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Synthesis and Crystal Structure of 1,3-Bis(5-formylpyrrol-2-yl)benzene and Its Conversion to a Macrocyclic Derivative

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This report details the synthesis and characterization of a new diformyl pyrrole derivative **2** and its macrocyclic derivative **3**. The new compounds were characterized by FT-IR, ^{13}C NMR, and ^{1}H NMR spectroscopies and via mass spectrometric analysis. The structure of **2** in the solid state was determined using X-ray diffraction methods (monoclinic, $P2_1/c$, a = 17.3760(7), b = 4.9719(2), c = 15.5374(5) Å, β = 105.892(2) °, V = 1291.00(9) Å^3, and Z = 4). The molecular structure is stabilized by N-H...O and C-H...O intermolecular hydrogen bonds. The present bisformylpyrrole derivative **2** provides a new precursor that may be useful in the synthesis of new, functional macrocyclic systems.

Key Words: Schiff Base, Bisformylpyrrole, Macrocycle, Crystal structure.

Introduction

The chemistry of macrocyclic systems continues to attract considerable interest, in part because these compounds often display extraordinary binding, complexation and self-assembling properties[1−3]. Porphyrin and porphyrin analogues remain among the most widely studied of all known macrocyclic systems[4−10]. Schiff base porphyrin analogues are a different class of macrocyclic compounds that have attracted attention due to their potential use in photodynamic and X-ray radiation therapy, as well as in potential MRI-contrast enhancing applications. More recently, such systems have been explored as anion binding agents and peroxynitrite decomposition catalysts, and as the basis for liquid crystals[11,12]. In addition, several expanded porphyrin Schiff base macrocycles have been shown to act as binucleating ligands, an area of effort

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that has received considerable attention within the broader scope of expanded porphyrin chemistry[13−20]. The usual approach to obtain Schiff base polypyrrolic macrocycles is via condensation reaction of substituted diformyl pyrrolic precursors with diamines. In this paper, we describe the synthesis and characterization of a novel dialdehyde, namely 1,3-bis(5-formylpyrrol-2-yl)benzene **2**, and its macrocyclic derivative **3**. The new compounds were characterized by ^{1}H-NMR, ^{13}C NMR, and FT-IR spectroscopies, as well as by MASS spectrometry.

Five-membered heteroaromatic rings are well recognized as central intermediates in organic synthesis[21]. Among the many systems of general interest, diformylpyrroles and their analogues are noteworthy. Such species are useful precursors in the synthesis of biologically active compounds[22] and have been used to construct novel expanded porphyrin-type macrocycles[23], including those displaying unusual chemical[24], coordination[25], or physical properties[26]. In spite of the growing interest in recent years in substituted pyrrole-2,5-dicarbaldehydes and their analogues, few procedures for their synthesis have been reported[27,28], with the Clezy[29] and Vilsmeier-Haack[27] procedures remaining the methods of choice. As detailed below, we show here how the latter method may be used to prepare the novel dialdehyde, 1,3-bis(5-formylpyrrol-2-yl)benzene.

Experimental

1,3-Bis(pyrrol-2-yl)benzene **1** was prepared according to the published procedure[30]. IR spectra were recorded on a Perkin-Elmer Spectrum One FT-IR (ATR sampling accessory) spectrophotometer. Nuclear magnetic resonance (NMR) spectra were obtained on a GE QE-300 spectrometer using DMSO-d_6 as the solvent. Mass spectra were obtained on a VG AustoSpec apparatus. Melting points were determined on an Electrothermal Gallenkamp apparatus. All reagents and solvents were obtained from commercial suppliers and were of reagent grade quality. The homogeneities of the products were tested after each step using TLC analysis.

Synthesis of 1,3-bis(5-formylpyrrol-2-yl)benzene (2)

Vilsmeier's reagent was prepared by adding $POCl_3$(32 mmol, 3.0 mL) dropwise under Ar to DMF (20 mL) at 273 K. Separately, 1,3-bis(pyrrol-2-yl)benzene (0.5 g, 2.4 mmol) was dissolved in DMF (8 mL) under Ar and the solution was cooled to 273 K. To this latter solution, the Vilsmeier reagent (2.4 equiv., 4.15 mL) was added dropwise with good stirring. The mixture was further stirred at 273 K for 1.5 h. Saturated aqueous sodium acetate solution (60 mL) was then added carefully and the resulting mixture was stirred for an additional 4 h at room temperature. The solution was extracted 3 times with ethyl acetate, and the extracts were washed with brine and water, dried over Na_2SO_4 and evaporated in vacuo to give **2** in the form of an analytically pure, light purple powder. Single crystals were obtained from methanol at room temperature via slow evaporation (yield 0.54 g, 85%, m.p. 523 K). ^{1}H NMR (300 MHz, DMSO-d_6): δ 6.93-6.94 (d, 2H), 7.12-7.13 (d, 2H), 7.47-7.50 (t, 1H), 7.84-7.86 (d, 2H), 8.45 (s, 1H), 9.52 (s, 2H), 12.38 (s, NH protons). ^{13}C NMR (75 MHz, DMSO-d_6): 109.34, 122.40, 124.84, 129.42, 131.38, 133.87, 139.20, 178.89. FT-IR (υ_{max}, cm^{-1}): 3279 (NH), 3064 (aromatic CH), 2797 (H-C=O), 1632 (C=O). CI-HRMS: m/z 265 $[M]^{+}$.

Synthesis of macrocycle (3)

To a round-bottom flask (100 mL) equipped with a magnetic stirrer were added methanol (80 mL), **2** (0.1 g, 0.37 mmol), and *m*-xylylenediamine (0.05 mL). Hydrochloric acid (2 drops) was added dropwise, and the reaction mixture was heated 333 K for 2 h, during which time a yellow precipitate formed. The reaction was cooled to room temperature. Vigorous stirring was then continued for an additional 2 h. The yellow product that precipitated out over the course of this time was then collected by vacuum filtration and washed with cold methanol and dried in vacuo (yield 0.12 g, 92%). ^{1}H NMR (300 MHz, DMSO-d_6): δ 4.70 (s, 8H), 6.58-6.59 (d, 4H), 6.69-6.70 (d, 4H), 7.20-7.23 (d, 4H), 7.29-7.34 (t, 4H), 7.55-7.57 (d, 4H), 8.24 (s, 4H), 8.31 (s, 4H), *NHs not seen.* ESI-HRMS: m/z 730 $[M]^+$.

Results and Discussion

Preparation and characterization of 2 and 3

The synthetic procedure, as outlined in the Scheme, starts with the synthesis of 1,3-bis(pyrrol-2-yl)benzene **1**[30]. Thus, N,N'-diallylisophthaldiamide was obtained from the reaction of isophthaloyl chloride with allylamine and triethylamine in dichloromethane. Reaction of N,N'-diallylisophthaldiamide with phosgene (to give the presumed imino chloride derivative), followed by intermediate reaction with potassium *tert*-butoxide in THF afforded **1** in 29% yield. Compound **1** was converted to its formylated derivative **2** via the Vilsmeier-Haack reaction. Condensation of this latter product, 1,3-bis(5-formylpyrrol-2-yl)benzene **2**, with *m*-xylylenediamine in methanol under dilute conditions produced the Schiff base macrocycle **3**.

All compounds were characterized by FT-IR, ^{1}H NMR, and ^{13}C NMR spectroscopies, as well as by mass spectrometry. In the IR spectrum of **2**, stretching vibrations ascribed to the NH (3279 cm^{-1}), H-C=O (2797 cm^{-1}), and C=O (1632 cm^{-1}) functional groups were recorded at the expected frequencies. Moreover, the observed vibrations were CH stretching vibrations at 3064 cm^{-1}, ascribed to an aromatic group or groups. In the ^{1}H NMR spectrum of **2**, the NH protons appear at 12.38 ppm. The aromatic protons appear at 7.47-8.45 ppm, while the pyrrolic protons are observed at 6.93-6.94 ppm and 7.12-7.13 ppm. ^{1}H NMR investigation of compound **3** provided the characteristic chemical shifts for the structure expected. In the MS spectrum, molecular ion peaks at m/z = 730 and 265 amu are observed for **3** and **2**, respectively (Figure 1).

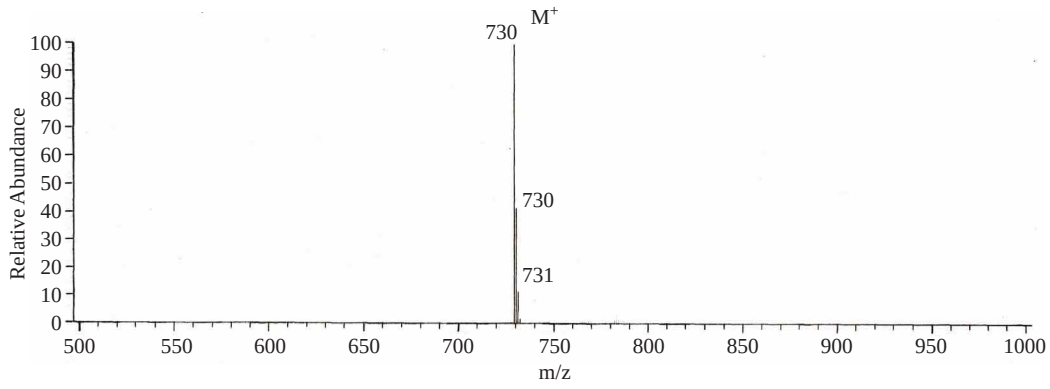
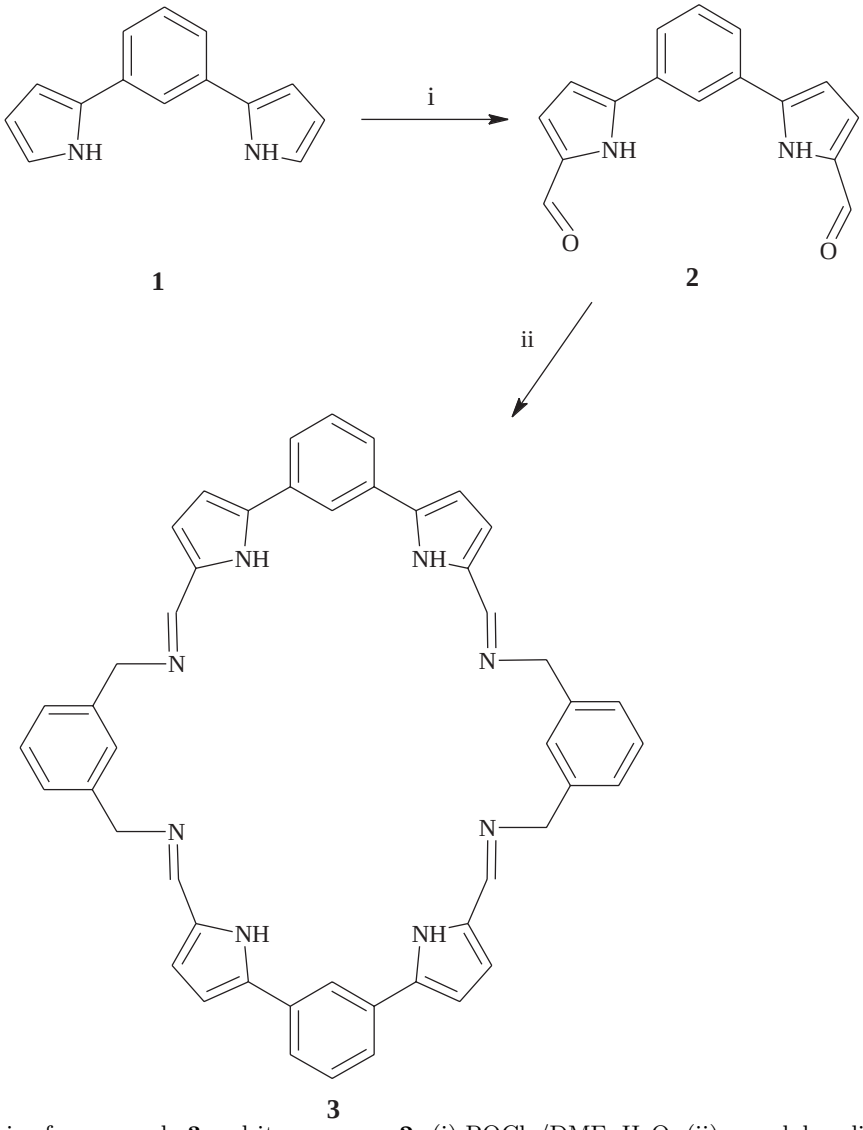


Figure 1. ESI MS spectrum of **3**.



Scheme. Synthesis of macrocycle **3** and its precursor **2**. (i) $POCl_3$/DMF, H_2O; (ii) *m*-xylylenediamine, methanol.

Description of the structure of 2

A suitable light purple crystal of **2** was mounted on a glass fiber. All measurements were obtained on a Bruker AXS SMART CCD[31] diffractometer with plane graphite monochromated MoK_α radiation. The data were collected at a temperature of 273(2) K to a maximum 2θ value of 56.0°, and 13,200 reflections were collected within the index ranges $-18 \leq h \leq 22$; $-6 \leq k \leq 6$; $-20 \leq l \leq 19$.

A summary of the experimental details for $C_{16}H_{12}N_2O_2$ is given in Table 1. The structure was solved by direct methods using SHELXS-97[32], and anisotropic displacement parameters were applied to non-hydrogen atoms in a full-matrix least-squares refinement based on F^2, using SHELXL-97 [32]. H atoms were positioned [0.86 (NH) and 0.93 Å (CH)] and constrained to ride on their parent atoms with U_{iso} (H)= 1.2 U_{eq} (C/N). Atomic scattering factors were taken from the International Tables for X-Ray Crystallography[33]. An ORTEP-3 [34] drawing with the atom-numbering scheme is shown in Figure 2. The bond lengths and angles are given in Table 2.

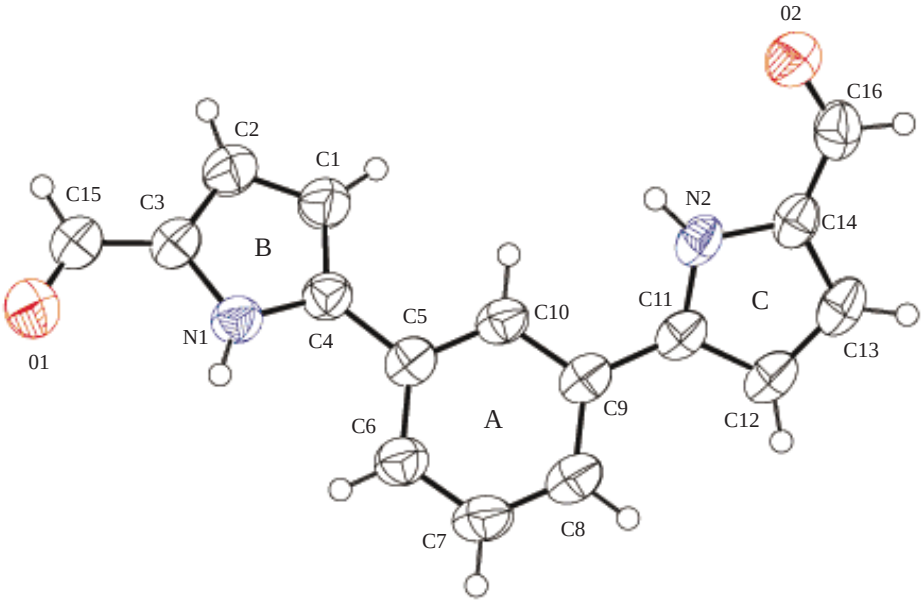


Figure 2. An ORTEP-3[34] drawing of **2** with atom numbering scheme. The displacement ellipsoids are drawn at the 50% probability level.

Table 1. Experimental details for 2.

Formula: $C_{16}H_{12}N_2O_2$
Formula weight = 264.28
Crystal system: Monoclinic
Space group: $P2_1/c$; Z = 4
a = 17.3760(7) Å
b = 4.9719(2) Å β = 105.892(2)°
c = 15.5374(5) Å
V = 1291.00(9) Å^3
D_x= 1.360 g cm^{-3}
μ(Mo K$_\alpha$) = 0.1 cm^{-1}
T = 273(2) K
F(0 0 0) = 552
Crystal size = 0.05 x 0.10 x 0.82 mm
Radiation: Mo K$_\alpha$
R = 0.0554
R_w = 0.1741
No. of unique data measured = 3098
No. of observed data with [I $\geq 2\sigma$(I)] = 1509
No. of parameters = 182
Goodness-of-fit = 1.00
$(\Delta\rho)_{max}$ = 0.20 eÅ^{-3}
$(\Delta\rho)_{min}$ = -0.17 eÅ^{-3}
Measurements: Bruker-SMART CCD area detector diffractometer
Program system: SMART[31]
Structure determination: SHELXS-97[32]
Refinement: SHELXL-97[32]

Table 2. Bond lengths (Å) and bond angles (°).

O1 - C15	1.221(4)	C13 - C14	1.389(3)
O2 - C16	1.229(4)	C1 - C4	1.378(4)
C9 - C11	1.459(4)	C2 - C3	1.376(4)
N1 - C3	1.373(3)	C3 - C15	1.419(4)
N1 - C4	1.349(3)	C4 - C5	1.471(3)
C11 - C12	1.401(4)	C5 - C6	1.394(4)
N2 - C11	1.362(3)	C5 - C10	1.386(4)
C12 - C13	1.385(4)	C6 - C7	1.380(4)
N2 - C14	1.374(3)	C7 - C8	1.381(4)
C1 - C2	1.384(4)	C8 - C9	1.396(4)
C14 - C16	1.415(4)	C9 - C10	1.397(3)
C3 - N1 - C4	109.9(2)	C7 - C8 - C9	120.4(2)
C11 - N2 - C14	110.5(2)	C10 - C9 - C11	121.0(2)
C2 - C1 - C4	108.1(2)	C8 - C9 - C10	118.0(2)
C1 - C2 - C3	107.6(2)	C8 - C9 - C11	121.0(2)
N1 - C3 - C15	123.8(2)	C5 - C10 - C9	121.8(2)
C2 - C3 - C15	129.1(2)	N2 - C11 - C12	106.7(2)
N1 - C3 - C2	107.1(2)	C9 - C11 - C12	129.5(2)
N1 - C4 - C1	107.4(2)	N2 - C11 - C9	123.8(2)
N1 - C4 - C5	124.2(2)	C11 - C12 - C13	107.8(2)
C1 - C4 - C5	128.5(2)	C12 - C13 - C14	108.2(2)
C4 - C5 - C6	122.7(2)	N2 - C14 - C13	106.7(2)
C6 - C5 - C10	119.1(2)	C13 - C14 - C16	129.4(3)
C4 - C5 - C10	118.2(2)	N2 - C14 - C16	123.8(2)
C5 - C6 - C7	119.7(3)	O1 - C15 - C3	126.8(3)
C6 - C7 - C8	121.0(3)	O2 - C16 - C14	125.6(3)

The molecule is composed of 3 planar rings: a central phenyl and 2 pyrrol rings. The dihedral angles between the rings are A/B= 20.6(1), A/C= 19.2(1) and B/C= 35.5(2)°. The intermolecular N-H...O and C-H...O hydrogen bonds (Table 3) cause the formation of one-dimensional polymeric chains parallel to the a axis (Figure 3).

Table 3. Hydrogen-bonding geometry (Å, °) for **2**.

	D-H	H...A	D...A	D-H...A
N1 - H1A ... $O1^{i}$	0.8598	2.0774	2.937(3)	177.54
N2 - H2A ... $O2^{ii}$	0.8599	2.1927	3.021(3)	161.67
C6 - H6A ... $O1^{i}$	0.9293	2.5200	3.335(3)	146.49
C10 - H10A ... $O2^{ii}$	0.9296	2.3900	3.294(3)	164.09

Symmetry codes: (i) -x,2-y,-z, *(ii)* 1-x,1-y,-z.

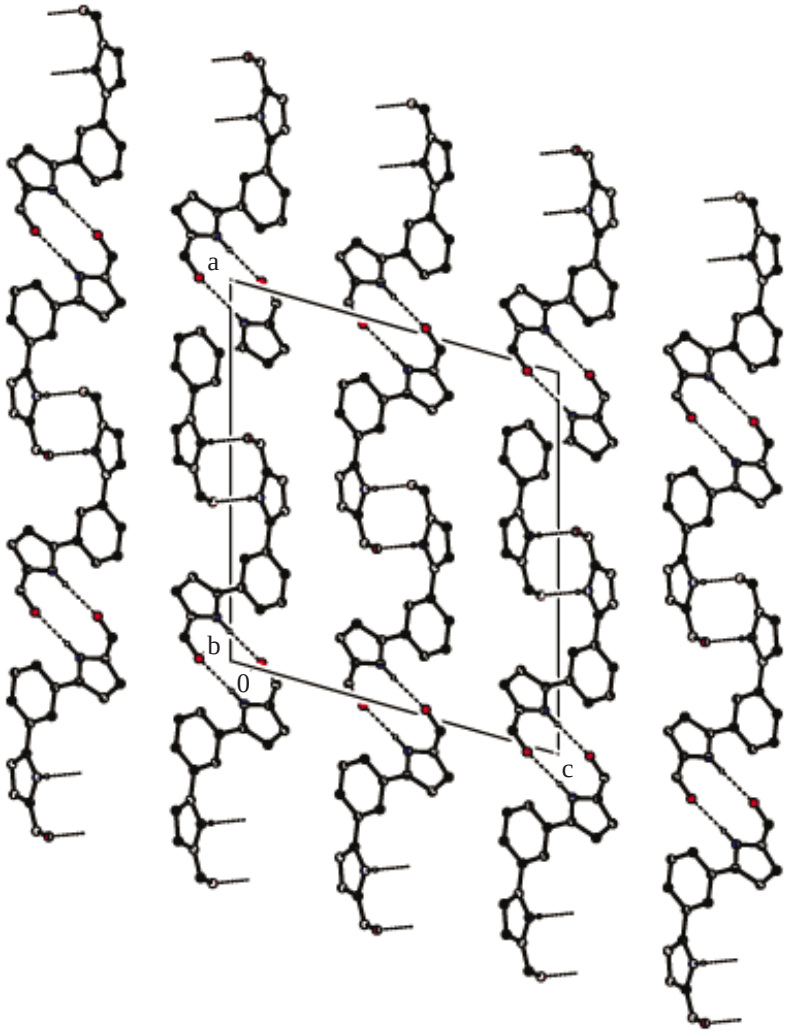


Figure 3. Packing of **2**. The hydrogen bonds are shown by dashed lines.

In summary, we have detailed the synthesis of a new, well-defined bisformylpyrrole derivative **2**. We think that it may be a new precursor for the construction of expanded porphyrin-type macrocyclic entities. As an initial demonstration, we have succeeded in condensing **2** with *m*-xylylenediamine to produce a [2+2] Schiff base macrocycle **3**, in high yield. Studies of this latter system are currently in progress, to generate new diformyl pyrrole derivatives.

Supplementary materials

CCDC 288069 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: C44 1223 336033; or deposit@ccdc.cam.ac.uk).

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