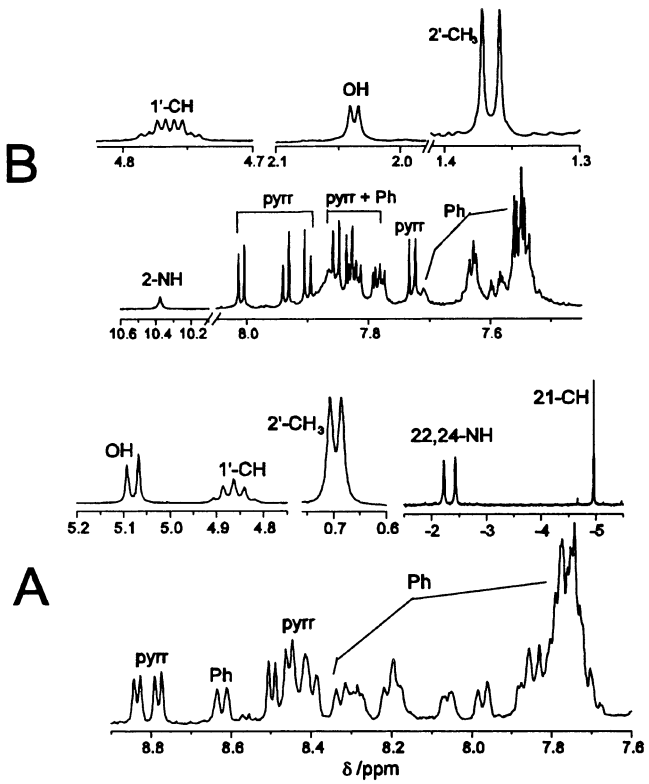
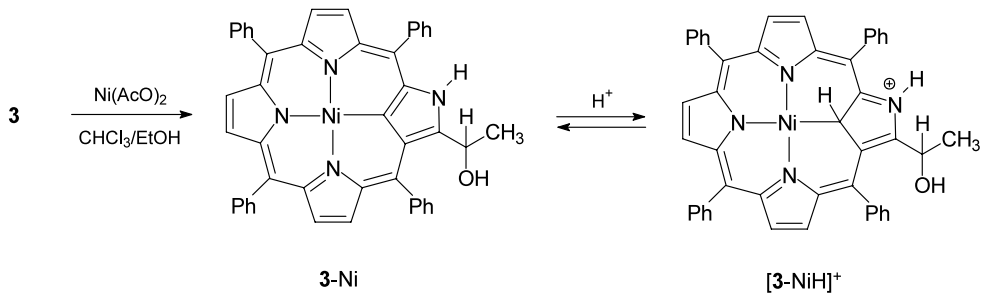


Figure 1. 500 MHz ^{1}H NMR spectra of **3** (trace A, $CDCl_3$, 233 K) and **3**-Ni (trace B, $CDCl_3$, 298 K). Assignments: pyrr–β-pyrrole protons, Ph–*meso*-phenyl protons. The other labels follow systematic numbering.

Protonation of **3** proceeds in two steps. The ^{1}H NMR titration with trifluoroacetic acid (TFA) at 223 K reveals the formation of a monocation at low TFA:**3** molar ratios (up to 1:1.2) with a proton attached to the outer nitrogen giving a signal at 14.52 ppm. The other signals are only slightly shifted with respect to those observed for the free base. At higher acid concentrations (from 2:1) the presence of two dicationic forms has been detected. They are best indicated by two well-separated sets of 21-CH and 2-NH signals: –1.15, 11.54 and –1.85, 10.88 ppm. The relative intensities of the sets vary with the concentration of acid. We attributed the presence of more than one form of the dication to the formation of a tight ion pair with a trifluoroacetate anion. Such a complex was observed previously for the *N*-methylated inverted porphyrin[11] but not for **1**.[4a]

Insertion of a nickel(II) ion into **3** was performed under mild conditions by refluxing its chloroform solution with ethanolic nickel(II) acetate (5-fold excess) for 1 h (Scheme 2). The resulting diamagnetic organometallic complex **3**-Ni[12] was purified by means of a silica column and crystallized from a dichloromethane/hexane mixture (yield 60%). As in the case of **1**[4a] or heptaalkyl *N*-confused porphyrins[5] the insertion reaction is combined with a proton abstraction from the 21-C and concurrent protonation of the external nitrogen. The ^{1}H NMR supports such a structure since the high-field signals of the inner protons disappear whilst a relatively broad peak attributed to 2-NH appears in



Scheme 2.

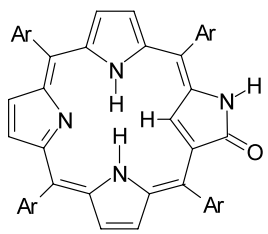
the low-field part of the proton spectrum (Fig. 1B). There is also significant alteration in the position of the OH signal which is shifted about 3 ppm upfield with respect to its position in **3**. Such a difference indicates in the nickel complex the lack of an internal hydrogen bond, which is present in the free base possessing unprotonated nitrogen that serves as an acceptor. The change in a spin–spin interaction of the 1′-CH and OH protons is reflected by significant lowering of their coupling constant upon metal coordination (6.7 Hz in **3** and 3.3 Hz in **3**-Ni), while J values for 1′-CH-2′-CH_3 coupling are similar in both cases (6.0 and 6.4 Hz, respectively).

The ^{1}H NMR-controlled titration of the **3**-Ni solution in $CDCl_3$ with TFA at 233 K allows observation of the protonation of the coordinating internal carbon atom (Scheme 2). Similar phenomena were reported for nickel(II) complexes of heptaalkyl *N*-confused porphyrins[5] and for nickel(II) and copper(II) complexes of **1** and its *N*-methylated analogue.[13] The most diagnostic spectral feature of such a protonation is a signal at −3 ppm that correlates in the ^{1}H, ^{13}C HMQC map with a signal at 36 ppm, i.e. in the region typical for aliphatic carbons. It is accompanied with a low-field shift of the 2-NH signal to 14.2 ppm. The environment of 21-C becomes pyramidal and asymmetric, thus, considering the asymmetry of 1′, one can expect the observation of diastereoisomers in the ^{1}H NMR spectrum of [**3**-NiH]$^+$. However, and probably due to the fast chemical exchange, only one form of the cationic complex can be observed in chloroform solution down to a temperature of 213 K. On the other hand, for a CD_2Cl_2 solution both the 21-CH and 2-NH signals broaden markedly on going from 213 to 183 K. Further careful lowering of the temperature causes splitting of both signals, each into two peaks of equal intensity (171 K), that can be accounted for by slowing down of the exchange rate and differentiation of the signals of the diastereoisomers. Alternatively, tight ion-pair formation with the trifluoroacetate anion can be proposed. Such an anion complexation even at room temperature was reported for the cations of nickel(II) complexes of hexa- and heptaalkyl inverted porphyrin.[5]

In the course of purification of **3** we have observed its gradual transformation into another inverted porphyrin that no longer contained the signal of the hydroxyethyl group in the ^{1}H NMR spectrum. The molecular mass of this system is lower by two units than that of **3**. The electronic spectrum is markedly altered with first Q-band red shifted by 30 nm. Apparently, autooxidation leads to the dehydrogenation of **3** with the concurrent formation of 3-acetyl-5,10,15,20-tetraphenyl-2-aza-21-carbaporphyrin **4**.[14] The conversion of **3** into **4** can also be accomplished with a variety of oxidants e.g. pyridinium dichromate (60% conversion after 24 h stirring in chloroform). We have also performed the reverse reaction reducing **4** by shaking its chloroform solution with aqueous sodium hyposulfite.

The ^{1}H NMR spectrum of **4** preserves the features of an inverted porphyrin with the 21-CH signal at −4.58 ppm ($CDCl_3$, 233 K), two high-field NH signals and the three AB systems of the β-pyrrole protons. The intense singlet at 2.74 ppm is attributed to the methyl group of the acetyl substituent in the position 3. It correlates with an aliphatic carbon signal at 29.1 ppm in the ^{13}C, ^{1}H HMQC spectrum as well as with a typical ketone carbon signal at 201.5 ppm and with a signal at 158.3 ppm, assigned to 3-C of the porphyrin skeleton, in the HMBC map.

There is yet another macrocyclic product that can be separated from the reaction mixture (1–2%). The molecular mass of this macrocycle is higher by 16 units than that of the unsubstituted inverted porphyrin **1**. A high-field doublet of 21-CH at −5.39 ppm in the ^{1}H NMR spectrum ($CDCl_3$, 298 K) indicates the aromatic character of this macrocycle. Significantly, there is a relatively broad signal at 8.50 ppm that disappears after addition of D_2O. These protons are spin–spin coupled ($J=1.2$ Hz) thus both are placed on the inverted pyrrole. Proton 21 correlates in HMBC with a carbon nucleus at 168.5 ppm that is in the region typical for amide carbons. There is no proton signal that can be attributed to 3-CH. These data allow the formulation of this compound as 3-oxo-5,10,15,20-tetraphenyl-2-aza-21-carbachlorin, **5**[15]—an inverted porphyrin that contains a lactam functionality. The formation of **5** may be combined with oxidative dealkylation/deacylation of inverted pyrroles **2**, **3** or **4**. However, we have observed traces of this macrocycle among the products of many Rothemund syntheses that did not involve a substituted pyrrole. Introduction of the carbonyl group on the perimeter of aromatic macrocycles was observed in the case of the inverted thiaporphyrin[7d] for which oxygenation occurred in the vicinity of the sulfur atom of the *S*-confused thiophene.



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In conclusion, we have shown the formation of an inverted porphyrin that contains an alkyl group introduced as an α-substituent by a pyrrole subunit. In a stochastic condensation reaction of the substituted and unsubstituted pyrroles with arylaldehyde catalyzed with methanesulfonic acid the most populated macrocycle is that bearing an alkyl group. The stepwise autooxidation of this substituent leads to inverted porphyrins containing functional groups in the vicinity of the outer nitrogen atom. This makes the systems versatile macrocyclic ligands with additional chelating/hydrogen bonding sites.

Acknowledgements

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9. Flash chromatography of the crude reaction mixture on a low-activity neutral alumina column gave a mixture of 1 and 2 in an approximate 1:2 molar ratio, as estimated on the basis of ^{1}H NMR spectra. Selected data for **2**: δ_H (500 MHz, $CDCl_3$, 293 K) 8.75 (1H, d, $J=4.6$ Hz), 8.73 (1H, d, $J=4.7$ Hz), 8.45 (1H, d, $J=4.6$ Hz), 8.39 (3H, overlapping doublets), 8.27 (2H, d, $J=7.7$ Hz), 8.15 (2H, d, $J=7.8$ Hz), 7.99 (4H, m), 7.60 (6H, m), 7.53 (6H, m), 2.4 (2H, q, $J=7.4$ Hz, 1′), 0.93 (3H, t, $J=7.4$ Hz, 2′), −2.08 (2H, b, 22, 24-NH), −4.90 (1H, s, 21); MS (ESI): calcd for $C_{46}H_{35}N_4$ ($[M+1]^+$): 644. Found: 643.6.
10. Selected data for **3**: λ_{max} (CH_2Cl_2)/nm 405 sh, 445, 510 sh, 546, 592, 736; δ_H (500 MHz, $CDCl_3$, 293 K) 8.83 (1H, d, $J=4.8$ Hz), 8.75 (1H, d, $J=4.8$ Hz), 8.49 (1H, d, $J=4.8$ Hz), 8.48 (1H, d, $J=4.8$ Hz), 8.45 (1H, d, $J=4.8$ Hz), 8.44 (1H, d, $J=4.8$ Hz), 8.30 (5H, m, b), 8.15 (1H, m, b), 8.05 (1H, m), 8.02 (1H, m), 7.78–7.73 (12H, overlapping multiplets), 4.84 (2H, m, $J=6.7$ Hz, OH+1′), 0.79 (3H, d, $J=6.0$ Hz, 2′), −2.09 (1H, b, NH), −2.21 (1H, b, NH), −4.86 (1H, s, 21); HRMS: calcd for $C_{46}H_{35}N_4O$ ($[M+1]^+$): 659.2805. Found: 659.2823.
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12. Selected data for **3**-Ni: λ_{max} (CH_2Cl_2)/nm 363, 430, 458 sh, 552, 589 sh, 711, 779; δ_H (500 MHz, $CDCl_3$, 293 K) 10.38 (1H, b, 2-NH), 8.01 (1H, d, $J=5.0$ Hz), 7.93 (1H, d, $J=5.2$ Hz), 7.90 (1H, d, $J=5.0$ Hz), 7.87 (2H, b), 7.85 (1H, d, $J=5.2$ Hz), 7.83 (1H, d, $J=5.2$ Hz), 7.82 (2H, m), 7.78 (2H, m), 7.73 (1H, d, $J=5.2$ Hz), 7.63 (2H, m), 7.60–7.54 (12H, overlapping multiplets), 4.76 (1H, dd, $^3J_1=6.4$ Hz, $^3J_2=3.3$ Hz, 1′), 2.04 (1H, d, $J=3.3$ Hz, OH), 1.36 (3H, d, $J=6.4$ Hz, 2′); HRMS: calcd for $C_{46}H_{32}N_4ONi$ ($[M]^+$): 714.1924. Found: 714.1983.
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14. Selected data for **4**: λ_{max} (CH_2Cl_2)/nm 410 sh, 453, 520 sh, 552, 598, 766; δ_H (500 MHz, $CDCl_3$, 293 K) 8.94 (1H, d, $J=5.0$ Hz), 8.86 (1H, d, $J=4.8$ Hz), 8.43 (4H, overlapping doublets), 8.33 (4H, dd, $^3J=6.3$ Hz, $^4J=1.0$ Hz), 8.12 (4H, overlapping multiplets), 7.85–7.67 (12H, overlapping multiplets), 2.70 (3H, s, 2′), −1.71 (1H, b, NH), −1.93 (1H, b, NH), −4.58 (1H, s, 21), HRMS: calcd for $C_{46}H_{33}N_4O$ ($[M+1]^+$): 657.2649. Found: 657.2619.
15. Selected data for **5**: λ_{max} (CH_2Cl_2)/nm 410 sh, 443, 537, 581, 635, 700, 785(sh); δ_H (500 MHz, $CDCl_3$, 293 K) 8.70 (1H, d, $J=4.6$ Hz), 8.60 (1H, d, $J=4.6$ Hz), 8.56 (4H, overlapping doublets), 8.50 (1H, b, 2-NH), 8.19 (4H, dd, $J=7.8$ Hz), 8.13 (4H, dd, $J=6.5$ Hz), 7.80–7.71 (12H, overlapping multiplets), −2.58 (1H, b, NH), −2.82 (1H, b, NH), −5.39 (1H, d, $J=1.1$ Hz, 21); HRMS: calcd for $C_{44}H_{31}N_4O$ [$(M+1]^+$): 631.2492. Found: 631.2473.