Synthesis of a Pyridine-containing Xanthoporphinogen-type Model. An Entrance to Heterocalixarenes

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A calix[4]arene, possessing four 2,6-pyridino moieties, has been characterized by means of *X*-ray structure analysis and represents the first example in the tetraheteroaryl series.

Macrocycles with pyrrole subunits have captured chemists' imaginations for over a century as documented by Baeyer in 1886 in his reported[1] condensation of pyrrole and acetone. Porphyrin chemistry further alludes to the importance of this combination.[2] The inclusion of furan in a porphyrin-like framework was attempted[3] and finally confirmed by Wright *et al.*[4] and Beals and Brown,[5] after which other electron-rich heteroaromatics were similarly incorporated.[6,7] The striking absence of any electron-deficient heteroaromatic moieties in such macrocycles is evident but reasonable in view of the normal Friedel–Crafts chemistry used in their construction. We herein report the synthesis of the first in a series of a new pyridine-containing xanthoporphinogens and entrance into the area of heterocalixarenes.

Recently, an elegant synthesis for the construction of pyrid-2-yl-2(1*H*)-pyridylideneacetonitrile was reported[8] in which the sodium salt of α-cyanoacetamide in dimethylformamide was treated with 6,6′-dibromo-2,2′-bipyridine.[9] Friedrich *et al.*[10] had shown that 2-chloropyridine reacts with MeCN and $NaNH_2$ to give *meso*-cyanodi(pyrid-2-yl)methane. Using a modification of this approach, MeCN was treated with LiH in 5% tetramethylethylenediamine (TMEDA)–benzene to generate lithioacetonitrile, which upon reaction with 2,2-bis(6′-bromopyrid-2′-yl)-1,3-dioxolane (**1**), prepared by the procedure of Newkome *et al.*,[11] afforded (22%) an orange crystalline macrocycle (**2**) (Scheme 1).† The ease of this macrocyclization is probably a result of the N-binding sites wrapping around an appropriate 'metal template' which ensures ring-closure.

The ^{1}H n.m.r. spectrum of (**2**) shows a singlet (2H) at δ 15.0

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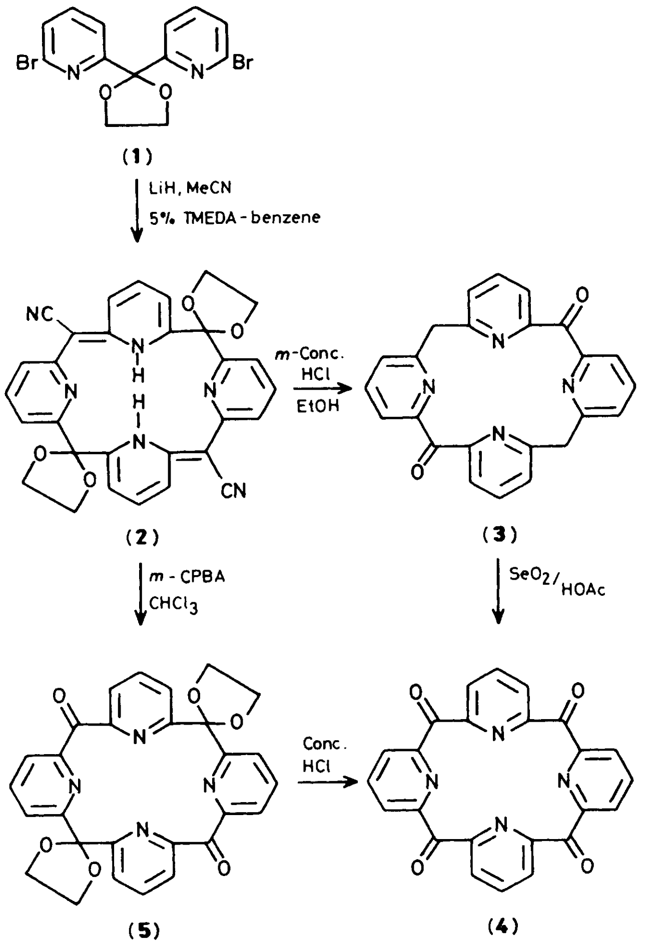
† *Selected data* for (**2**): m.p. 350—360 °C (decomp.); ^{1}H n.m.r. ($CDCl_3$) δ 4.14—4.34 (m, 8H, acetal), 6.84—6.95 (m, 4H), 7.20—7.53 (m, 8H), 15.04 (br. s, 2NH); ^{13}C n.m.r. δ 65.0, 65.5 (acetal), 70.4 (*C*CN), 105.4 (OCO), 110.0 (*C*-3), 120.1 (C-5), 122.1 (C≡N), 136.9 (C-4), 151.3 (C-6), 154.0 (C-2); i.r.(KBr) 2190 cm^{-1} (C≡N).



Scheme 1

for the strongly H-bonded N–H–N protons,[8] which were not readily exchanged in D_2O at 25 °C. Acetal and pyridine hydrogens show complicated patterns indicative of a non-planar cyclic structure. Supportive ^{13}C n.m.r. data for (**2**) show ten signals; the subring carbons appear at expected positions,[12] except C-3 which appears at δ 110.0, and the methine bridge carbon at δ 70.4, which is similar to open-chain analogues.[12,13] The i.r. spectrum shows a conjugated nitrile absorption at 2190 cm^{-1}. The spectral data clearly indicate that (**2**) exists as a conjugated system.

Figure 1 illustrates the crystal structure‡ of (**2**), which exists in the tautomeric form; C(12) and C(24) are planar and two pyridines are protonated. This tautomeric form renders each conjugated dipyridylmethine unit nearly planar: the 15 atom unit containing N(1), N(4), and N(5) is planar to within 0.18 Å, and the atoms of the corresponding unit containing N(2), N(3), and N(6) lie within 0.08 Å of a common plane. These two planes intersect at an angle of 94.7°. Examination of Corey–Pauling–Koltun (CPK) models indicates that the *syn* orientation of the two acetal rings allows conjugation of the dipyridylmethine units, while the *anti* orientation would prohibit it.

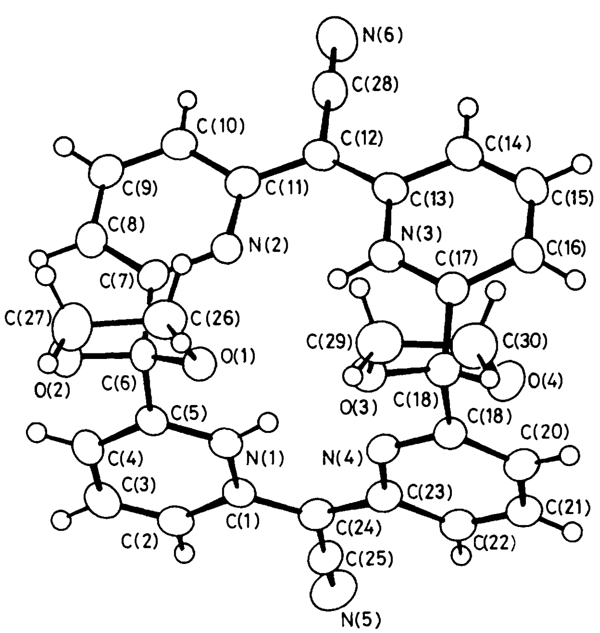


Figure 1. The *X*-ray structure of tetrapyridine (**2**). The two hydrogen atoms shown on N are half-populated, with similar half-populated protonation of N(2) and N(4).

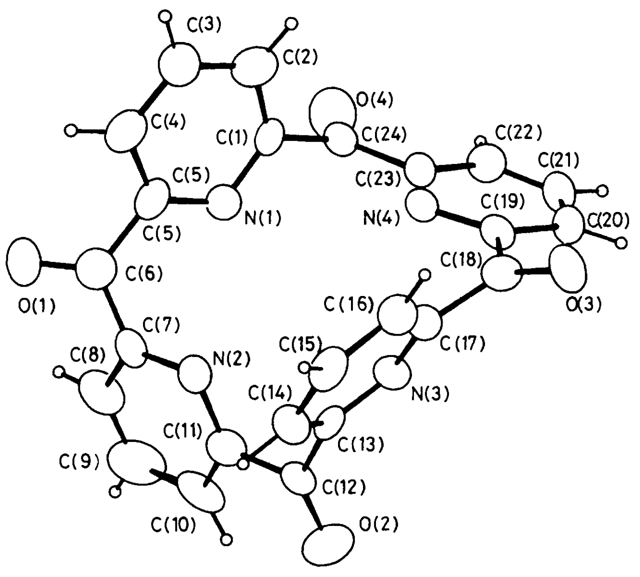


Figure 2. The *X*-ray structure of tetraketone (**4**), illustrating the molecular conformation and numbering scheme.

Macrocycle (**2**) was hydrolysed with alcoholic HCl to give dione (**3**), which was insoluble in most organic solvents. The ^1H n.m.r. spectrum of (**3**) showed a singlet at δ 4.11 with the pyridine hydrogens appearing as a complicated pattern in the heteroaromatic region. Without separation, crude (**3**) was oxidized with SeO_2 to afford a dark grey oil, which was chromatographed (silica gel; 10% HOAc–EtOH) to give

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‡ *Crystal data:* (**2**) $C_{30}H_{22}N_6O_4\cdot 1/2CH_2Cl_2$, triclinic, space group $P\bar{1}$, $a = 11.417(2)$, $b = 11.556(2)$, $c = 11.982(2)$ Å, $\alpha = 104.36(2)$, $\beta = 105.58(1)$, $\gamma = 111.69(1)°$, $Z = 2$, $R = 0.053$ for 2661 observed data ($1° < \theta < 30°$), Mo-K_α radiation, $\lambda = 0.71073$ Å. The CH_2Cl_2 solvent molecule is disordered.

Crystal data: (**4**) $C_{24}H_{12}N_4O_4$, monoclinic, space group $P2_1/c$, $a = 15.932(1)$, $b = 11.2384(5)$, $c = 11.8585(7)$ Å, $\beta = 110.226(6)°$, $Z = 4$, $R = 0.060$ for 2844 observed data ($2° < \theta < 67°$), Cu-K_α radiation, $\lambda = 1.54184$ Å.

Atomic co-ordinates, bond lengths and angles, and thermal parameters, have been deposited at the Cambridge Crystallographic Data Centre. See Notice to Authors, Issue No. 1.

[80% from (**2**)] the desired tetraketone (**4**), as colourless crystals ($CHCl_3$). Alternatively, (**4**) was prepared by the oxidation of (**2**) with *m*-chloroperbenzoic acid (*m*-CPBA) to give diacetal (**5**), which was deprotected with conc. HCl to afford [70% from (**2**)] tetraketone (**4**). The symmetric cyclic structure of (**4**) was initially confirmed by its ^{13}C n.m.r. spectrum: δ 125.7(C-3), 137.8(C-4), 155.1 (C-2), and 195.0 (C=O).

Figure 2 illustrates the molecular structure of (**4**)‡ which is severely distorted from a planar conformation into a saddle shape, with N-lone pairs pointing alternately above and below the best plane of the four nitrogen atoms. The nitrogen atoms form an approximate square, with N · · · N distances ranging from 3.012(4) to 3.388(4) Å, angles ranging from 86.7(3) to 93.5(3)°, and maximum deviation from the best plane 0.113(2) Å. The closest distance across the diagonal of this approximate square is 4.406(4) Å. The eight N–C–C–C torsion angles in the 16-membered heterocycle range from −93.6(2)° to 47.2(2)°. The N–C bond distances average 1.342 Å, C=O distance 1.211 Å, aromatic C–C 1.379 Å, and nonaromatic C–C 1.500 Å.

This new macrocyclic system (**4**), which possesses an unusually crowded cavity with 8*N*-electrons, is the first example of a pyridine-containing xanthoporphinogen-type model,[9] and a modified calixarene[14] containing a pyridyl subunit.

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