Vilsmeier Formylation of 5,10,15-Triphenylcorrole: Expected and Unusual Products

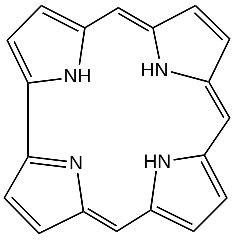
Roberto Paolesse,*[a] Sara Nardis,[b] Mariano Venanzi,[b] Marco Mastroianni,[b] Michele Russo,[b] Frank R. Fronczek,[c] and Maria Graça H. Vicente[c]

Abstract: 5,10,15-Triphenylcorrole (**1**) reacts with the Vilsmeier reagent ($POCl_3$/DMF) to give the corresponding 3-formyl derivative **3** as the major product. The regioselectivity of the reaction was proven by X-ray crystallography and only traces of the 2-formyl isomer were observed. A more polar product is also observed and this compound becomes the major product when an excess of DMF is used for the preparation of the Vilsmeier reagent, while the formation of the 3-formyl isomer is almost completely suppressed. X-ray crystallography allowed us to identify this compound as the fully substituted N-ethane bridged derivative **4**, formed from the attack of the Vilsmeier reagent at the inner core of the macrocycle. This compound is unique among porphyrinoid macrocycles, and further confirms the peculiarity of corrole chemistry.

Keywords: corroles · hydroformylation · porphyrinoids · synthetic methods

Introduction

Corrole is the prototypical example of contracted porphyrins **I**, with one of the *meso*-carbon bridges missing. This type of tetrapyrrole macrocycle was first reported by Johnson and Kay, more than thirty years ago,[1] but only recently more attention has been devoted to the chemistry of this macrocycle.[2] The recent availability of efficient and facile syntheses of *meso*-substituted corroles has probably been the starting point for the impressive flourishing of corrole-related papers appearing in literature in the last few years.[3] The chemistry of 5,10,15-triphenylcorrole (**1**) in fact parallels that of 5,10,15,20-tetraphenylporphyrin, in that it constitutes a convenient starting platform from which more complex molecular architectures can be built.



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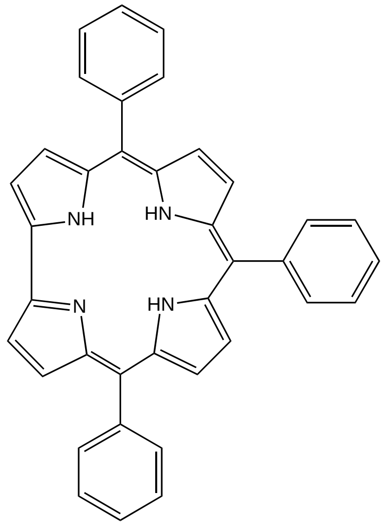

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Following this idea, interesting examples of β functionalization of *meso*-phenylcorroles have been reported in the literature,[4] although this field is still in its infancy when compared with that of porphyrin synthetic chemistry.[5] Furthermore, β functionalization of corroles presents higher potential complexity compared with porphyrins, because of the lower symmetry of the corrole system, which can lead to a large number of possible isomers.[4d] Among the various reactions, we have been particularly interested in the formylation reaction, because in the case of porphyrins, it

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[a] Prof. Dr. R. Paolesse
Dipartimento di Scienze e Tecnologie Chimiche
Università di Roma “Tor Vergata” and CNR-IMM
00133 Roma (Italy)
E-mail: roberto.paolesse@uniroma2.it

[b] S. Nardis, Prof. Dr. M. Venanzi, M. Mastroianni, M. Russo
Dipartimento di Scienze e Tecnologie Chimiche
Università di Roma “Tor Vergata”, 00133 Roma (Italy)

[c] Prof. Dr. F. R. Fronczek, Prof. Dr. M. G. H. Vicente
Department of Chemistry, Lousiana State University
Baton Rouge, LA 70803 (USA)

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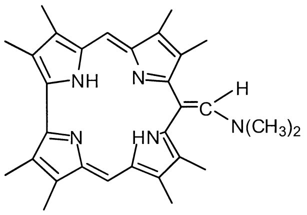
represents the easiest way to introduce a carbon atom at a macrocyclic peripheral position. The Vilsmeier reaction is generally the method of choice to carry out this addition.[5, 6] In the case of porphyrins, the formylation reaction is generally performed on the Ni^{II} or Cu^{II} porphyrin complex, which both activates the macrocycle towards electrophilic substitution and prevents inner core protonation under the acidic conditions; the metal ion is subsequently easily removed to give the free-base formyl-substituted porphyrin in good yields. In the case of corroles this approach is more problematic, because the demetalation step is not easy; to the best of our knowledge, only one example of demetalation procedure of a Mn^{III} corrole has been recently reported.[7]

On the other hand we discovered that β-alkylcorroles are reactive under the Vilsmeier reaction conditions, even as free-base,[8] although the reaction product was **2** instead of the expected formyl derivative, demonstrating once again the peculiar chemistry of corroles.



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Following this approach we report herein the results obtained when the Vilsmeier reaction was carried out on **1**.

Results and Discussion

The Vilsmeier reaction was carried out on **1** by adding the Vilsmeier reagent POCl$_3$/DMF (1:110 molar ratio) to a solution of this macrocycle in dry dichloromethane, and the final mixture was stirred at room temperature under nitrogen. The progress of the reaction was monitored by UV/Vis spectrophotometry and TLC: when all starting material had disappeared, a saturated aqueous NaHCO$_3$ solution was added to hydrolyze the imine derivative.

The crude product was purified by column chromatography on silica gel. Elution with CH$_2$Cl$_2$ afforded a green band as the major product (58 % yield), along with a trace amount (< 1 % yield) of a faster eluting fraction, while with CH$_2$Cl$_2$/CH$_3$OH (9:1) a polar green fraction (15 % yield) was isolated. Spectroscopic characterization of the major fraction confirmed the success of the reaction. The FAB mass spectrum showed a molecular peak expected for the formation of a monoformylated product ($M^+ = 554$), while the UV/Vis spectrum showed a split and red-shifted Soret band. Furthermore the ^{1}H NMR spectrum (Figure 1) showed a resonance signal at $\delta = 9.86$ ppm, attributed to the formyl group, a singlet at $\delta = 9.20$ ppm due to the β-hydrogen atom on the substituted pyrrole, and six doublets for the other β-pyrrolic protons.

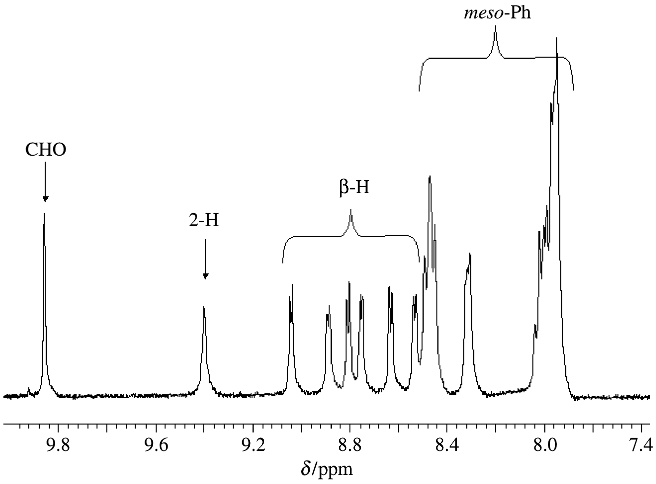
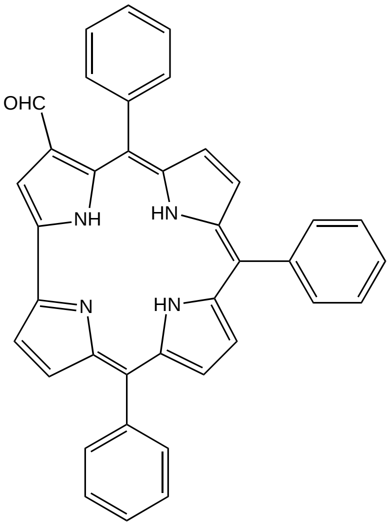


Figure 1. ^{1}H NMR spectrum of **3** in CDCl$_3$ (aromatic region).

In the case of monosubstitution, four isomers are possible for the corrole macrocycle. X-ray characterization of a single crystal obtained by slow diffusion of CHCl$_3$ into hexane allowed us to identify this isomer as the 3-formyl-5,10,15-triphenylcorrole **3** (see Figure 2).



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This result is in accord with a previous report by Gross and co-workers,[4d] confirming that the position 3 of the corrole ring is the most reactive towards electrophilic substitution reactions, even more so than the less hindered position 2. The corrole macrocycle exhibits a nonplanar distortion (Figure 2), which is attributed to the steric hindrance caused by the three inner-core hydrogen atoms. The mean deviation of the 23 macrocyclic atoms from their mean plane is 0.152 Å, with maximum deviation 0.299(2) Å for C7. The rings containing N23 and N24 are nearly coplanar, as a result of the N23-H ··· N24 intramolecular hydrogen bond. These rings, along with C15 which joins them, exhibit a mean deviation of 0.058 Å and maximum deviation of 0.097(2) Å (for N24). The N21 ring forms a dihedral angle of 15.0(1)° from the 11-atom plane, while the ring containing N22 is tipped out of plane in the opposite direction, forming a dihedral angle of 15.6(1)° with

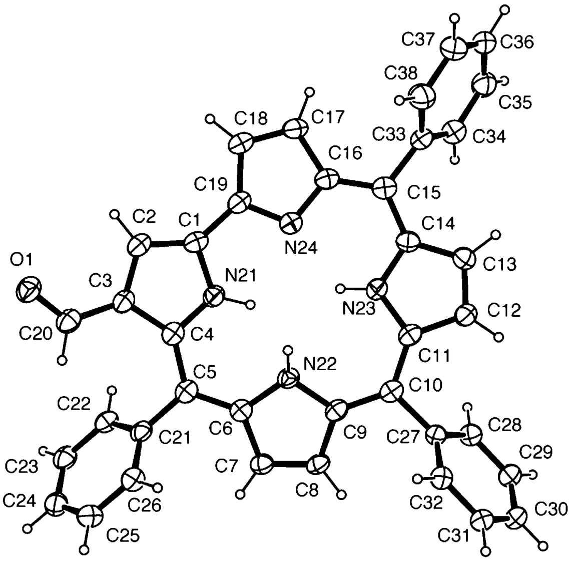


Figure 2. Molecular structure of **3** determined by X-ray crystallography.

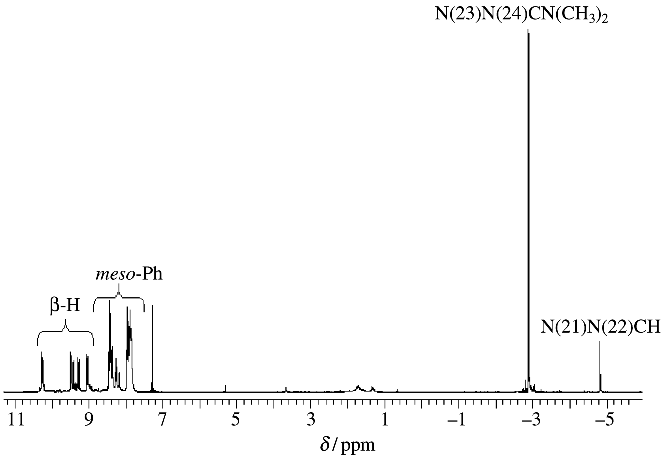
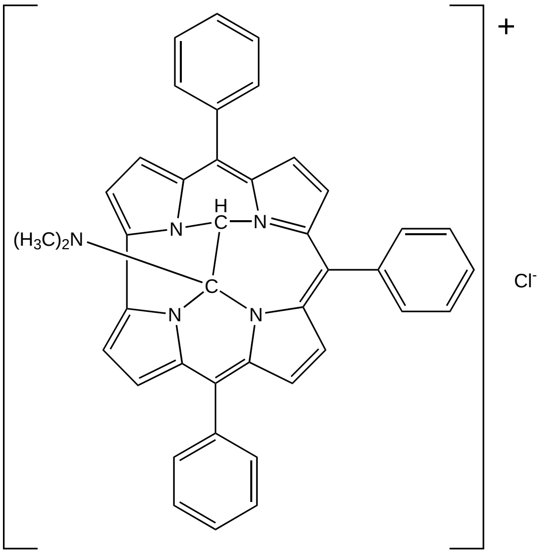


Figure 3. ^{1}H NMR spectrum of **4** in $CDCl_3$.



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the 11-atom plane. The planes of N21 and N22 thus form a dihedral angle of 20.8(1)°. N22 forms an intermolecular hydrogen bond with the formyl oxygen O1 ($N \cdots O$ 2.881(3) Å; $N{-}H \cdots O$ 169(2)°), and thus the corrole molecules form centrosymmetric hydrogen-bonded dimers.

The faster eluting fraction obtained from the column chromatography was further purified by preparative TLC. The spectroscopic characterization of this compound supported its identification as a monoformylated isomer. The FAB mass spectrum showed the molecular peak expected for a monoformylated isomer, and in the ^{1}H NMR spectrum a signal at $\delta = 11.1$ ppm due to a formyl group proton was present. Although the low amount obtained prevented a complete spectroscopic characterization of this product, the low-field resonance of the formyl proton in the ^{1}H NMR spectrum with respect with that observed in **3**, reasonably indicated this product as the 2-formyl derivative. The close resemblance of this chemical shift with those found for *meso*-formyl corroles is in part attributed to the absence of a vicinal phenyl group, which causes the high-field shift observed for **3**.

The more polar product was further purified by column chromatography on alumina grade III, using a mixture of CH_2Cl_2/CH_3OH (99:1) for elution. We expected this product to be a bisformylated corrole, but the spectroscopic characterization ruled out this hypothesis. For example the FAB mass spectrum showed a molecular ion at m/z 592, which could not be attributed to a bisformylated corrole. The electronic absorption spectrum was characterized by a split Soret-like band around 410 nm and three Q-bands at 526, 560 and 650 nm. Moreover, the ^{1}H NMR spectrum (Figure 3) did not show resonance signals attributable to formyl groups, but presented signals in the $\delta = -2$ to -5 ppm range, strongly suggesting the presence of substituents at the inner core of the macrocycle.

X-Ray crystallography again assisted us in characterizing this compound as **4** (see Figure 4). This product is formed by the attack of the Vilsmeier reagent at the macrocyclic core. To the best of our knowledge such a reaction has never been previously reported in the case of porphyrins, and for β-alkylcorrole we had no evidence of a similar reactivity.

This result can be rationalized in terms of the high acid character of **1** compared with both the porphyrin and β-alkylcorrole macrocycles. It is important to note that if a higher amount of DMF was used **4** became the major reaction product (60 % yield) and the formation of **3** was almost completely suppressed (3 % yield). A large excess of DMF can lead to the partial formation of the corrole anion, which is attacked by the Vilsmeier reagent. The reaction of a further unit of this reagent is then necessary to give the inner core ethane bridging group. A plausible reaction pathway leading to **4** is reported in Scheme 1.

The structure of the cation in $[C_{41}H_{29}N_5]Cl \cdot 2H_2O$ is shown in Figure 4. The insertion of a C–C bond into the core of the corrole forms a ring system containing additional six- and seven-membered rings. The C38–C39 bond length, 1.554(6) Å is normal, as are the bonds from these two C atoms to N (1.445(6) – 1.478(6) Å). Formation of these bonds causes the

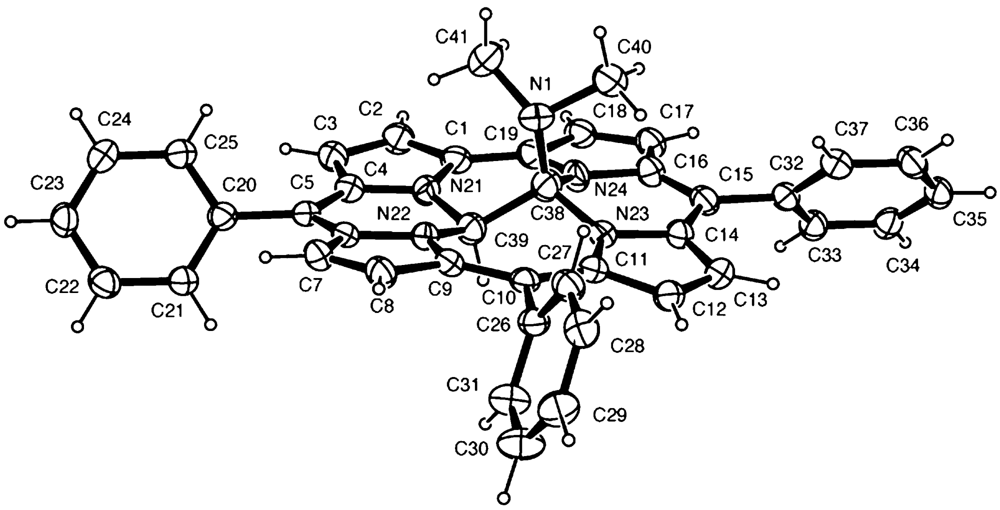
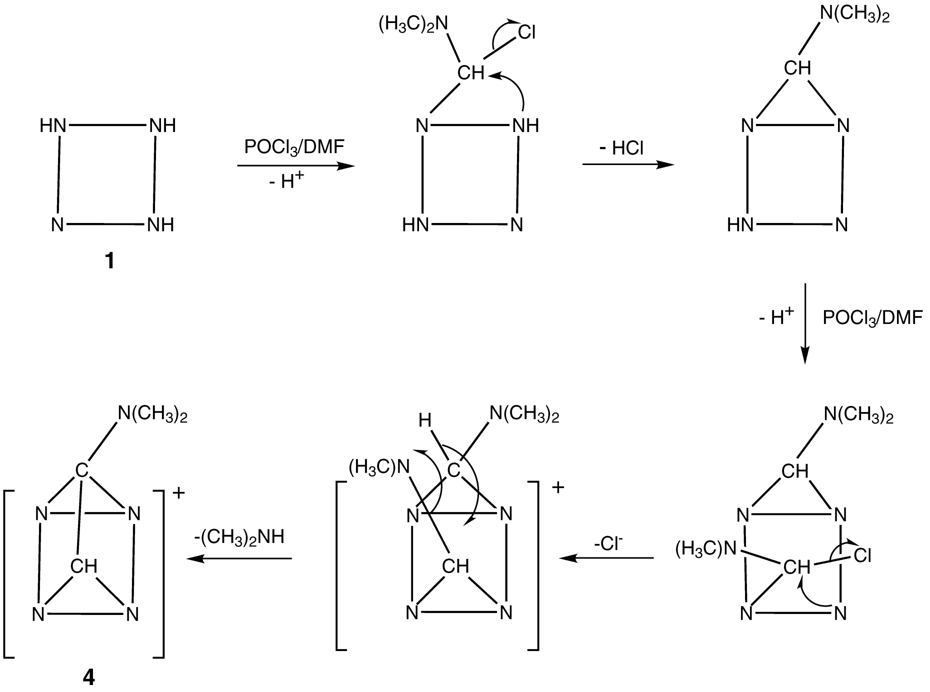


Figure 4. Molecular structure of the cation in **4** determined by X-ray crystallography.



Scheme 1. Schematic representation of the reaction pathway leading to **4**

23-atom corrole macrocycle unit to become more planar than in **3**, with the atoms of this unit exhibiting a mean deviation of 0.103 Å from coplanarity, and a maximum deviation of 0.238(4) Å for C13. C38 lies 0.520(5) Å out of this plane, and C39 lies 0.315(5) Å out of plane on the opposite side.

Owing to these intriguing characteristics, we decided to carry out the photophysical characterization of such a species. The emission spectrum of **4** is reported in Figure 5. Both lifetime (Figure 6) and quantum yield (0.082) observed for **4** are similar to those observed for **1** and analogous derivatives,[9] while a smaller Stokes-shift was observed between the lowest absorption and the fluorescence band (10 nm). This result indicates that the distortion occurring in going from the ground state to the fluorescent excited state is low, probably due to the rigid molecular framework.

Another surprising characteristic of **4** derived from the recorded CD spectrum (Figure 7). Although we have no evidence for the mechanism of its reaction pathway, the formation of **4** seems to have requisite of stereospecificity. The minima observed in the CD spectrum corresponded to the split Soret-like absorbance band, providing evidence for the chiral nature.

Conclusion

The Vilsmeier formylation of **1** confirms the peculiar chemistry of corrole, because in addition to **3**, the unique N-alkyl-substituted derivative **4** has been separated and fully characterized.

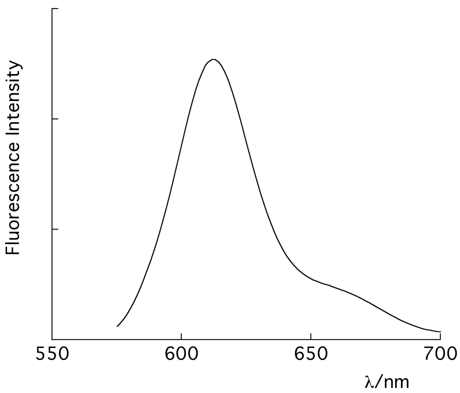


Figure 5. Steady-state fluorescence spectrum of **4** in CH_2Cl_2.

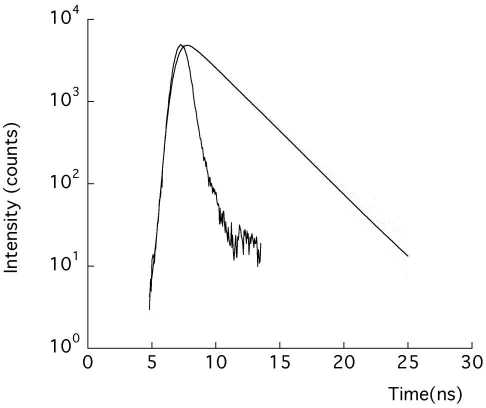


Figure 6. Time-resolved fluorescence spectrum of **4** in CH_2Cl_2.

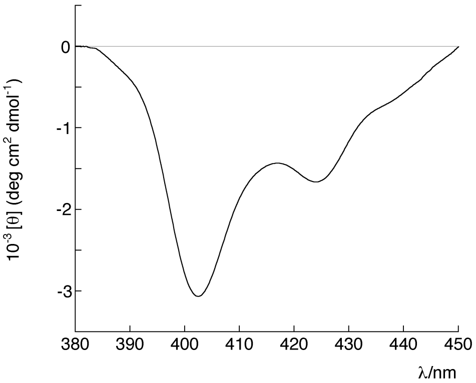


Figure 7. CD spectrum of **4** in CH_2Cl_2.

Experimental Section

Instrumentation: ^1H NMR spectra were recorded with a Bruker AM400 (400 MHz) spectrometer. Chemical shifts are given in ppm relative to tetramethylsilane (TMS). Routine UV/Vis spectra were measured on a Varian Cary 50 Spectrophotometer, whereas more delicate measurements were performed on a Perkin Elmer λ18 Spectrophotometer equipped with a temperature-controlled cell holder. Steady-state fluorescence spectra were recorded on a SPEX Fluoromax, operating in single-photon counting (SPC) detection mode (excitation $\lambda = 559$ nm). The quantum yield of the investigated compound (0.082 in CH_2Cl_2) was obtained by using Rhodamine 101 in ethanol as reference.

Time-resolved fluorescence experiments were measured on a CD900, SPC lifetime apparatus from Edinburgh Instruments. Excitation at 559 nm was achieved by using ultrapure hydrogen as filling gas (full width half maximum (FWHM) = 1.2 ns at 300 mmHg gas pressure, 30 kHz repetition rate). The experimental time decays were fitted by a nonlinear least-squares analysis to exponential functions by an iterative deconvolution method.

All fluorescence experiments were carried out in quartz cells, using freshly prepared solutions previously bubbled for 20 min with ultrapure argon.

Circular dichroism (CD) measurements were performed on a Jasco J-600 instrument with appropriate quartz cells ($l = 1$ cm, molar concentrations: 1.10^{-5} M in CH_2Cl_2). Data were reported as molar ellipticity. Mass spectra (FAB) were recorded on a VG Quattro Spectrometer using *m*-nitrobenzyl alcohol (NBA, Aldrich) as a matrix in the positive-ion mode.

Materials: Silica gel 60 (70–230 mesh) was used for column chromatography. Reagents and solvents (Aldrich, Merck or Fluka) were of the highest grade available and were used without further purification. CH_2Cl_2 used for the spectrophotometric measurements was stored over activated molecular sieves.

General procedure for the Vilsmeier reaction of 1: The Vilsmeier reagent was prepared by cooling DMF (0.6 mL, 7.8 mmol) to 0 °C and adding $POCl_3$ (0.6 mL, 6.4 mmol) under nitrogen; the reagent was then added dropwise to a solution of **1** (30 mg, 0.06 mmol) in CH_2Cl_2 (10 mL). The resulting mixture was allowed to reach room temperature and stirred under nitrogen. The progress of the reaction was monitored by UV/Vis spectroscopy; after three hours there was no evidence of the absorptions of the starting material. A saturated solution of $NaHCO_3$ (10 mL) was then added and the mixture stirred for one hour; the organic phase was separated, washed with water, dried on Na_2SO_4, and the solvent evaporated. The crude mixture was dissolved in CH_2Cl_2, and column chromatography (silica gel, CH_2Cl_2 eluent) afforded **3** as a green band, together with traces of a faster eluting band. Pure **3** was obtained as green crystals after crystallization from CH_2Cl_2/hexane (19 mg, 58 % yield), A third band was eluted by adding CH_2Cl_2/MeOH (90:10) to the column. The product was further purified by chromatography on neutral alumina (Brockmann Grade III, CH_2Cl_2/MeOH 99:1 eluent). Crystallization from CH_2Cl_2/Hexane (1:2) gave crystals of **4** (5 mg, 15 % yield).

When the same reaction was carried out using a larger amount of DMF (1.2 mL) to prepare the Vilsmeier reagent, the subsequent chromatographic workup afforded **3** (1 mg) and **4** (21 mg) in 3 and 60 % yield, respectively.

Spectroscopic data for **3**: ^1H NMR (400 MHz, $CDCl_3$): $\delta = 9.86$ (s, 1 H), 9.20 (s, 1 H), 8.85 (d, 1 H; $J = 4.0$ Hz), 8.69 (d, 1 H; $J = 4.3$ Hz), 8.64 (d, 1 H; $J = 4.8$ Hz), 8.54 (d, 1 H; $J = 4.0$ Hz), 8.43 (d, 1 H; $J = 4.8$ Hz), 8.35 (d, 1 H; $J = 4.5$ Hz), 8.28 (m, 4 H), 8.10 (m, 2 H), 7.82 ppm (m, 9 H); UV/Vis (CH_2Cl_2): λ_{max} ($\varepsilon \times 10^{-3}$) = 424 (82.4), 445 (65.0), 605 (18.9), 650 nm (16.2); MS (FAB): *m/z* (%): 554 (30).

Dark green crystals of corrole **3** were grown from chloroform/hexane. $C_{38}H_{26}N_4O$, $M_r = 554.6$, monoclinic space group $P2_1/c$, $a = 18.486(3)$, $b = 10.990(3)$, $c = 13.692(5)$ Å, $\beta = 96.495(12)^\circ$, $V = 2763.8(13)$ Å^3, $Z = 4$, $\rho_{calcd} = 1.333$ g cm^{-3}, $Mo_{K\alpha}$ radiation ($\lambda = 0.71073$ Å; $\mu = 0.08$ mm^{-1}), $T = 100$ K, 42731 data were collected on a Nonius KappaCCD detector, $R = 0.055$ ($F^2 > 2\sigma$), $R_w = 0.125$ (all F^2) for 5433 unique data having $\theta < 26.0^\circ$ and 397 refined parameters.

Spectroscopic data for **4**: ^1H NMR (400 MHz, $CDCl_3$): $\delta = 10.26$ (d, 1 H; $J = 4.7$ Hz), 10.24 (d, 1 H; $J = 4.7$ Hz), 9.48 (d, 1 H; $J = 4.9$ Hz), 9.42 (d, 1 H; $J = 5.0$ Hz), 9.30 (d, 1 H; $J = 4.5$ Hz), 9.26 (d, 1 H; $J = 4.5$ Hz), 9.06 (d, 1 H; $J = 4.6$ Hz), 9.04 (d, 1 H; $J = 4.6$ Hz), 8.41 (m, 6 H), 7.84 (m, 9 H), −2.90 (s, 6 H), −4.84 ppm (s, 1 H); UV/Vis (CH_2Cl_2): λ_{max} ($\varepsilon \times 10^{-3}$) = 405 (94.0), 426 (42.6), 526 (5.1), 560 (6.7), 600 nm (15.3); luminescence (CH_2Cl_2, (excitation $\lambda = 559$ nm): $\lambda_{max} = 612$ nm, $\phi = 0.082$, $\tau = 2.8$ ns (±0.1); MS (FAB): *m*/*z* (%): 592 (40).

Black single crystals of corrole **4** were grown from chloroform/hexane. $[C_{41}H_{29}N_5]Cl \cdot 2H_2O$, $M_r = 663.2$, monoclinic space group $P2_1/n$, $a = 13.417(6)$, $b = 15.120(7)$, $c = 16.781(9)$ Å, $\beta = 104.51(2)^\circ$, $V = 3296(3)$ Å^3, $Z = 4$, $\rho_{calcd} = 1.337$ g cm^{-3}, $Mo_{K\alpha}$ radiation ($\lambda = 0.71073$ Å; $\mu = 0.16$ mm^{-1}), $T = 100$ K, 19464 data were collected on a Nonius KappaCCD detector, $R = 0.086$ ($F^2 > 2\sigma$), $R_w = 0.241$ (all F^2) for 6389 unique data having $\theta < 26.0^\circ$ and 445 refined parameters.

CCDC-192399 (**3**) and CCDC-192400 (**4**) 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 CB21EZ, UK; fax: (+44)1223-336033; or deposit@ccdc.cam.ac.uk).

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