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Facile synthesis of *ortho*-pyridyl-substituted corroles and molecular structures of analogous porphyrins

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ABSTRACT

The reactions of 5-(2-pyridyl)dipyrromethane with either pyridine-2-carboxaldehyde or pentafluorobenzaldehyde provided the expected corroles in 22–24% yields when performed according to the protocol perfected for such molecules, while porphyrins were the main products from reactions carried out in hot propionic acid. The *ortho*-pyridyl-substituted porphyrins were characterized by X-ray crystallography, thus revealing the first molecular structures of such molecules. The new corroles were transformed into water-soluble derivatives via N-alkylation of the pyridyl groups, leading to the first *ortho*-pyridylium-substituted corroles.

Porphyrins with *para*-pyridylium groups at their four *meso*-C positions are the most intensively investigated in biochemical and medicinal applications. On top of their extensive utilization as photodynamic therapy (PDT) agents and as superoxide dismutase (SOD) mimics,[1,2] they were recently shown to bind to G-quadruplex DNA, and the corresponding metal complexes were disclosed as decomposition catalysts of peroxynitrite.[3,4] The somewhat less commonly used *ortho*-pyridylium-substituted porphyrins are much more potent with regard to the last aspect;[5] and porphyrins with fewer than four pyridinium groups are often more effective in various applications.[6] Synthetic methodologies for the preparation of porphyrin analogs with pyridinium groups are much less developed and their potential has started to be uncovered only recently. The latest examples are binding of *para*-pyridylium-substituted corroles and porphyrazines to G-quadruplex DNA, intercalation of the manganese complex of a bis-*para*-pyridylium-substituted corrole into double-stranded DNA, and very efficient catalytic decomposition of peroxynitrite by the latter.[7,8] In the only earlier example, comparison of analogous corrole and porphyrin derivatives with three remote *ortho*-pyridylium-substituents revealed that the former is more synthetically accessible and more potent with regard to inhibition of endothelial cell proliferation, tumor progression, and metastasis in an in vivo model of cancer.[9] This largely unexplored potential of corroles initiated the present research which has focused on the synthesis of derivatives with *ortho*-pyridylium-substituents. In addition to the successful preparation of several such compounds, the first molecular structures of porphyrins with fewer than four pyridyl groups are reported.

The starting material for the new derivatives was 5-(2-pyridyl)dipyrromethane (**1**),[10] which was reacted with either pyridine-2-carboxaldehyde (**2**) or pentafluorobenzaldehyde (**3**) by two different synthetic approaches: that perfected by the research group of Gryko for corroles ([aldehyde]/[**1**]/[TFA, 66 mM] = 1/2/4 in CH_2Cl_2 at rt, followed by oxidation) and the propionic acid/reflux method that is commonly used for porphyrins (Scheme 1: routes a and b, respectively).[11] The former methodology yielded only corroles in quite respectable chemical yields: 24% of **4** and 22% of **5** from the reactions of **1** with **2** and **3**, respectively.[12,13] The structure of corrole **5**, with *ortho*-pyridyl rings at C5 and C15 and one pentafluorophenyl ring at the C10 position, reveals that no (or no severe) scrambling occurred during the reaction.[14] Very different results were obtained when the same aldehydes were reacted with **1** according to route b: only small amounts of the same corroles (3% of **4** from **2** and 5% of **5** from **3**) were isolated, the major products were porphyrins (20% of **6** from **2** and 10% of **7** from **3**), and highly significant scrambling occurred in the reaction between **1** and **3**.[15,16] The *meso*-positions of the new porphyrin (**7**) produced in the latter case are substituted with one C_6F_5 and three pyridyl groups rather than two of each as would be expected from the applied reagents.

The ^{1}H NMR characteristics of corroles, 4 β-pyrrole doublets with *J* coupling constants of 4.1–4.9 Hz,[17] were clearly evident for **4** and **5**. The resonances of the *ortho*-pyridyl groups were significantly broader, which may be attributed to the presence of various atropoisomers (and equilibrium between them, vide infra) with regard to the positioning of the nitrogen atoms above and below the macrocyclic ring. Porphyrins **6** and **7** were also easily identified by their ^{1}H NMR spectra, displaying one singlet for all the β-pyrrole H atoms of **6** and two doublets of 2H and one singlet of 4H for **7**, perfectly consistent with the symmetry of these compounds. The corroles and porphyrins displayed similar electronic spectra, with

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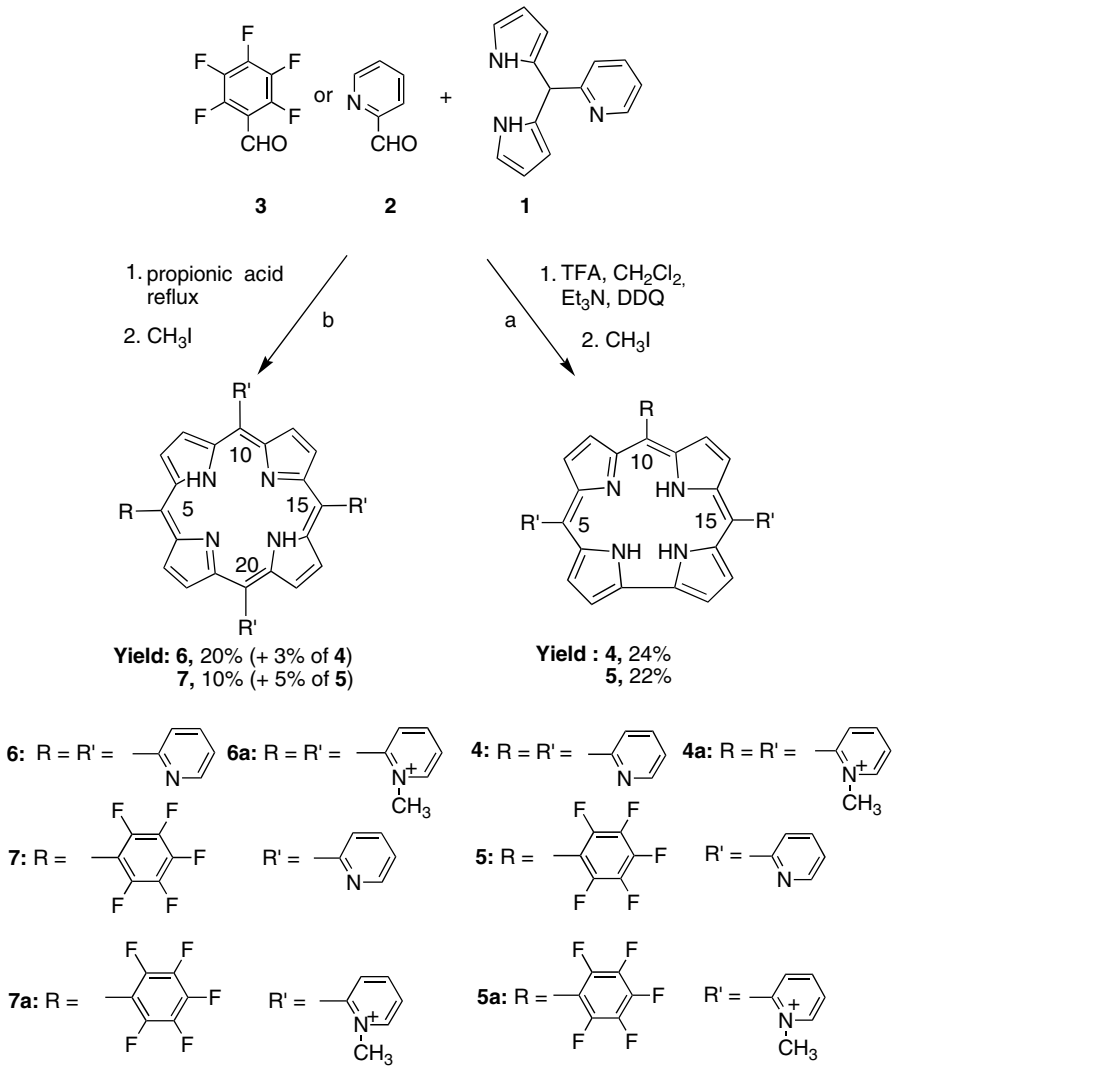

Scheme 1.

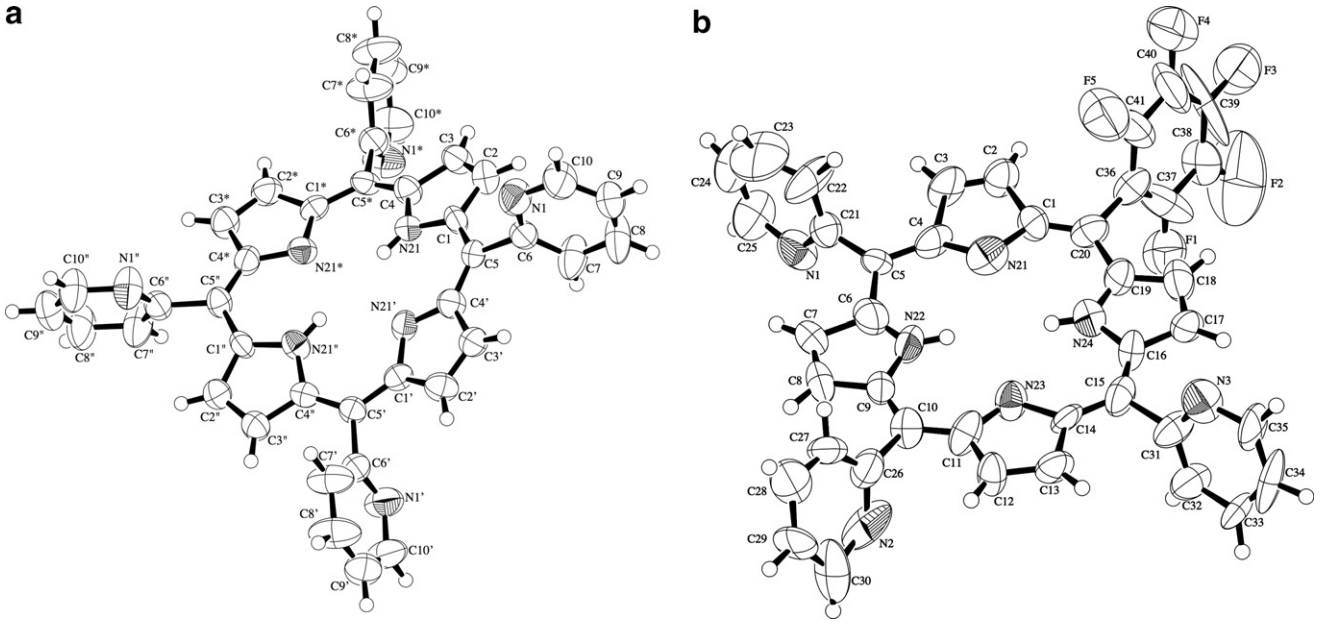

Figure 1. ORTEP presentations with 50% probability thermal ellipsoids of the X-ray structures of porphyrins (a) **6** and (b) **7**.

larger molar absorption coefficients (ε) for the latter. More detailed structural information was obtained for the porphyrins, which provided X-ray quality crystals.[18]

The ORTEP drawings (Fig. 1) of **6** and **7** reveal that each of the porphyrins crystallized in the form of one particular atropoisomer: αβαβ and ααβ, for **6** and **7**, respectively, where α and β symbolize the relative positioning of the *ortho*-pyridyl nitrogen atoms. The macrocyclic framework in **6** is ruffled, with 18° dihedral angles between the pyrrole subunits, and the four pyrrole nitrogen atoms deviate by 0.05 Å above and below the mean plane of the N4 coordination core. On the other hand, the *ortho*-pyridyl and pyrrole rings are practically perpendicular (89.1°) and the greater than 4 Å distance between individual porphyrin molecules in the unit cell clearly rules out intermolecular π–π interactions. The last conclusion also holds for porphyrin **7**, where the dihedral angle between two neighboring macrocycles is 62°. This porphyrin is, however, much more planar than **6**: the four nitrogen atoms define an almost perfect plane (with deviations of 0.001 Å and 0.02 Å for the two different molecules) and the mean deviation of all the atoms from the N4 plane does not exceed 0.05 Å.

All four derivatives (**4**–**7**) were converted in >95% yield into the respective *N*-methylpyridylium corroles and porphyrins (**4a**, **5a**, **6a**, and **7a**) via their reaction with iodomethane.[19] Close inspection of the ^{1}H NMR spectra of the corrole derivatives revealed that all the possible atropoisomers were formed in the statistically predicted ratio: ααα, ααβ, and αβα for the tris-pyridylium-substituted **4a**, and αα and αβ for the bis-pyridylium-substituted **5a**,[20] where α and β represent opposite positioning of the *N*-methyl groups relative to the macrocycle plane. This information was deduced from the number and relative integration of the resonances attributed to the methyl groups, such as the 1:1 ratio of singlets at 4.13 and 4.15 ppm for **5a**. For **4a**, each isomer has two identical (on C5 and C15) and one different (on C10) methyl groups; and three such 2:1 pairs were evident in a 1:2:1 ratio for the ααα, ααβ, and αβα atropoisomers, respectively. The separation of atropoisomers was successfully carried out by HPLC (Fig. 2a and b), but despite several methods being applied for evaporation of the isolated fractions, those of **4a** isomerized back to the original distribution of atropoisomers. This previously noticed phenomenon (in related porphyrins)[21,22] did not occur for **5a**, whose atropoisomers were successfully isolated in quite pure form (Fig. 2b).

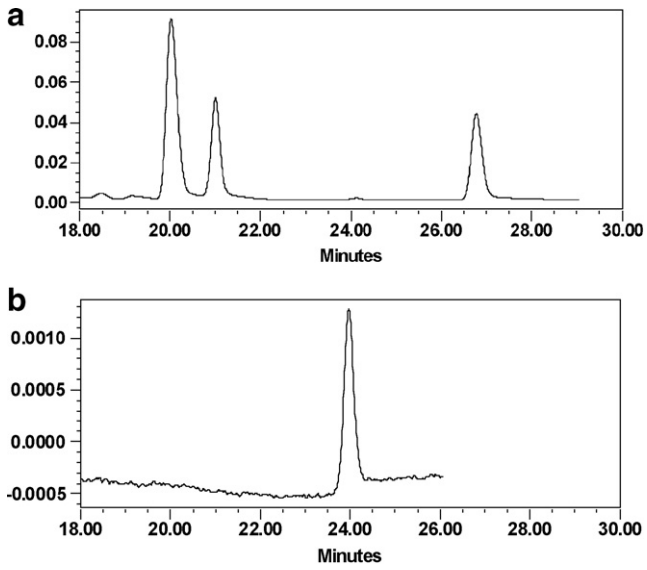

Figure 2. HPLC chromatograms of (a) the atropoisomeric mixtures of **4a** and of (b) the isolated atropoisomer of **5a**.

This work reports the successful synthesis of the first corroles that carry *ortho*-pyridylium groups. These derivatives will be applied in the near future in medicinal applications where corroles have started to display significant advantages relative to other metal-chelating agents.

Acknowledgments

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12. *Reaction conditions and purification*: Compound **1** (0.4 mmol), appropriate aldehyde (0.2 mmol), and trifluoroacetic acid (62 μL, 0.8 mmol) were dissolved in CH_2Cl_2 (12 mL) at room temperature. Triethylamine (112 μL, 0.8 mmol) was added after 1 h, followed by CH_2Cl_2 (308 mL) and DDQ (90 mg, 0.4 mmol), and stirring was continued for a further 10 min prior to evaporation to dryness and subsequent column chromatography on silica. The second band from the mixture obtained from the reaction with **2** (eluted with ethyl acetate/*n*-hexane, gradually increasing from 3:1 to 100% ethyl acetate and to 10% methanol in ethyl acetate) provided a major fraction that contained corrole **4** and a few impurities. A second chromatographic treatment (from 3:1 ethyl acetate/*n*-hexane to 3% *n*-hexane in ethyl acetate to 5% methanol in ethyl acetate) provided pure **4** (25 mg, 24% yield), R_f (silica, ethyl acetate) = 0.24. The second band (bluish-green colored) from the mixture obtained from the reaction with **3** (eluted with ethyl acetate/*n*-hexane, from 1: 4 to 1: 2) provided a fraction that contained corrole **5**. Final purification was achieved by preparative thin-layer chromatography (silica plate, ethyl acetate/*n*-hexane, 3:4) to afford pure **5** (27 mg, 22% yield), R_f (silica, ethyl acetate/*n*-hexane, 2:3) = 0.81.
13. *5,10,15-Tris(2-pyridyl)corrole* (4): MS (MALDI-TOF): *m*/*z* (%): 528.3 ([M−H]$^-$, 100%); 530.5 ([M+H]$^+$, 100%). ^{1}H NMR (500 MHz, C_6D_6): δ 8.81 (br s, 2H), 8.79 (d, ^3J(H,H) = 4.12 Hz, 2H), 8.67 (br s 1H), 8.65 (d, ^3J(H,H) = 4.35 Hz, 2H), 8.44 (d, ^3J(H,H) = 4.12 Hz, 2H), 8.23 (d, ^3J(H,H) = 4.58 Hz, 2H), 8.04 (d, ^3J(H,H) = 7.56 Hz, 2H), 7.91 (d, ^3J(H,H) = 7.33 Hz, 1H), 7.34 (m, 3H), 6.92 (m, 3H). UV–vis (ethyl acetate): λ_{max}, nm ($\varepsilon \times 10^{-3}$) 418 (36.3), 582 (6.7), 614 (4.4). *10-(Pentafluorophenyl)-5,15-bis(2-pyridyl)corrole* (5). MS (MALDI-TOF): *m*/*z* (%): 617.0 ([M−H]$^-$, 100%); 619.2 ([M+H]$^+$, 100%). ^{1}H NMR (300 MHz, C_6D_6): δ 8.74 (br s, 2H), 8.61 (d, ^3J(H,H) = 4.12 Hz, 2H), 8.22 (d, ^3J(H,H) = 4.67 Hz, 2H), 8.09 (d, ^3J(H,H) = 7.96 Hz, 2H), 7.71 (d, ^3J(H,H) = 4.94 Hz, 2H), 7.06 (m, 4H), 6.42 (m, 2H), −1.47 (br s, 3H). ^{19}F (282 MHz, C_6D_6): δ −138.36 (dd, ^3J(F,F) = 25.3 Hz, ^4J(F,F) = 5.6 Hz, 2F), −154.16 (t, ^3J(F,F) = 22.6 Hz, 1F), −162.96 (td, ^3J(F,F) = 25.4 Hz, ^4J(F,F)=8.5 Hz, 2F). UV–vis (EtOAc): λ_{max}, nm ($\varepsilon \times 10^{-3}$) 416 (48.5), 578 (10.3).
14. For factors affecting scrambling, see: Koszarna, B.; Gryko, D. *J. Org. Chem.* **2006**, *71*, 3707–3717.
15. *Reaction conditions and purification*: Samples of **1** (0.4 mmol) and appropriate aldehyde (0.2 mmol) were dissolved in 10 mL of propionic acid, and the reaction mixture was heated to reflux for 40 min. After evaporation of the propionic acid, the residue was washed with hot water and neutralized with NH_4OH (25%). The solid material was separated by column chromatography on silica. Separation of **4** and **6**, formed in the reaction with **2**, was achieved by column chromatography (silica, ethyl acetate/*n*-hexane, 1:3 for **4** and 10% *n*-hexane in ethyl acetate for **6**). Pure **4** (5 mg, 5% yield) and **6** (25 mg, 20% yield) were obtained by thin-layer chromatography (silica, ethyl acetate).

Recrystallization of **6** ($CHCl_3$/*n*-heptane) provided X-ray quality crystals. R_f (silica, methanol/ethyl acetate, 3:1) = 0.65. Partial separation between **5** and **7**, formed in the reaction with **3**, was achieved by column chromatography (silica, ethyl acetate/*n*-hexane, 1:3 for **5** and 2:1 for **7**). Pure **5** (4 mg, 3% yield) and **7** (14 mg, 10% yield) were obtained by separation on preparative silica gel plates (ethyl acetate/*n*-hexane, 3:4 for **5** and 4:1 for **7**). Recrystallization of **7** (CH_2Cl_2/*n*-hexane) provided X-ray quality crystals. R_f (silica, ethyl acetate) = 0.56.

16. *5,10,15,20-Tetrakis(2-pyridyl)porphyrin* (**6**): MS (MALDI-TOF): *m*/*z* (%): 619.2 ($[M+H]^+$, 100%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 9.16 (d, ^3J(H,H) = 7.50 Hz, 4H), 8.89 (s, 8H), 8.23 (d, ^3J(H,H) = 7.5 Hz, 4H), 8.09 (m, 4H), 7.72 (m, 4H), −2.79 (s, 2H). UV–vis (CH_2Cl_2): λ_{max}, nm ($\varepsilon \times 10^{-3}$) 414 (126.4), 512 (15.5). *5-Pentafluorophenyl,10,15,20-tris(2-pyridyl)porphyrin* (**7**): MS (MALDI-TOF): *m*/*z* (%): 708.2 ($[M+H]^+$, 100%). ^{1}H NMR (500 MHz, C_6D_6): δ 8.99 (d, ^3J(H,H) = 4.81 Hz, 2H), 8.92 (s, 4H), 8.90 (m, 2H), 8.87 (m, 1H), 8.62 (d, ^3J(H,H) = 4.81 Hz, 2H), 7.75 (m, 3H), 7.32 (m, 3H), 7.02 (m, 3H), −2.54 (s, 2H). ^{19}F (282 MHz, C_6D_6): δ −137.91 (m, 2F), −152.97 (t, ^3J(F,F) = 21.4 Hz, 1F), −162.71 (m, 2F). UV–vis (CH_2Cl_2): λ_{max}, nm ($\varepsilon \times 10^{-3}$) 410 (100.2), 510 (12.7), 586 (4.5).
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18. The diffraction measurements were carried out on a Nonius Kappa CCD diffractometer, using graphite monochromated Mo Kα radiation (λ = 0.7107 Å) at ca. 110 K. Crystal data for **6**: $C_{40}H_{26}N_8$; *M*W = 618.69; *a* = 14.918(3) Å; *b* = 14.918(3) Å; *c* = 13.490(3) Å; *V* = 3002(1) Å^3; tetragonal space group *I*-42*d*; *Z* = 4; D_{calcd} = 1.369 g/cm^3; μ(MoK$_\alpha$) = 0.084 mm^{-1}; 2623 unique reflections; *R* = 0.0424 (*wR* = 0.093) for 773 reflections with $I \geqslant 2\sigma I$); *R* = 0.0878 (*wR* = 0.1139) for all unique data. Crystal data for **7**: $C_{41}H_{22}F_5N_7$; *M*W = 707.66; *a* = 26.899(5) Å; *b* = 10.829(2) Å; *c* = 11.590(2) Å; β = 99.93(3)° *V* = 3325(1) Å^3; monoclinic space group *Pc*; *Z* = 4; D_{calcd} = 1.413 g/cm^3; μ(MoK$_\alpha$) = 0.106 mm^{-1}; 5677 unique reflections; *R* = 0.0914 (*wR* = 0.220) for 2719 reflections with $I \geqslant 2\sigma I$); *R* = 0.1860 (*wR* = 0.2471) for all unique data. The deposition numbers at the Cambridge Crystallographic Data Centre are CCDC 682223 and 682224 for compounds **6** and **7**, respectively.
19. Corroles **4** and **5** were dissolved in a minimum volume of DMF, excess iodomethane (100 equiv) was added to the solutions, and reaction mixtures were stirred at room temperature overnight. A small amount of methanol and a three fold excess of diethyl ether were added to the reaction mixtures. Precipitated products were collected and washed with addition of portions of diethyl ether.
20. *5,10,15-Tris(N-methyl-2-pyridiniumyl)corrole* (**4a**): This was obtained in 94% yield as a mixture of three atropoisomers in a ratio of 50.1/22.7/21.0. Up to 6% of products that were N-alkylated at the pyrrolic nitrogen atoms could be separated by either column chromatography or HPLC. R_f silica = 0.46 (acetonitrile/H_2O/KNO_3(aq), 8:1:1). MS (MALDI-TOF) ES$^+$ (CH_3CN): *m*/*z* (%): 575 ($[M+H]^+$, 10%), 560 (40%), 545 (100%), 287 ($[M/2]^+$, 100%). ^{1}H NMR (300 MHz, CD_3CN): δ 9.19 (d, ^3J(H,H) = 4.39 Hz, 2H), 9.11 (m, 3H), 8.69 (m, 6H), 8.56 (d, ^3J(H,H) = 4.25 Hz, 2H), 8.54 (d, ^3J(H,H) = 4.53 Hz, 2H), 8.39 (m, 3H), 8.31 (d, ^3J(H,H) = 4.53 Hz, 2H), 4.21 (s, 2H), 4.18 (s, 2H), 4.16 (s, 1H), 4.09 s, 1H), 4.05 (s, 2H), 4.01 (s, 1H). UV–vis (acetonitrile): λ_{max}, nm ($\varepsilon \times 10^{-3}$) 408 (8.0), 436 (8.2), 626 (3.3). *10-(Pentafluorophenyl)-5,15-bis(N-methyl-2-pyridiniumyl)corrole* (**5a**): This was obtained in 95% yield as a mixture of two atropoisomers in a 49.2/46.0 ratio. Up to 4% of products that were N-alkylated at the pyrrolic nitrogen atoms could be separated by either column chromatography or HPLC. R_f = 0.55 (acetonitrile/H_2O/KNO_3(aq), 8:1:1). MS (MALDI-TOF) ES$^+$ (CH_3CN): *m*/*z* (%): 648.2 $[M+H]^+$, 100%), 633.2 (85%), 324.1 ($[M/2]^+$, 100%). ^{1}H NMR (300 MHz, CD_3CN): δ 9.15 (d, ^3J(H,H) = 4.16 Hz, 2H), 9.12 (d, ^3J(H,H) = 6.46 Hz, 2H), 8.69 (m, 4H), 8.56 (d, ^3J(H,H) = 4.74 Hz, 2H), 8.52 (d, ^3J(H,H) = 4.22 Hz, 2H), 8.49 (d, ^3J(H,H) = 4.67, Hz, 2H), 8.31 (t, ^3J(H,H) = 6.59 Hz, 2H), 4.15 (s, 3H), 4.13 (s, 3H). ^{19}F (282 MHz, CD_3CN): δ −141.01 (m, 2F), −158.21 (t, ^3J(F,F) = 19.4 Hz, 1F), −165.01 (m, 2F). UV–vis (acetonitrile): λ_{max}, nm ($\varepsilon \times 10^{-3}$) 412 (4.8), 436 (5.1), 628 (2.3). A Waters 2996 HPLC system was used for HPLC separation of the atropoisomers utilizing a SymmetryPrep 300 Å™ C_{18} 5 lm packing column (size 19 × 150 mm) at ambient temperature. Elution gradient at 5 mL/min: For **5a**: 0–5–20–45 min, 80% A–70% A–65% A–60% A; For **4a**: 0–5–25–40 min 90%A–85% A–80% A. Solvent A: deionized water, 20 mmol triethylamine, pH 2.7 adjusted with concentrated trifluoroacetic acid. Solvent B: acetonitrile, HPLC grade. Injection volume: 200 lL.
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