Isoporphyrins

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Metal-Assisted One-Pot Synthesis of Isoporphyrin Complexes

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Abstract: *Zinc and cadmium complexes of meso-arylisoporphyrins carrying a pyrrolyl or dipyrrinyl substituent at the sp^3 carbon atom were obtained through a simple one-pot variation of the Alder–Longo porphyrin synthesis. Key to the formation and stabilization of isoporphyrins is the presence of metal acetates during the oxidative macrocyclization step. The characteristic Q-bands of isoporphyrins are found in the NIR region between 750 nm and 880 nm. All of the isolated pyrrolyl- and dipyrrinyl-appended isoporphyrins are stable under typical laboratory conditions and allow chemical transformations like BF_2 coordination, transmetalation, and ligand exchange.*

Isoporphyrin can be understood as a non-classical tautomeric form of porphyrin, in which one of the N-bound protons is shifted to an outer *meso*-carbon atom, accompanied by the loss of macrocyclic aromaticity (Figure 1). Such tautomers were first proposed during work towards the synthesis of chlorophyll *a* in the 1960s as dehydrogenated phlorins,[1] and are discussed as intermediates in the catabolism of heme.[2] The formation of isoporphyrins upon attack by a nucleophile like methanol or water on oxidized metal porphyrins has been reported.[3] All these derivatives are very sensitive and show a high tendency to decompose either by ring opening or by re-aromatization to the starting metal porphyrin. Despite this instability, several reports of their amazing spectroscopic and electrochemical properties have appeared,[4] and in two cases, crystallographic information was obtained.[5]

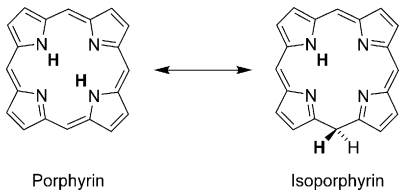
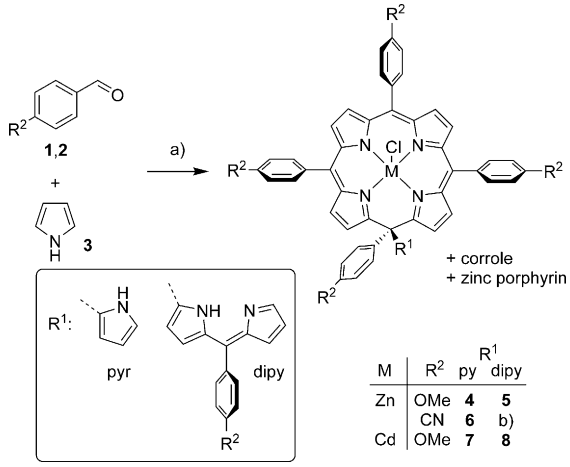


Figure 1. Isoporphyrin as a tautomeric form of porphyrin.

The high reactivity of isoporphyrins has led to the development of a multistep access to this intriguing compound class. It was found that the presence of a *meso*-CMe_2 bridge effectively inhibits both aromatization and oxidative ring opening of the isoporphyrin.[6] By following this synthetic concept, several stable isoporphyrin derivatives have been studied.[7] The exceptional optical properties of isoporphyrins, and in particular their strong NIR absorptions between 750 nm and 950 nm, have recently been exploited in the field of biomedicine, where isoporphyrins have been shown to act as potent in cell photosensitizers for photodynamic therapy.[8] The recently reviewed potential of these compounds in biomedical research, NIR sensing, and as model system in bioporphyrin degradation studies,[9] calls for a simple and straightforward preparation of stable derivatives. We have now found a solution to this problem: the metal-assisted one-pot procedure detailed in Scheme 1.



Scheme 1. Metal-assisted preparation of metal isoporphyrins **4**–**8**. a) 1. HCl/MeOH, $M(OAc)_2{\cdot}2H_2O$; 2. *p*-Chloranil, $M(OAc)_2{\cdot}2H_2O$, $CHCl_3$, 60 °C. b) Only trace amounts.

Our approach is based on the extensively used acidic condensation of aryl aldehydes with pyrrole, followed by oxidation, which has been known as the Adler–Longo porphyrin synthesis since 1967.[10] The products originating from this sequence are numerous,[11] and variations of the method provide one-step availability of prominent non-natural porphyrinoids such as N-confused porphyrins,[12] corroles,[13] and subporphyrins,[14] but also produce expanded porphyrins,[12b,15] dipyrromethanes,[16] and phlorins.[17] When we investigated the Gryko method, which optimizes the formation of A_3-triarylcorroles,[18] we found that upon addition of zinc acetate, not only the expected corrole and

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porphyrin, but also two new macrocycles formed. Both new compounds could be isolated by chromatographic methods and were spectroscopically identified as the chloridozinc complexes of tetra(4-methoxyphenyl)isoporphyrins carrying an α-pyrrolyl- (**4**) or a α-dipyrrinyl residue (**5**) at the bridging sp^3 carbon atom. Similar observations were made with the electron-deficient 4-cyanobenzaldehyde, as well as with cadmium acetate as a template reagent, resulting in the new isoporphyrins **6**–**8** (Scheme 1).

A crystal structure could be obtained for the zinc complex **4**. The compound crystallizes from *n*-pentane and dichloromethane at ambient temperature in thick black needles. The molecular structure and selected bond lengths and angles are given in Figure 2.

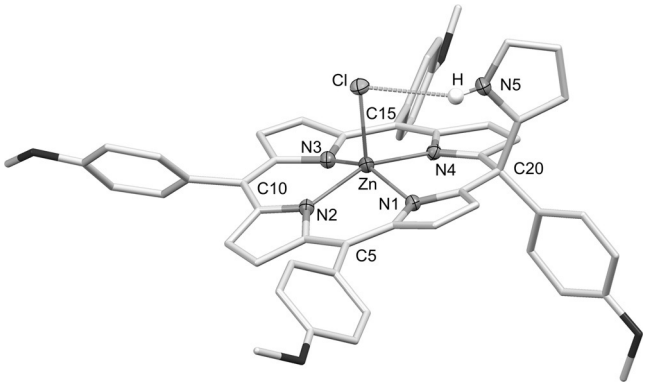

Figure 2. Molecular structure of **4**. Selected bond lengths and interatomic distances/Å: Zn–N1 2.129(3), Zn–N2 2.081(3), Zn–N3 2.101(3), Zn–N4 2.125(3), Zn–Cl 2.324(1), C4–C5 1.371(5), C5–C6 1.438(5), C9–C10 1.431(5), C10–C11 1.394(5), C14–C15 1.449(5), C15–C16 1.374(5), C1–C20 1.499(5), C19–C20 1.510(5), C20–C_{phenyl} 1.545(5), C20–$C_{pyrrolyl}$ 1.531(5), Cl–H 2.649, Cl···N 3.331. Thermal ellipsoids are set at 50% probability. Most hydrogen atoms are removed for clarity.

The broken π conjugation of **4** becomes apparent from the structural details of the sp^3 *meso*-carbon atom C20. All four C–C bond lengths are larger or equal to 1.499(5) Å, which supports the expected single-bond character. The angles at the *meso* carbon atoms C5, C10, and C15 were in the range of 125.3(3)°–125.4(3)°, while this angle is reduced to 118.3(3)° for C20. Such values compare well with literature precedents[5b,7a] and match almost perfectly with a recently described tetraaryl derivative. The other C-C-C angles at C20 were determined to be between 115.2(3)° and 102.9(3)°, and indicate a quarternary and distorted tetrahedral carbon center.

The macrocyclic conformation of **4** is governed by a strong saddling mode that superimposes a ruffling submode. This conformation is distinct from the literature findings, where ruffling modes with only small saddling contributions are reported independent of the peripheral substitution. The origin of this change in conformation appears to be the binding situation of the central zinc atom in **4**. The large and charged chlorido ligand of **4** increases the doming mode of the zinc ion. This mode is found at 0.31 Å in both reported compounds, which carry a methanol and an aquo ligand, respectively, while for **4**, a large displacement of 0.477 Å from the N_4 mean-squares plane is evident.

The peripheral pyrrole ring is oriented with the NH moiety towards the chlorine atom and forms a hydrogen bond with a Cl···H distance of 2.649 Å, and with an N-H···Cl angle of 148.26°. This hydrogen bond is also evident in solution and can be detected by the deshielding effect on the ^{1}H NMR resonances of the pyrrole NH moieties of **4**, **6**, and, **7** at $\delta =$ 10.43 ppm, 10.37 ppm, and 9.91 ppm, respectively. For comparison, the pyrrolic NH groups of dipyrromethanes, as well as those of different pyrrolyl-substituted porphyrinoids, give signals between $\delta = 8.3$ ppm and 7.7 ppm,[16,19] while these resonances shift to $\delta \approx 10.6$ ppm in α-pyrrolyl BODIPYs with a similar N-H···F hydrogen bond.[20] Further characteristic signals are the upfield-shifted resonances of the pyrrolic β-protons between $\delta = 6.76$ ppm and 6.21 ppm and the ^{13}C-NMR resonances for the quarternary bridging carbon atoms between $\delta = 56.0$ ppm and 54.8 ppm.

The dipyrrinyl-substituted derivatives **5** and **8** show unexpected behavior in the NMR spectra. While for **5**, only broad resonances are detected, the cadmium derivative **8** provides sharp doubled signal sets in the ^{1}H NMR and ^{13}C NMR spectra (Figure 3). The broadening and signal doubling may originate either from a dimerization/association process, or from the presence of two slowly interconverting diastereomers, carrying the axial chlorido ligand at the same or the opposite side to the dipyrrinyl substituent. Addition of [D_5]pyridine results in NMR spectra of higher symmetry, as expected for the break-up of aggregates and monomerization, or alternatively for ligand exchange and six-fold coordination. In order to distinguish between these forms, DOSY spectra of **7** and **8** with and without [D_5]pyridine addition were measured. The diffusion coefficients of all samples were determined to be in the range $0.58–0.66 \times 10^{-9}$ $m^2 s^{-1}$. This result provides a strong argument for the presence of monomers even for the dipyrrinyl derivatives **5** and **8**.

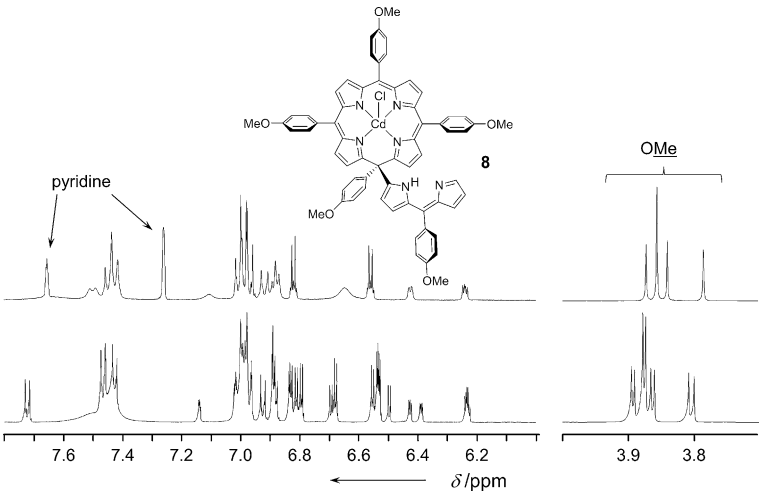

Figure 3. ^{1}H NMR spectra of **8** in CD_2Cl_2: mixture of diastereomers (bottom trace) and the six-coordinate cation after the addition of [D_5]pyridine (top trace).

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The UV/Vis spectra of isoporphyrins **4**–**8** are typical for this tetrapyrrolic π system and differ mainly in the presence of a pyrrolyl versus a dipyrrinyl side chain. The spectra for the cadmium species **7** and **8** are displayed in Figure 4. The Soret-like absorption band of **7** is found at $\lambda = 466$ nm, and the Q bands extend into the NIR region with maxima at $\lambda = 773$ nm and 852 nm. For the dipyrrinyl derivative, these Q bands are slightly blue-shifted to $\lambda = 757$ nm and 840 nm, and the Soret band appears split at $\lambda = 437$ nm and 490 nm, presumably owing to coupling with the dipyrrin major absorption. The zinc derivatives reveal very similar patterns and only small shifts of 20 nm or less for the individual absorption bands, without a general trend. Weak solvatochromic behavior is found, which points to minor charge-transfer contributions to the major absorption bands (see the Supporting Information).

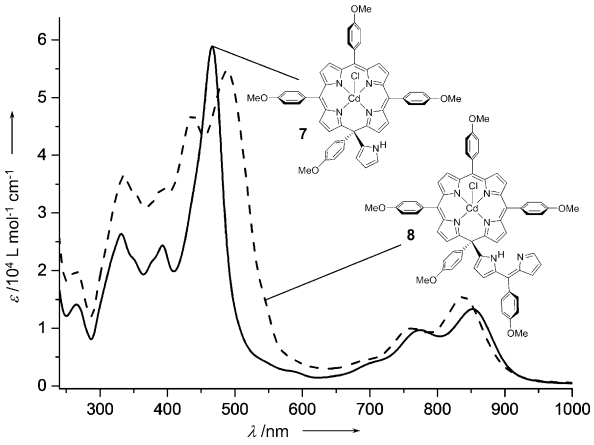


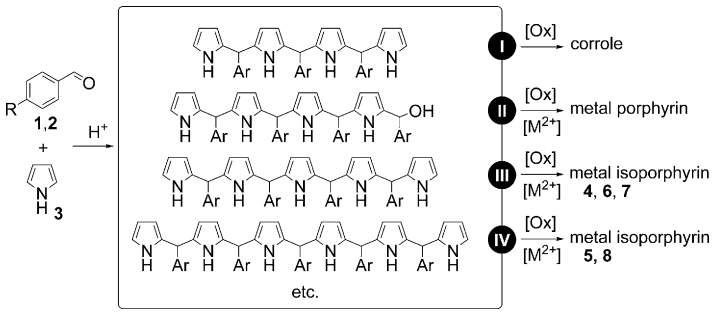
Figure 4. UV/Vis spectra (CH_2Cl_2) of cadmium isoporphyrins **7** (——) and **8** (-----).

As a probe of the role of the template reagents in the reaction sequence leading to the methoxy derivatives **4** and **5**, zinc acetate was added either at the condensation step alone, at the oxidation step alone, or at both steps. Interestingly, the presence of zinc acetate during the oxidation step was found to be vital for isoporphyrin formation, while the absence of the template reagent during the initial condensation step increases the yield of isoporphyrins **4** and **5** from 9.6% and 5.1% to 18.2% and 11.6%, respectively. At the same time, the triarylcorrole is formed in 10% yield if zinc acetate is present during the whole procedure, and in about 26% if only one of the consecutive steps is performed in the presence of this template reagent. The zinc porphyrin is generated in about 12% in all cases. Assuming the initial formation of linear oligopyrroles during the condensation step,[21] this study shows, that 1) the presence of the acetate salts disturbs the condensation to linear oligopyrroles, and 2) the linear penta- and hexapyrrolic intermediates form metal chelates after (partial) dehydrogenation, which favor oxidative ring closure to isoporphyrins rather than to sapphyrins and other expanded porphyrins (Scheme 2). It should be mentioned that the formation of pyrrolyl- or dipyrrinyl-substituted porphyrins,[19a,22] chlorins, and phlorins[17,23] from linear penta- and hexapyrroles has occasionally been reported in the past.

Preliminary studies of chemical transformations on the new isoporphyrins showed that the axial chloride ligand of the zinc pyrrolyl derivative **4** and of the cadmium dipyrrinyl derivative **8** is easily abstracted by the action of $AgSbF_6$ to yield stable cationic metal chelates that are valuable precursors for ligand-exchange studies. In addition, the dipyrrinyl derivatives **5** and **8** were transformed into isolable BODIPY-appended isoporphyrins in yields of 48% and 66% through a standard method using $BF_3{\cdot}Et_2O$, and the Hünig base $(i\mathrm{Pr})_2\mathrm{EtN}$. Such BODIPY–porphyrinoid conjugates are much studied in energy transformation.[24] Robust NIR-absorbing isoporphyrin conjugates of BODIPYs are now available in two simple steps from commercial starting materials.

An attempt to demetalate **5** by the addition of a strong acid resulted in metal-free material without the typical optical spectrum of an isoporphyrin. Such an observation has been described before[7b] and was interpreted as rapid decomposition of the tetrapyrrole. In our hands, this process was found to be reversible. Addition of copper(II) acetate to demetalated **5** recovers an isoporphyrin-type optical spectrum. After standard workup, the transmetalated copper complex could be isolated in 92% yield. The slightly rhombic X-band EPR spectrum of this copper chelate (71 K; see the Supporting Information) shows g values of $g_1 = 2.217$, $g_2 = 2.049$, and $g_3 = 2.048$, and hyperfine coupling parameters $A_1(\mathrm{Cu}) = 177$ G, $A_2(\mathrm{Cu}) = 15$ G, and $A_3(\mathrm{Cu}) = 15$ G. A comparison of these values with those of copper complexes of tetraarylporphyrins and of several ring-contracted porphyrinoids clearly demonstrates the presence of the spacious isoporphyrin N_4 cavity through the large g_1 and the small $A_1(\mathrm{Cu})$ values.[25] This new option for transmetalation reveals new facets of the coordination chemistry of the intriguing isoporphyrin ligand.

In summary, we have developed a very simple and straightforward one-pot procedure for the preparation of stable isoporphyrins. With this method, up to 250 mg of an individual isoporphyrin is available within one day in the laboratory, and chemical postfunctionalization is possible to increase the palette of accessible derivatives. We are convinced that this finding will give isoporphyrin chemistry the impetus necessary for the broader development of this interesting macrocycle.



Scheme 2. Proposed scheme for macrocycle formation from the metal acetate templated variant of the Adler–Longo porphyrin synthesis.

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Keywords: isoporphyrins · macrocycles · NIR dyes · porphyrinoids · templated synthesis

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[26] CCDC 1476842 (**4**) contains the supplementary crystallographic data for this paper. These data are provided free of charge by Cambridge Crystallographic Data Centre.

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