Organic LETTERS

Letter

pubs.acs.org/OrgLett

Porphyrins and Corroles with 2,6-Pyrimidyl Substituents

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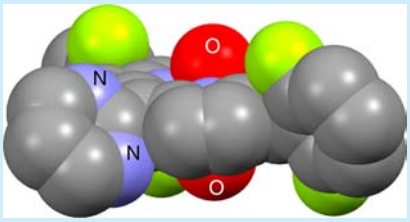
Supporting Information

ABSTRACT: Corroles and porphyrins with 2,6-pyrimidyl substituents are reported for the first time, together with the spectroscopic data and the crystal structures of the free-base porphyrin and of the phosphorus and cobalt complexes of the corrole.



Metal complexes of porphyrin and corrole derivatives with basic nitrogen atoms in close proximity with their N4 coordination core are of large utility in many applications.[1] The main precursors of such complexes are compounds **1**−**3** of Figure 1, with either *ortho*-pyridyl or *N*-methylimidazolyl groups on their respective *meso*-C atoms.[2]

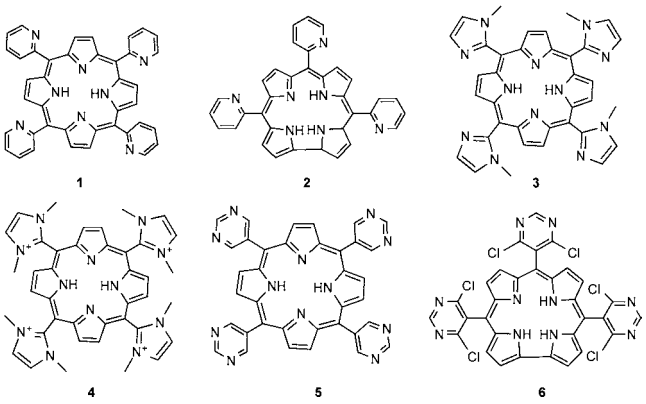


Figure 1. Selected previously reported porphyrins and corroles with N-heterocyclic substituents.

Common to all of these examples is that they exist as a mixture of atropoisomers that differ in the relative positioning of the N atoms relative to the macrocycle plane.[2b] For utilization as drug candidates,[3] they are commonly alkylated as to become water-soluble. Another consequence of the positive charges in the vicinity of the coordinated metal ion is the induction of the so-called *ortho*-effect,[4] which also accelerates the superoxide dismutation rate by manganese(III) porphyrins.[5] Alkylation does not resolve the atropoisomer issue for the *ortho*-pyridyl-substituted compounds **1** and **2**, but methylation of tetra(*N*-methylimidazolyl)porphyrin (**3**) leads to a derivative that is a single isomer (**4**).[2]

Within the course of our investigations on corroles as catalysts for medicine-relevant and many other applications,[6] we became interested in derivatives with *meso*-pyrimidyl substituents because such compounds would not suffer from the atropoisomer problem, have nitrogen atoms in the vicinity of the N4 coordination core, and could also be of sufficient solubility in water. To our surprise, neither corroles nor porphyrins with 2,6-pyrimidyl moieties were ever reported. The closest examples are tetra(3,5-pyrimidyl)porphyrins and analogous corroles with either two or three 3,5-pyrimidyl groups (Figure 1) **5** and **6**, respectively.[7,8] However, the nitrogen atoms in these macrocycles are too remote from the N4 metal-coordination core to affect metal-centered processes. We now report the synthesis of corroles with one and two 2,6-pyrimidyl substituents (**7** and **8**),[9] including the crystal structures of the corresponding phosphorus (**10**) and cobalt (**11**) chelates of the former,[10] as well as of tetra(2,6-pyrimidyl)porphyrin (**9**). The latter compound was characterized by X-ray crystallography, and it also displays high solubility in water.

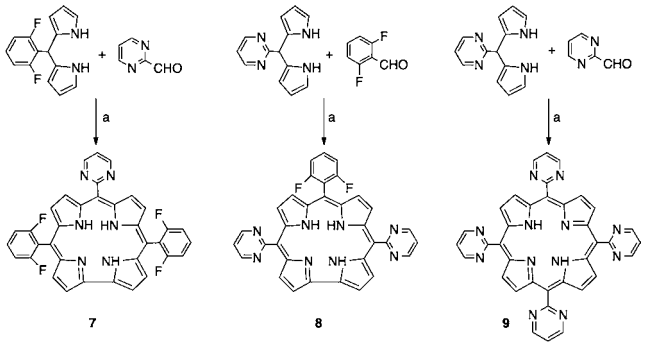
The most straightforward procedure for the preparation of the target molecules would be the direct cyclo-condensation of pyrrole with 2-pyrimidinecarboxaldehyde, in a 1:1 ratio for obtaining the porphyrin and a 1:3 ratio for preferring the corrole. The synthetic toolbox for accessing this kind of products is quite large, but neither tris(2,6-pyrimidyl)corrole nor tetra(2,6-pyrimidyl)porphyrin were obtained when the reaction was performed by any of the applied reaction conditions. The attention was hence driven to the methodology promoted by Gryko,[11] which is ideal for the synthesis of A2B corroles: derivatives with a unique substituent on C10 and two identical substituents on C5 and C15 *meso C atoms* of the macrocycle. It consists of the condensation of 5-substituted dipyrromethane with aldehyde in a 2:1 ratio, catalyzed by an acid whose concentration must be optimized, especially when one of the reagents contains basic atoms.[11b] The synthesis of corroles with one and two 2,6-pyrimidyl substituents was

Received: May 3, 2015
Published: June 17, 2015

DOI: 10.1021/acs.orglett.5b01297
Org. Lett. 2015, 17, 3214−3217

achieved by the combinations of 2-pyrimidinecarboxaldehyde with 5-(2,6-difluorophenyl)dipyrromethane and of 2,6-difluorobenzaldehyde with 5-(2,6-pyrimidyl)dipyrromethane, respectively (Scheme 1). The successful synthesis of the two A2B

Scheme 1. Synthetic Approach to 2,6-Pyrimidyl-Subsituted Corroles and Porphyrin



[a](1) Dipyrromethane/aldehyde/TFA (0.8/0.4/1.2 mmol) in CH_2Cl_2 (25 mL) for 1 h at rt. (2) NEt_3 (1.2 mmol, followed by DDQ (1 mmol) in CH_2Cl_2 (600 mL) for 10 min. (3) Column chromatography in silica, for isolation of **7**, **8**, and **9**, in chemical yield of 8%, 5%, and 12%, respectively.

corroles, **7** and **8**, encouraged the attempt of preparing the A3 corrole via condensation of 5-(2,6-pyrimidyl)dipyrromethane with 2-pyrimidinecarboxaldehyde. However, only traces of the targeted tris(2,6-pyrimidyl)corrole were obtained, unexpectedly accompanied by the tetra(2,6-pyrimidyl)porphyrin (**9**).

The three metal-free macrocycles were characterized by electronic and NMR spectroscopy. The characteristic features include the *β*-pyrrole ^{1}H NMR chemical shifts: a singlet at 9.01 ppm for **9** and four doublets with *J* coupling constants of 4.3−5.0 Hz for both **7** and **8**.[12] The number of ^{19}F NMR resonances was also consistent with the symmetry of the corroles; the near-UV (Soret) and visible (Q) bands of the porphyrin and the corroles were quite similar. The porphyrin also afforded X-ray quality crystals, which allowed for the deduction of the following details of its molecular structure (Figure 2).

The porphyrin ring in the two crystallographically independent molecules is essentially planar (except for the two inner pyrrole H atoms which deviate slightly up and down to minimize collision). The dihedral angles between the *meso*-substituted pyrimidine rings and the porphyrin macrocycle are 49.9(1)° and 89.6(1)° in one species and 62.4(1)° and 78.2(1)° in the other molecule, within the range of commonly observed values in various derivatives of the related tetraarylporphyrin moieties. In the crystal the molecules are arranged in a herringbone fashion.

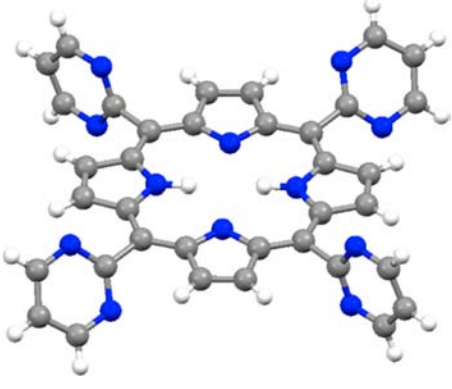
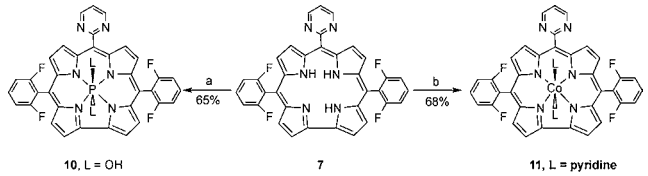


Figure 2. Perspective view of tetra(2,6-pyrimidyl)porphyrin, **9**.

Phosphorus corroles were most recently identified as excellent photosensitizers and used for light-induced elimination of microorganisms,[13] while cobalt corroles are very potent electrocatalysts for the reduction of protons into hydrogen and also powerful sensors of gaseous compounds.[14] We have hence inserted both phosphorus and cobalt into corrole **7**, which led to the isolation of the *trans*-dihydroxo-phosphorus corrole **10** and the *trans*-bispyridine cobalt(III) corrole **11**, respectively (Scheme 2). X-ray quality crystals were obtained for both complexes.

Scheme 2. Synthesis of Complexes 10 and 11, the Phosphorous and Cobalt(III) Chelates of 7, Respectively



[a]$POCl_3$/pyridine/Ar/reflux, followed by column chromatography on silica. [b]$Co(OAc)_2{\cdot}4H_2O$/pyridine/reflux, followed by column chromatography on silica.

The *trans*-dihydroxo-phosphorus corrole (**10**), depicted in Figure 3, is characterized by an almost perfectly flat structure.

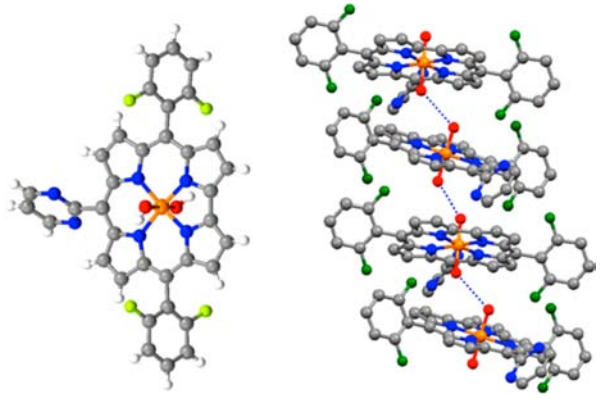


Figure 3. Perspective view of *trans*-dihydroxo-phosphorus corrole, **10**, and illustration of the hydrogen-bonding (dotted lines) assembly of corrole units arranged along the *c*-axis of the crystal.

The P−N(pyrrole) and P−O(hydroxyl) bond distances in the square-bipyramidal environment around the central P atom are within 1.811−1.860(4) Å and 1.639−1.688(4) Å. The dihedral angles of the two 2,6-difluorophenyl aryl groups and the N(pyrrole)$_4$ plane of the corrole ring are 63.9(1)° and 67.1(1)°, that of the 2,2-pyrimidyl with respect to the N_4-plane being 56.0(1)°. An interesting feature of this crystal structure is the extended hydrogen-bonding association between the hydroxyl groups of neighboring corrole species columned along the *c*-axis of the crystal. The corresponding intermolecular OH···O hydrogen bond is 2.862(4) Å. The crystal structure of **10** thus consists of hydrogen-bonded chains of the corrole species (their surface being lined with C−H bonds) aligned parallel to each other along *c*, with molecules of

DOI: 10.1021/acs.orglett.5b01297
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the *n*-hexane crystallization solvent trapped in a disordered manner between such columns. In terms of future applications, the structure also allows for the determination of the closest distance between the OH proton and the basic nitrogens of the pyrimidyl moieties (of the same corrole), which was determined to be about 2.2 Å.

Complex **11** crystallized as a benzene solvate. It displays the characteristics of a six-coordinate corrole complex with two pyridyl axial ligands coordinated to the central Co-ion and a nearly planar macrocyclic ring (Figure 4). The Co−N(pyrrole) and Co−N(pyridine) bond distances in the octahedral coordination environment are within 1.868−1.902(2) and 1.981−1.990(2) Å, respectively. The dihedral angles of the two 2.6-difluorophenyl aryl groups and the $N(pyrrole)_4$ plane of the corrole ring are 70.3(1)° and 86.7(1)°, that of the 2,2′-pyrimidyl with respect to the N_4-plane being 53.2(1)°. In **10** and **11** lack of protons in the ortho positions of the pyrimidyl ring allows for its considerably more flattened orientation with the respect to the corrole macrocycle than is observed for the 2,6-difluorophenyl aryls. Consequently, the observed distances of the pyrimidyl nitrogens from the corrole-inserted ions are relatively short, within 5.49−5.54 Å. A relevant comparison can be made also with the corresponding twist angles of the 10-substituted aryl ring in other metalated triphenylcorroles. Thus, e.g., in the cobalt triphenylcorrole derivative the central phenyl group is rotated by 63° with respect to the corrole plane.[15] In the platinum triphenylcorrole moiety the respective dihedral angle between the meso-phenyl ring at the 10-position and the corrole plane is even higher, 73° (as opposed to 56° in **10** and 53° in **11**).[16] In the crystal of **11**, the corrole entities are arranged in zones (centered at $a = 1/2$) parallel to the *bc* plane, with the pyrimidine substituent oriented within this zone. Molecules of the benzene crystallization solvent are accommodated in channel voids (that propagate along the *b*-axis) between the outward-directed (approximately along *a*) difluorophenyl arms from adjacent layers of the corrole species.

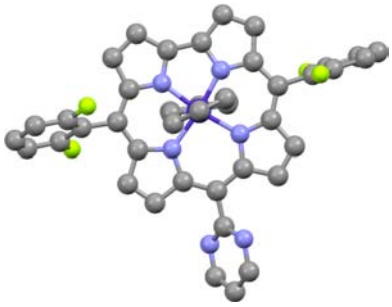

Figure 4. Molecular structure of the six-coordinate cobalt(III) corrole **11**.

Complex **11** is obtained as a diamagnetic (low-spin d^6) cobalt(III) complex, which is clearly evident by its ^{1}H NMR spectrum that discloses sharp and nonshifted resonances (Figure 5A). Anaerobic insertion of cobalt into porphyrins leads to cobalt(II), which is either fully or partially oxygenated upon exposure to air, a factor that strongly depends on solvents and axial ligands.[14] This was also the case for porphyrin **9**, whose cobalt complex was isolated after aerobic workup. A very well resolved ^{1}H NMR spectrum was obtained in pyridine-d_5 solution (Figure 5B), consistent with a low-spin cobalt(III) complex. On the other hand, the NMR spectrum in noncoordinating solvents was very broad and shifted to low field as expected for a d^7 cobalt(II) complex. Further indication for that assignment was obtained by the EPR spectrum of the complex in frozen MeOH (Figure 5C): the diagonal components of the *g*-tensor (g_1 = 2.450, g_2 = 1.999) are consistent with axial symmetry, and the high-field signals revealed low-resolved splitting due to hyperfine interaction between the unpaired electron and the ^{59}Co nucleus ($I = 7/2$) with an $A_2(^{59}Co)$ coupling constant of about 10.0 G.[17]

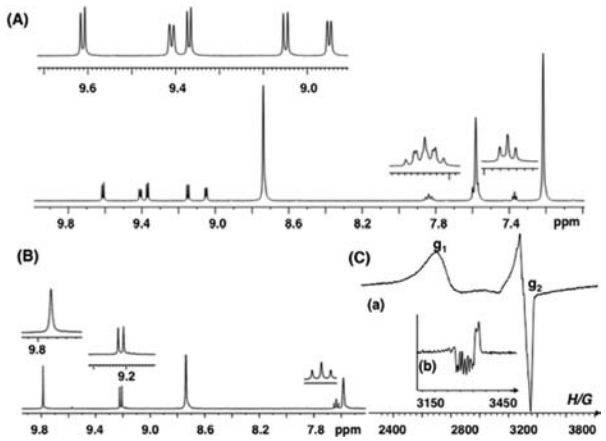

Figure 5. ^{1}H NMR spectra of the cobalt(III) complexes of corrole **11** (A) and porphyrin **9** (B) (in pyridine-d_5) and the EPR spectrum of the cobalt(II) complex of porphyrin **9** in frozen MeOH (110 K). The inset of (C) displays the second derivative of the high-field signal.

Concluding, we report novel porphyrin and corrole derivatives, substituted by aryls with two basic N atoms in the *ortho*-positions on their respective *meso*-C atoms, as a significant contribution to what may be considered as a "second renaissance" in terms of newly accessible corroles.[18] The spectroscopic data and information obtained from the crystal structures of the phosphorus and cobalt complexes are of prime importance for their utilization in the many applications where such derivatives may be expected to be of large utility.

■ ASSOCIATED CONTENT

Supporting Information

Detailed synthetic procedures, crystallographic data, and original spectra. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b01297.

■ AUTHOR INFORMATION

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work was supported by a grant from the Israel Science Foundation. The funding of Irena Saltsman by the Center for Absorption in Science, Ministry of Immigration, is also acknowledged (KAMEA Foundation).

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(9) *General procedure for preparation of the A_2B-pyrimidylcorroles* **7**−**8** *and A_4-pyrimidylporphyrin* **9**: Trifluoroacetic acid (1.2 mmol) was added to a protected from light solution of the respective dipyrromethane (0.8 mmol) and aldehyde (0.4 mmol) in dichloromethane (25 mL) at room temperature. Triethylamine (1.2 mmol) was added after 1 h, followed by dichloromethane (600 mL) and DDQ (1.04 mmol), and stirring was continued for a further 10 min prior to solvent evaporation under reduced pressure and subsequent column chromatography on silica. Pure compounds were obtained after elution with ethyl acetate/hexanes mixtures. Yields of **9**, **7**, **8**: 12%, 8%, and 5% respectively. X-ray quality crystals of **9** were obtained by slow crystallization from a methanol/benzene solution.
(10) An about 100-fold excess of $POCl_3$ (200 μL, 2.15 mmol) was added to the heated to reflux solution of **7** (20 mg, 38 μmol) in pyridine (5 mL) under argon. Reaction progress was monitored by UV−vis spectroscopy. The color of the reaction mixture immediately changed from deep purple to pink. The solvent was evaporated, after which the residue was dissolved in CH_2Cl_2 and passed through a short column of silica with ethyl acetate/methanol (12:1) as eluent. A pink colored fluorescence band was collected, providing 14 mg of **10** (21 μmol, yield 65%). X-ray quality crystals of this complex were obtained by slow recrystallization from CH_2Cl_2/heptane.
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DOI: 10.1021/acs.orglett.5b01297
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