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N21,N22 Cis-Bridged Tetraarylporphyrins from Oxidation of Tetraarylporphinatoiron(II)–Carbene Complexes

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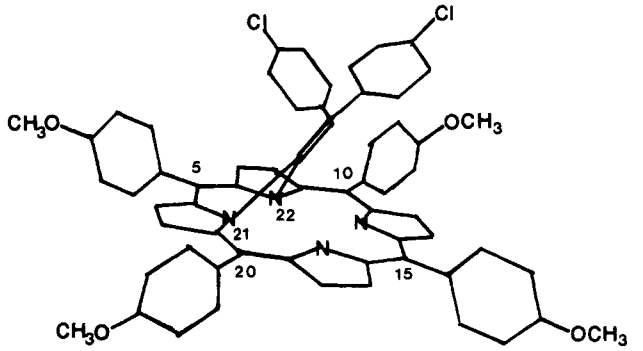
Porphinatoiron–carbene complexes are of interest in both reductive and oxidative vinylidene of xenobiotics by cytochrome P-450. As a result of our investigation into redox chemistry of vinylidene carbene complexes generated from tetraarylporphinatoiron compounds and 1,1,1-trichloro-2,2-bis(*p*-chlorophenyl)ethane[1] (DDT) or 1,1,1-trichloro-2,2-bis(*p*-methoxyphenyl)ethane (DMDT), we wish to report a novel intramolecular rearrangement of an iron–carbene complex, yielding hitherto unreported N21,N22 cis-bridged vinylidenetetraarylporphyrins. The rearrangement suggests a possible mechanism for P-450 destruction during reductive metabolism of halocarbon anesthetics[2-5] and oxidative metabolism of "suicide inactivators".[6-9]

Tetraanisylporphinatoiron(II)–[2,2-bis(*p*-chlorophenyl)-vinylidene]carbene complex was formed and oxidized by employing published procedures.[10-12] Under N_2 and using degassed solvents, a 9:1 dichloromethane (CH_2Cl_2)–methanol (MeOH) solution (2 mL) containing DDT (6 mg, 0.017 mmol) was added over 3 h to a 9:1 CH_2Cl_2–MeOH solution (5 mL) of tetraanisylporphinatoiron(III) chloride (FeTAPCl; 10 mg, 0.012 mmol) in the presence of iron powder (150 mg). Filtration followed by addition of excess $FeCl_3$ oxidant (10 mg) in 9:1 CH_2Cl_2–MeOH (1 mL) yielded a deep green solution on stirring for 16 h. During oxidation, a discrete intermediate with characteristic optical and ESR spectra was observed.[13]

In the absence of methanol (evaporation of solvent from carbene complex under N_2 and addition of the oxidant to a reconstituted CH_2Cl_2 solution), formation of the green color was rapid. The major reaction product was isolated as an intense green band by preparative TLC on neutral alumina [4:1 trichloromethane ($CHCl_3$)–MeOH eluant] after prepurification by column chromatography on neutral alumina ($CHCl_3$ followed by 4:1 $CHCl_3$–MeOH eluant); yield 6.2 mg (52%) of purple crystalline solid; mp 242 °C dec.

This product has been identified as the N21,N22 cis-bridged porphyrin compound I.[14] The optical spectrum of I in CH_2Cl_2



I

is the rhodoporphyrin type, characteristic[15,16] of N-alkylated *meso*-tetraarylporphyrins (Figure 1): λ_{max} (ϵ) 453 (1.04×10^5), 560 (6.58×10^3), 605 (1.97×10^4), 645 nm (7.89×10^3).

The field desorption mass spectrum indicates a 1:1 adduct of tetraanisylporphyrin (TAP) and [2,2-bis(*p*-chlorophenyl)-vinylidene]carbene and displays the reported tendency[15,16] of N-alkylated porphyrins to form abundant ions up to 3 mass units higher than the molecular ion: *m/e* 285, 284, 283, 282, 281, 280, 279 (MH^+·). Consistent with the proposed structure I, the electron impact mass spectrum (70 eV) of the species afforded by heating I to 240 °C on a solid probe was identified as that of 1,1-bis(*p*-chlorophenyl)ethylene,[17] the product from the expected thermolytic dealkylation of vinylidene-bridged porphyrin.[18] An alternative structure for I in which 1,2 migration of a *p*-chlorophenyl would yield a 2-carbon *cis*-stilbenoid bridge would be expected under these conditions to produce abundant ions 1 and 2 mass units less as a result of electrocyclic closure of *cis*-stilbene to a phenanthrene[19] and/or elimination of diarylacetylene.[20] The ^1H NMR spectra (250 MHz, CD_2Cl_2) at 25 and −70 °C are given in Figure 2. In the spectrum recorded at 25 °C (Figure 2a), the anisyl protons [quartets, with doublets centered at δ 8.41 and 7.58, 8.36 and 7.54, 8.0 and 7.31, 7.31 and 7.10 (16 H, J = 8.6 Hz)] are distinguished from those of the pyrrole β protons [quartets with doublets centered at δ 9.35 and 9.20, 9.15 and 8.62 (8 H, J = 4.3 Hz)] by comparison of chemical shift with the corresponding protons of TAP.[22] In addition, the coupling constants of the quartets ascribed to anisyl groups correspond closely to the anisyl coupling constants in TAP, while the smaller coupling constants

(1) Abbreviations used: 1,1,1-trichloro-2,2-bis(*p*-chlorophenyl)ethane, DDT; 1,1,1-trichloro-2,2-bis(*p*-methoxyphenyl)ethane, DMDT; *meso*-tetraanisylporphinatoiron chloride, FeTAPCl; *meso*-tetraanisylporphyrin, TAP.

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(13) Optical spectrum in CH_2Cl_2 was characterized by a broadened Soret band at 428 nm and a broad low intensity absorbance at 670 nm. ESR (CH_2Cl_2, 77 K) was characterized by a strong asymmetric transition at $g \sim 3.4$ and a weak transition at $g = 2$, suggesting a species with rhombic distortion[27] and an intermediate spin state.

(14) Analogous adducts have been prepared from FeTAPCl with DMDT and from tetraphenylporphinatoiron with DDT.

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(22) NMR (250 MHz, CD_2Cl_2):singlet (8 pyrrole H) at δ 8.91, quartet (16 anisyl H) with doublets centered at δ 7.32 and 8.16, J = 8 Hz, and singlet (12 methoxy H) at δ 4.13.

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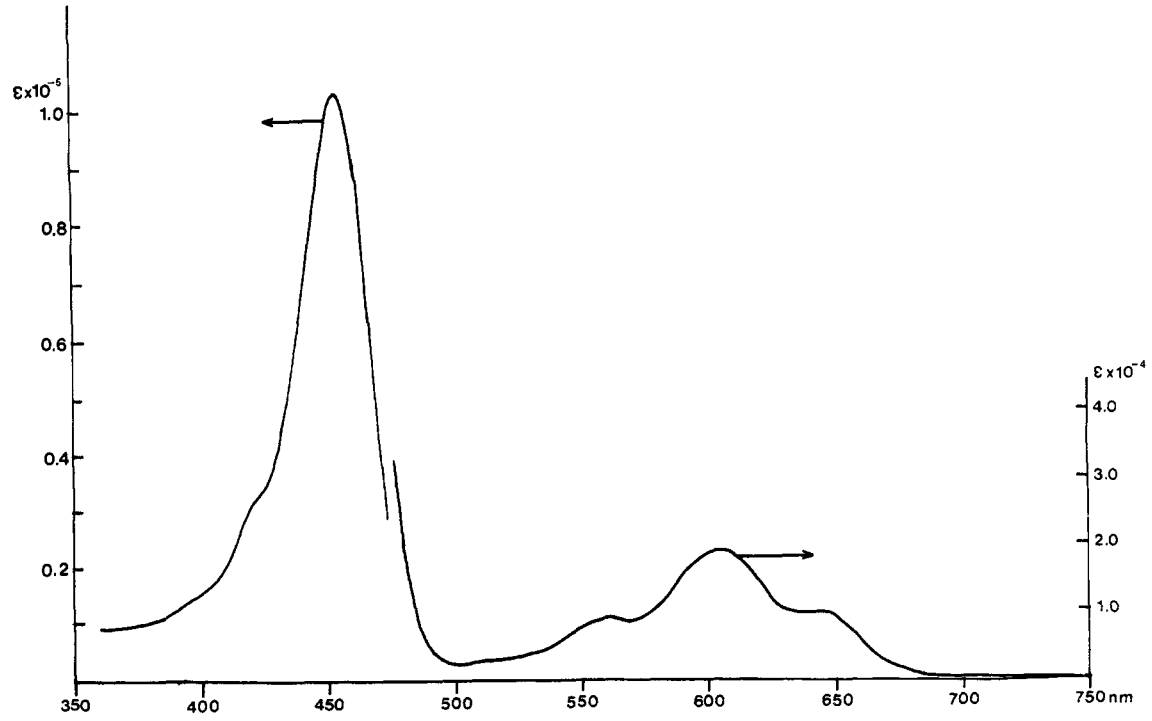

Figure 1. UV–visible spectrum (CH_2Cl_2) of compound I.

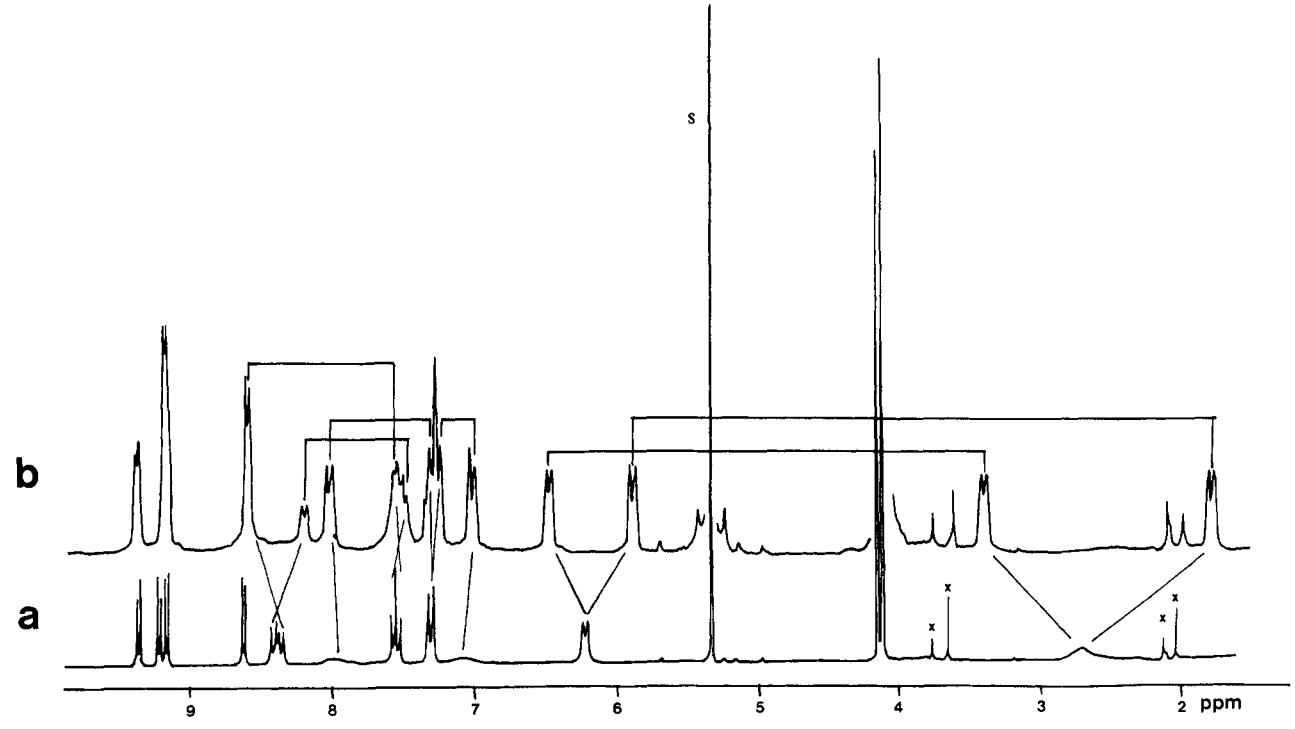

Figure 2. ^1H NMR (250 MHz, CD_2Cl_2) at (a) 25 and (b) −70 °C. Coupled anisyl and *p*-chlorophenyl resonances are indicated in (b) by brackets. The corresponding resonances in (a) are indicated by lines between (a) and (b) and were established from a series of spectra recorded at intermediate temperatures. Peaks "s" and "x" are from residual solvent protons and solvent impurities, respectively.

of the pyrrole quartets are consistent with those reported for pyrrole ring protons.[23] The upfield resonances of the remaining aromatic protons, which are assigned to the *p*-chlorophenyls [δ 6.22 (4 H, J = 7.2 Hz) and 2.71 (br, unresolved, 4 H)], arise from shielding effects of the porphyrin ring current.

The two sets of pyrrole quartets and the anisyl methoxy resonances [δ 4.15 (partially resolved doublet, 6 H) and 4.12 (s, 6 H), which appear in $CDCl_3$ as three singlets in 1:1:2 ratio] require that the adduct have a σ plane diagonally bisecting the porphyrin ring through two meso positions. Structure I satisfies this symmetry requirement. Hindered rotation of the *p*-chlorophenyl groups would be expected to resolve the ortho and meta *p*-chlorophenyl protons into the two nonequivalent highly shielded sets which are observed in the low temperature ^1H NMR spectrum (Figure 2b). The interchange of the sets by slow rotation was confirmed by observation of spin saturation transfer[24] in the

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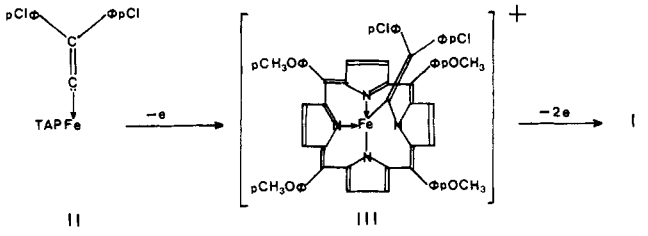
low-temperature spin-decoupling study performed to identify sets of coupled protons. Models indicate that the anisyl substituents at C10 and C20 (related by reflection in the σ plane) should be deshielded by the *p*-chlorophenyls. Interaction with the bridging group should also restrict rotation and resolve the *o*- and *m*-anisyl protons into nonequivalent sets above and below the porphyrin plane. Spin saturation transfer between protons of the two most deshielded anisyl quartets demonstrates rotational interchange of the protons which are above- and below-plane sets. Rotation is still hindered at ambient temperature (coalescence into a single quartet through rapid rotation on an NMR time scale is not observed from −70 to 25 °C). Hence, these quartets have been assigned to the C10 and C20 anisyls.

The C5 and C15 anisyl substituents are indistinguishable at 250 MHz, resulting in the two remaining anisyl quartets representing the ortho and meta protons on opposite faces of the porphyrin plane. Less hindered rotation than for the C10 and C20 anisyls would be expected and is evident in the NMR spectrum at 25 °C which indicates relatively rapid rotation on the NMR time scale (broadened resonances at δ 7.1 and 8.0 suggest a coalescence temperature slightly above 25 °C). The σ plane and the bridging vinylidene are confirmed by ^{13}C NMR, which shows three sp^3 carbon resonances for the anisyl methoxy groups (62.89 MHz, CD_2Cl_2: δ 56.08, 56.13, and 56.25 are the only ^{13}C resonances with shifts <113 ppm) and two resonances (62.89 MHz, $CDCl_3$: δ 160.7, 129.7) for the vinylidene carbons.

We propose the following scheme for the formation of I:



Preliminary optical and ESR spectra of III are consistent with the proposed structure.[13] An analogous reaction of (carboethoxy)carbene and cobalt(II) octaethylporphyrin has been reported[25,26] to occur through an intermediate similar to the proposed intermediate III in which the carbene has inserted into a cobalt–pyrrole bond. Compound III, unlike the cobalt complex, cannot disproportionate to the cis-bridged porphyrin by a redox pathway but requires an additional two-electron oxidation; so stability of III in the absence of excess oxidant is expected.

The proposed reaction scheme is without precedent in porphinatoiron chemistry; however, a compound obtained by reversible one-electron oxidation[12] of the [2,2-bis(*p*-chlorophenyl)-vinylidene]carbene complex of tetraphenylporphinatoiron is more likely to have structure III than the suggested iron(IV) ylide. A footnote in ref 12 reports that further irreversible oxidation yields an unidentified compound, having an optical spectrum identical with the tetraphenylporphyrin analogue of I. Reference 12 is entirely consistent with our proposed reaction scheme.

P-450–carbene complexes are strongly implicated in both oxidative and reductive metabolism of compounds known to inactivate P-450. A mechanism such as the proposed scheme may be operative in the inactivation of the enzyme. An intermediate similar to III could explain the observation[8] that P-450 substrates with terminal unsaturation are the only efficient suicide inactivators which produce iron-free N-alkylated porphyrin derivatives.

Acknowledgment. This work was supported by PHS Grant 1R01-CA 28622-01 and American Cancer Society Institutional Grant 1N 15U. We are grateful to Professor M. Brookhart for helpful discussions.

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Symmetry in Synthesis. Preparation and Methylation of Spiro Dilactones

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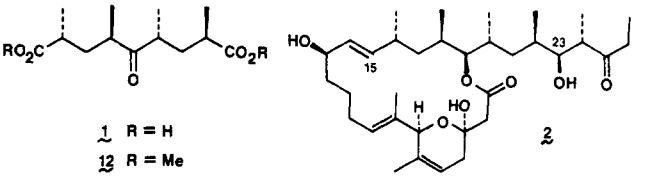
Increase in molecular complexity by simultaneous reaction at two or more symmetrically and, therefore, functionally equivalent sites is a potentially powerful and relatively unexplored synthetic concept. We describe here an efficient, highly stereoselective scheme for the construction of a single diastereomer of the keto diacid **1**, a molecule whose every other carbon atom is chiral, which utilizes this notion in a sequential fashion. The structural similarity between **1** and the C_{15}–C_{23} fragment of the agylcon (**2**)[2] of the

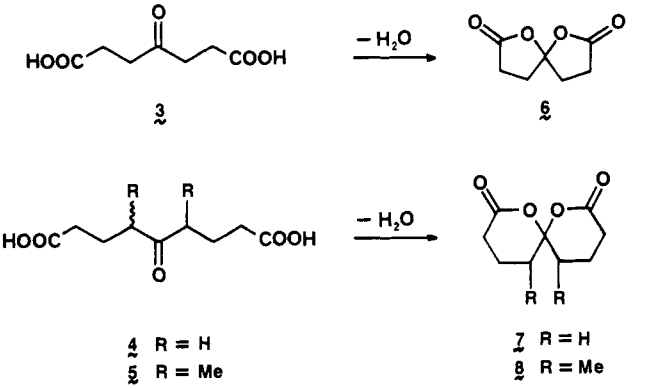


1 R = H
12 R = Me

2

venturicidinmacrolide antibiotics catalyzed this investigation. The chemistry of sprio dilactones plays an important role in this study.

Keto diacids **3**[3] and **4**[4] were prepared by known procedures. The dimethyl keto diacids **5** were synthesized as a nearly 1:1 mixture of meso and *d,l* isomers by twofold Michael reaction[5] of the pyrrolidine enamine of 3-pentanone with 3 equiv of methyl acrylate followed by acidic hydrolysis of the enamine [77% yield of keto diesters,[6a] bp 142–144 °C (1.25 torr)] and saponification (95% of mixture, mp of *d,l*-**5**[6a,7] 86–89 °C). Dehydration of **3** by dissolution in neat acetyl chloride at room temperature was accompanied by vigorous gas evolution and provided the known,[8] racemic spiro[4.4]dibutyrolactone (**6**). Similar treatment of **4**



3 → **6**

4 R = H
5 R = Me

7 R = H
8 R = Me

gave the spiro[5.5]divalerolactone **7** (66%, mp 143–144 °C)[6a] as the major of several products.[9] Brief exposure of the ~1:1

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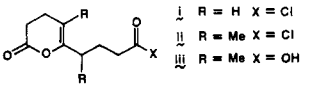
(9) Included among these undesired products was the enol lactone acid chloride i.



i R = H X = Cl
ii R = Me X = Cl
iii R = Me X = OH

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