A versatile building block for pyrazole–pyrrole hybrid macrocycles†

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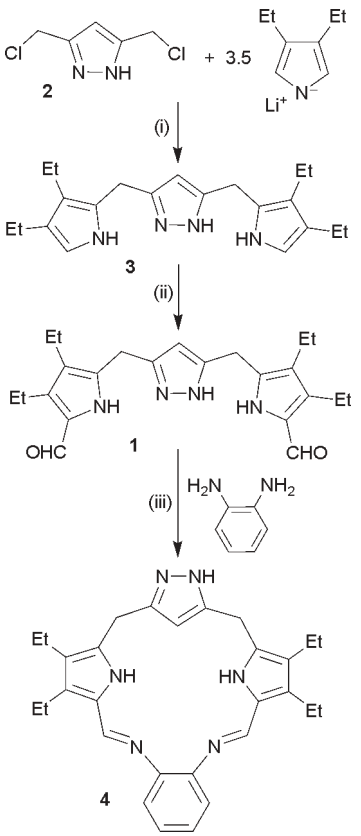
This contribution describes the synthesis of a novel pyrazole–pyrrole building block and its use in the formation of a non-aromatic, Schiff base-type macrocycle incorporating a chromophore and H-bonding donor and acceptor functionalities inside and outside of the macrocycle, which makes it predestined for molecular recognition systems.

The development of oligopyrrolic macrocycles that can be used as ligands for metals, hosts for molecular recognition, or as chromophores has aroused enormous interest in the past decades.[1] In particular, a number of oligopyrrolic non-aromatic and aromatic macrocycles containing imine linkages have been designed and studied.[2] Representative for the latter class, customarily referred to as expanded porphyrins, are the texaphyrins, porphocyanines, and other examples.[3,4] Non-aromatic oligopyrrolic, imine-based macrocycles have been prepared already some time ago, prominent among them the accordion porphyrins,[5] and were recently featured by Sessler, Love and others.[6,7] The bulk of these and related macrocycles contain pyrrole moieties though macrocycles incorporating other heterocycle moieties have also become known.[1]

It has been amply demonstrated that pyrazole moieties are versatile bridging ligands in dinuclear metal assemblies.[8,9] Further, pyrazoles combine H-bond donor and acceptor capabilities in the same functionality. This aspect makes them particularly interesting for the design of molecular recognition systems for carboxyl groups when incorporated, for instance, into polyamine macrocycles.[10]

The absence of pyrazole-containing pyrrolic macrocycles may be, in part, due to the absence of suitable pyrazole-based building blocks. We will introduce here the synthesis of a novel pyrazole–pyrrole building block and its application in the synthesis of a prototype pyrazole–pyrrole-containing macrocycle that can be regarded as the pyrazole-analogue to texaphyrinogen. We will further demonstrate by single-crystal diffractometry and UV-vis spectroscopy the potential utility of this macrocycle in molecular recognition events.

The key building block **1**, a diformylated 3,5-bis(pyrrol-2-ylmethyl)pyrazole, was synthesized in a two-step procedure in overall satisfying yields (Scheme 1). Nucleophilic substitution of 3,5-bis(chloromethyl)-1*H*-pyrazole (**2**)[11] with 4.0 eq. of the Li-salt of 3,4-diethylpyrrole,[12] generated the novel 3,5-bis(pyrrol-2-ylmethyl)pyrazole **3** in 90% isolated yield. Just as its pyrrole-only analogues, the tripyrranes, dipyrrolylpyrazole **3** is of limited stability and is not easily purified.[13] However, Vilsmeier–Haack-type formylation of **3** generates the stable and solid bisaldehyde **1** in up to 88% yield (at a 1.0 mmol scale). Both novel compounds **1** and **3** posses all the expected spectroscopic and analytical properties to confirm their structures (see ESI†).



Scheme 1 *Reaction conditions*: (i) CH_2Cl_2 (dry), −78 °C, 24 h; (ii) 10 eq. DMF (dry), 8 eq. benzoyl chloride, 0 °C 2 h, r.t. 4 h, followed by hydrolysis; (iii) 40 eq. TFA, N_2-atm., reflux, 20 h.

Oligopyrrolic bisaldehydes are building blocks of wide utility in cyclocondensation reactions using a range of nucleophiles, in particular diamines to form imine linkages.[3–7] Thus, acid-catalyzed reaction of **1** with 1,2-phenylenediamine produces a yellow compound in yields up to 90% (at a 0.5 mmol scale). Its composition, as ascertained by high resolution (+)ESI-MS, was determined to be $C_{29}H_{35}N_6$, as expected for the (monoprotonated) reaction product of the 1 : 1 condensation product of **4** with phenylenediamine. The ^1H and ^{13}C NMR spectra of compound **4**

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† Electronic supplementary information (ESI) available: Preparation, spectral and analytical data for **1**, **3** and **4**. Further views of the molecular structures of **4**·2EtOH and $[\mathbf{4}H]^+\cdot(CF_3CO_2^-)\cdot H_2O$. See DOI: 10.1039/b614049a

demonstrate its twofold symmetry. The presence of diagnostic signals for an imine functionality (at 8.15 and 146.1 ppm, respectively; sharp imine band at 1614 cm^{-1} in the IR spectrum), the phenylene protons (singlet at 7.17 ppm) and the 4-position of the 3,5-disubstituted pyrazole moiety (at 5.67 ppm) further suggest the formation of a macrocycle. Both pyrazole and pyrrole NH protons are substantially broadened in the ^1H NMR spectrum (in $CDCl_3$), indicative of their involvement in intra- or inter-molecular H-bonds. In addition, methylene protons at 3.88 ppm show that the macrocycle does not contain a fully conjugated π-system. Accordingly, the yellow color (λ_{max} = 332 nm) of low absorptivity (log ε_{332} = 4.37) and the characteristics of the UV-vis spectrum are not at all porphyrin-like (broad band around 350 nm, no discernable Q-bands; Fig. 1). All these, and other, spectroscopic data identify this compound as the Schiff base macrocycle **4** (Scheme 1), see ESI.† The structure of **4** is ultimately confirmed by single-crystal X-ray structure analysis (see below).‡

Macrocycle **4** is the pyrazole analogue to the macrocyclic, non-aromatic precursors of texaphyrins, the texaphyrinogens.[3] Though in contrast to the latter, **4** has resisted our attempts towards oxidation to a fully aromatic system (using DDQ, *p*-chloranil, $BaMnO_4$ or MnO_2, in the absence or presence of a range of transition metal ions and/or bases) to date. Pyrazole derivatives, owing to the presence of two electronegative nitrogens in the macrocycle, are known to be much less reactive than pyrroles toward electrophilic attacks and oxidations.[14] Considering further the reported difficulties of oxidizing texaphyrinogen to the fully aromatic analogue, this finding is not altogether surprising.[3c] A pronounced basicity of **4** was noted, hence isolation and purification of **4** necessitated basic alumina to generate free base **4**.

Fig. 2 shows the molecular structure of free base **4**·2EtOH as determined by X-ray diffractometry of a crystal of **4** grown from a saturated EtOH solution. The macrocycle assumes a non-planar, bowl-shape conformation. While the imine functionalities and the two sp^2 carbon-linked pyrrole moieties are each idealized co-planar, the angle between the mean planes of the pyrrole moieties and the phenylene ring is 41°. The sp^3 carbon-linked pyrazole ring is slanted by about 80° with respect to the phenylene plane. Interestingly, the nitrogen atoms of the pyrazole ring are positioned outside of the macrocycle cavity, which was also shown in molecular modelling studies to be the prevalent conformation in

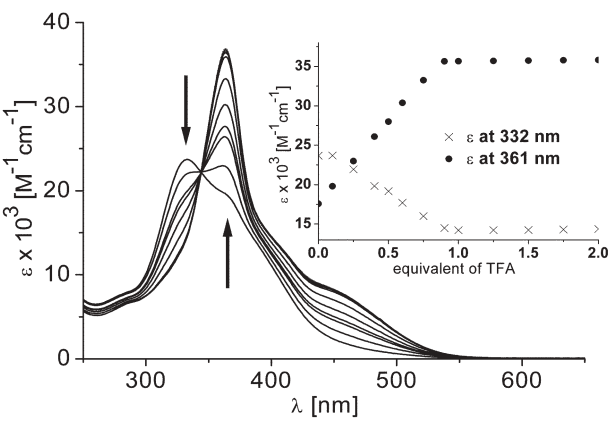

Fig. 1 UV-vis spectrophotometric titration of a $CHCl_3$ solution of **4** (4.2×10^{-5} M) with 0 to 2 eq. TFA, isosbestic point at 344 nm.

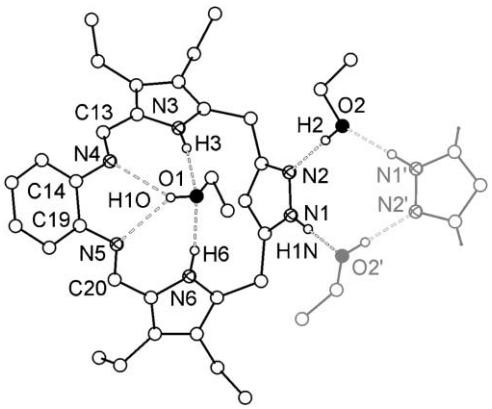

Fig. 2 Solid-state structure of **4**·2EtOH as determined by single-crystal X-ray diffraction analysis. All hydrogen atoms not involved in hydrogen bonding and the disorder of the C_2H_5 group have been omitted for clarity. Selected atom distances (Å) and angles (°): N3···O1 2.906(2), O1···N4 2.962(2), O1···N5 2.934(2), O1–H1O 0.82(3), N6···O1 2.920(2), N1···O2′ 2.783(2), N1–H1N 0.92(3), O2···N2 2.778(2), O2–H2 0.87(3), N4–C13 1.283(3), N5–C19 1.416(3); N3–H3···O1 172(3), O1–H1O···N4 143(3), O1–H1O···N5 141(3), N6–H6···O1 171(2), N1–H1N···O2′ 179(2), O2–H2···N2 179(3). Symmetry transformation used to generate equivalent atoms (′): $-x$, y, $0.5 - z$.

pyrazole-based polyamine macrocycles.[5b] The pyrazole nitrogens are thus not engaged in intramolecular H-bonding but they give rise to intermolecular H-bonds to two molecules of EtOH, whereby one nitrogen acts as H-bond donor, the other as acceptor. These co-crystallized solvents act as bridges between two neighbouring macrocycles that display their pyrazole nitrogens in a complementary fashion toward each other. One more (disordered) EtOH molecule is found H-bonded in a four point arrangement to both imine nitrogens and both pyrrole NH protons. Evidently, the cavity of **4** is well suited to accommodate ROH guests through its combined H-bond donor/acceptor arrangement.

A photometric titration of **4** with TFA results in the formation of a new, mono-protonated species displaying a bathochromically shifted UV-vis spectrum (Fig. 1). Presumably, only one of the two imine nitrogens is protonated, even in the presence of excess TFA (up to four equivalents). Accordingly, **4** in the presence of TFA loses its twofold ^1H NMR symmetry. For example, the phenylene signals (at 7.17 ppm) split into two doublets of doublets, and a new signal at 11.15 ppm (protonated imine) was observed.

The inferred site of protonation was confirmed by single-crystal X-ray crystallography, shown in Fig. 3. Upon protonation, the phenylene–imine–pyrrole portion of the macrocycle now takes up a more planar conformation, reducing the angle between the mean planes of the pyrrole moieties and the phenylene ring to 18°. The pyrazole moiety assumes essentially the same conformation as in the free base form, albeit the ring is only slanted about 65° in relationship to the phenylene plane. The planarization – with, presumably, concomitant rigidification – of the chromophore is also seen in its sharpened and increased UV-vis absorption (Fig. 1).

These changes are brought about by protonation of a single imine moiety, thus also altering the intramolecular H-bond pattern. The protonated imine functionality switched from being a H-bond acceptor in free base **4** to a H-bond donor bonded to, in this case, a molecule of a three-point bound trifluoroacetate that

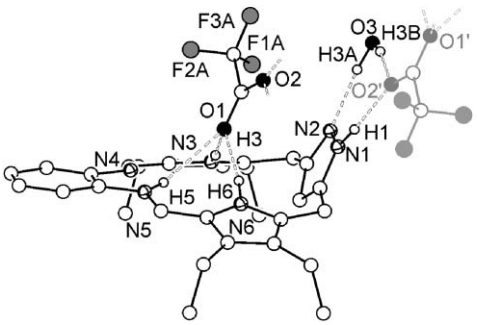

Fig. 3 Solid-state structure of $[\mathbf{4}H]^+(CF_3COO^-)\cdot H_2O$ as determined by single-crystal X-ray diffraction analysis. All hydrogen atoms not involved in hydrogen bonding and the disorder of the CF_3 group have been omitted for clarity. Selected atom distances (Å) and angles (°): N3···O1 2.931(3), N5···O1 3.242(3), N6···O1 2.824(3), N1···O2′ 2.838(3), O3···N2 2.912(3), O3···O2′ 2.749(3); N3–H3···O1 170(3), N5–H5···O1 145(2), N6–H6···O1 166(3), N1–H1···O2′ 164(3), O3–H3A···N2 164(4), O3–H3B···O2′ 161(4). Symmetry transformation used to generate equivalent atoms (′): $1 - x$, $2 - y$, $2 - z$.

sits above the mean plane of the macrocycle and acts as H-bonding bridge to the pyrazole NH functionality of a second molecule of $[\mathbf{4}H]^+$. This propensity of $[\mathbf{4}H]^+$ to form H-bonded aggregates could also be detected in its (+)ESI-MS spectrum, showing a range of dimer structures held together by single protons (see ESI†). The number of well defined and switchable H-bond donor and acceptor opportunities at the in- and out-side of the macrocycle, combined with a chromophore that is sensitive to changes in the H-bond pattern and protonation state, make macrocycle **4** unique and suggest these compounds for applications in molecular recognition systems.

In summary, the pyrazole–pyrrole hybrids **1** and **3** provide a new and useful building block for the construction of macrocycles containing pyrazole and pyrrole moieties, with the novel Schiff's base macrocycle **4** as a first example described herein. We are currently exploring the use of **4** in the formation of a range of macrocycles, including the cyclocondensation with **3** to form the pyrazole analogues of hexaphyrin or Furuta's 'doubly N-confused hexaphyrin'.[13,15]

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Notes and references

‡ *Crystal data*: **4**·2EtOH: $C_{33}H_{46}N_6O_2$, M = 558.76, monoclinic, space group $P2/c$ (no. 13), a = 19.8688(8), b = 7.9486(5), c = 21.8773(8) Å, β = 111.266(3)°, V = 3219.8(3) Å^3, T = 133(2) K, Z = 4, μ = 0.073 mm^{-1}, 62 808 measured reflections, 5588 independent reflections, R_{int} = 0.0979, $R1$ [$I > 2\sigma(I)$] = 0.0506, $wR2$ (all data) = 0.1263, CCDC 622593. $[\mathbf{4}H]^+(CF_3COO^-)\cdot H_2O$: $C_{31}H_{37}F_3N_6O_3$, M = 598.67, triclinic, space group $P\bar{1}$ (no. 2), a = 8.8877(7), b = 11.7586(9), c = 14.9846(12) Å, a = 111.537(6), β = 91.417(6), γ = 94.439(6)°, V = 1449.9(2) Å^3, T = 133(2) K, Z = 2, μ = 0.103 mm^{-1}, 27 128 measured reflections, 4999 independent reflections, R_{int} = 0.0914, $R1$ [$I > 2\sigma(I)$] = 0.0533, $wR2$ (all data) = 0.1339, CCDC 622594. X-Ray data were collected on a STOE IPDS II diffractometer (graphite-monochromated Mo-Kα radiation, λ = 0.71073 Å) by use of ω scans. The structures were solved by direct methods and refined on F^2 using all reflections with SHELX-97.[16] All non-hydrogen atoms were refined anisotropically. Hydrogen atoms which were not involved in hydrogen bonding were placed in calculated positions and assigned to an isotropic displacement parameter of 0.08 Å^2. The positional and isotropic thermal parameters of all nitrogen and oxygen-bound hydrogen atoms were refined without any restraints or constraints. The C_2H_5 group of one ethanol solvent molecule in **4**·2EtOH as well as the F_3C group of the CF_3COO^- anion in $[\mathbf{4}H]^+(CF_3COO^-)\cdot H_2O$ are disordered about two positions (occupancy factors of 0.648(13)/0.352(13) and 0.729(3)/0.271(3), respectively). Face-indexed absorption corrections for were performed numerically with the program X-RED for **4**·2EtOH (T_{max}/T_{min} = 0.9717/0.7983).[17] For crystallographic data in CIF or other electronic format see DOI: 10.1039/b614049a

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