Synthesis and Characterization of Alkylated Isobacteriochlorins, Models of Siroheme and Sirohydrochlorin†

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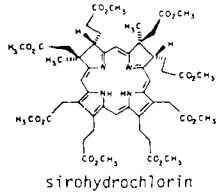
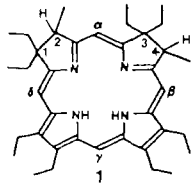
ABSTRACT: Synthetic analogues of sirohydrochlorin, the demetalated siroheme prosthetic group of nitrite and sulfite reductase as well as a vitamin B_{12} biosynthetic intermediate, have been prepared. The synthesis involves the oxidation of octaethylporphyrin to various porphyrin diketones and the conversion of the diketones to methylated hydrocarbons via the use of methyllithium and HI reducing reagents. Three isomeric alkylated isobacteriochlorins could be obtained by this method. Also synthesized was an alkylated chlorin. The dimethyl-*gemini*-octaethylisobacteriochlorins (DMOEiBC's) exhibit spectral properties almost identical with those of sirohydrochlorin. ^{1}H NMR spectra (180 MHz) show that the inner nitrogen protons of DMOEiBC are shifted to δ 3.6, indicating the reduced ring-current effect of isobacteriochlorins. Visible and IR absorption spectra further suggest that isobacteriochlorins in solution may consist of at least two tautomers which are in rapid equilibrium. A tentative assignment was made which suggests that the tautomer with two diagonally localized nitrogen protons is the principal form at room temperature. DMOEiBC's can be oxidized to yield cation radicals but cannot be dehydrogenated by quinones. The oxidation potentials of DMOEiBC are less positive than those of the corresponding chlorin or porphyrin, as evidenced by cyclic voltammetric studies. The low oxidation potential coupled with the stability imparted by the alkyl substituents makes the alkylated isobacteriochlorin an ideal compound to undergo facile ring oxidation/reduction processes.

A common prosthetic group in two redox enzymes which catalyze the six-electron reduction of sulfite to hydrogen sulfite (sulfite reductase) and of nitrite to ammonia (nitrite reductase) has recently been isolated and named siroheme (Murphy et al., 1973, 1974; Vega et al., 1975). The demetalated ligand, sirohydrochlorin, was identified as an isobacteriochlorin-type


sirohydrochlorin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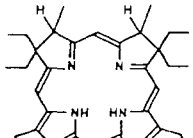
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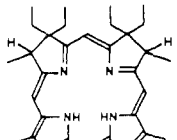
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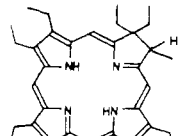
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derivative of uroporphyrin (Murphy et al., 1973). The complete stereostructure of sirohydrochlorin was established only very recently when it was realized that this compound is also an intermediate in the vitamin B_{12} biosynthetic pathways (Battersby et al., 1977; Deeg et al., 1977; Scott et al., 1978). Siroheme has been shown to be the terminal reduction site where substrates receive electrons from the electron-transport chain, but the mechanism by which siroheme mediates this remarkable multielectron reduction is unknown at present (Losada, 1976). The study of this prosthetic group has been difficult because of the scarcity of material as well as insufficient knowledge concerning the chemistry of isobacteriochlorin. Suitable model compounds, therefore, seem to be essential for understanding the physicochemical properties of siroheme and sirohydrochlorin. We report here the synthesis and characterization of a family of alkylated isobacteriochlorins (**1**–**3**) which are close structural analogues of sirohydrochlorin. Also synthesized is an alkylated chlorin (**4**).

Experimental Section

Octaethylporphyrin (OEP)[1] was synthesized according to Wang & Chang (1979). ^{1}H NMR spectra were recorded on a Bruker WH-180 instrument. Absorption spectra were measured by using either a Cary 17D or a Cary 219 spectrometer. IR spectra were recorded on a Perkin-Elmer Model 237B spectrometer. Mass spectra were obtained on a Finnigan 4000 system using a solid probe. Cyclic voltammetry was performed with a Bioanalytical Systems CV-1A unit. The synthesis of isobacteriochlorins from OEP is outlined by Scheme I.

Oxidation of OEP. The procedure was based on that of Inhoffen & Nolte (1969) with modifications. OEP (2 g) was dissolved in 200 mL of concentrated sulfuric acid (*d* 1.84), cooled in an ice bath, and stirred with a Teflon-coated magnetic bar. To this solution was added dropwise 36 mL of 3% H_2O_2 such that the temperature was kept below 10 °C. After the addition was completed (~15 min), the green solution was stirred an additional 10 min at 0 °C and then at room temperature for 12 min. The reaction was quenched by pouring the solution into a large beaker containing 200 g of sodium acetate and 500 g of crushed ice. The next day, ten batches of such reaction mixtures were combined and filtered. The precipitates were washed with water and redissolved in 1000 mL of methylene chloride. This solution was washed in a separatory funnel with water, separated, and evaporated to dryness.

The crude product was chromatographed into two fractions on a 2 × 12 in. silica gel (Baker 3405) column. The first fraction was collected with hexane/methylene chloride (40:60

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[1] Abbreviations used: DDQ, 2,3-dichloro-5,6-dicyano-1,4-benzoquinone; DMOEiBC, dimethyl-*gemini*-octaethylisobacteriochlorin; MeOEC, methyl-*gemini*-octaethylchlorin; OEC, octaethylchlorin; OEiBC, octaethylisobacteriochlorin; OEP, octaethylporphyrin; TPiBC, *meso*-tetraphenylisobacteriochlorin; TPP, *meso*-tetraphenylporphyrin.

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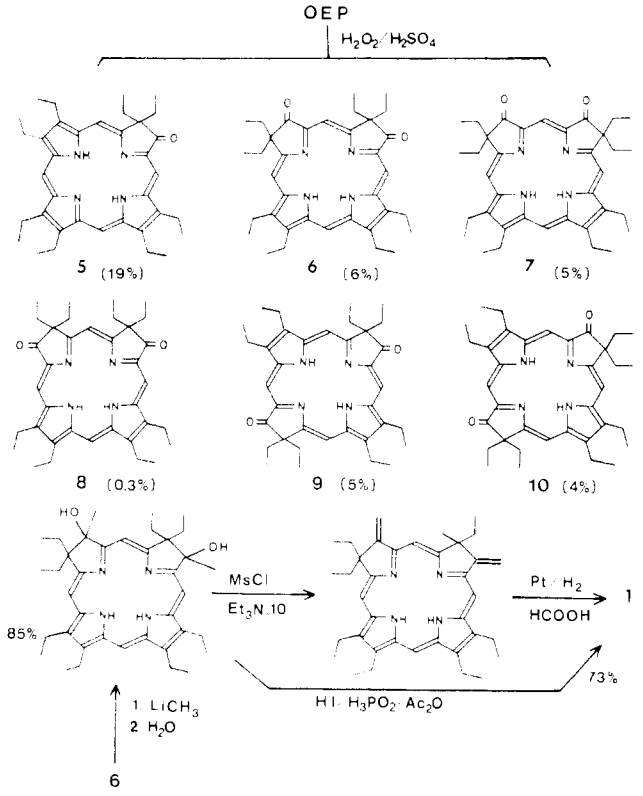
Scheme I



volume) until the eluant became green. The second fraction was eluted with pure methylene chloride. The compounds collected were rechromatographed on a silica gel column using the same solvents. The order of elution was **5** (dark brown), **9** (violet), **8** (blue), **10** (brown), **6** (green), and lastly **7** (yellow-green). Diketones **6**–**8** were always contaminated with small amounts of triketones and should be recrystallized from methylene chloride/methanol before use. These compounds were characterized by absorption and NMR spectra which are in close agreement with those reported by Inhoffen & Nolte (1969).

Methylation of the Ketones. Freshly prepared methyllithium in ether (10 g of MeI, 1 g of Li and 100 mL of ether) was pipetted into an ether solution of the porphyrin diketone at room temperature until the solution turned red. The reaction mixture was quenched and washed with water; the ether layer was separated and evaporated. The crude product was chromatographed on a silica gel column (Baker 3405) with methylene chloride as eluant.

Hydriodic acid (5 mL, *d* 1.7) was stirred and cooled in an ice bath, while 5 mL of acetic anhydride followed by 1 mL of 50% hypophosphorous acid was added. The dihydroxyisobacteriochlorin (250 mg) dissolved in 5 mL of acetic acid was mixed with 2 mL of the freshly prepared $HI/Ac_2O/H_3PO_2$. The mixture was warmed at 60 °C for 10 min, cooled in ice, and diluted with 100 mL of water. The crude product was collected by filtration and purified by chromatography on a 1 × 10 in. silica gel column using hexane/CH_2Cl_2 (30:70 v/v) as eluant. The compound collected was recrystallized in a minimum amount of CH_2Cl_2/methanol to yield shining red crystals, mp 190 °C.

^{1}H NMR, visible, and IR spectra of the dimethyl-*gemini*-octaethylisobacteriochlorins (DMOEiBC's) are shown in Figures 1–4. All three isomeric DMOEiBC's gave similar mass spectra: *m/e* 566 (M^+), 537 ($M^+ - 29$), and 283 ($M^+/2$). Anal. Calcd for $C_{38}H_{54}N_4$ (2,4-DMOEiBC): C, 80.51; H, 9.60; N, 9.89. Found: C, 79.82; H, 9.78; N, 9.67.

Results and Discussion

Synthetic isobacteriochlorins can be prepared conveniently from OEP and TPP either by sodium/isoamyl alcohol reduction of FeOEP (Eisner, 1957; Stolzenberg et al., 1980) or by diimide reduction of ZnTPP (Whitlock et al., 1969; Spaulding et al., 1980). One of the undesirable properties of these tetrahydroporphyrins is that they undergo rather facile dehydrogenation reactions in the presence of oxygen, light, and other oxidizing materials, such as ferric salts or quinones, to yield chlorins and porphyrins (Scheer & Inhoffen, 1978). The instability of such compounds often hinders successful preparation and extensive examination of their metal derivatives. Sirohydrochlorin, on the contrary, is notably much more stable and does not dehydrogenate at all (Murphy et al., 1973; Deeg et al., 1977). As dehydrogenation cannot readily occur on the alkylated isobacteriochlorin system, we consider that alkylation of the ring is an essential structural feature that must be retained in a true sirohydrochlorin model. The synthesis of such a compound is without precedent in the literature. A novel geminal dimethyltetrahydroporphyrin which bears partial structural resemblance to the sirohydrochlorin skeleton has just been reported (Montforts et al., 1979). The special expertise, however, required in this lengthy (more than 30 steps from commercially available materials) and demanding synthesis does not seem to lend itself to be a practical route to sirohydrochlorin model compounds.

Our synthesis begins with the easily obtainable OEP, which has been shown to react with hydrogen peroxide in acid medium to form a variety of gemini ketones (Inhoffen & Nolte, 1969; Bonett et al., 1969). These compounds probably are formed by a pinacol–pinacolone rearrangement of the intermediate diols. We have optimized the reaction conditions such that the combined yield of the porphyrin diketones consistently exceeds 20%.

Separation of the isomeric diketones is quite straightforward, and the conversion of the keto porphyrins to methylated isobacteriochlorins can be achieved via a two-step process (Scheme I). The $HI/H_3PO_2/Ac_2O$ mixture is very effective for converting the tertiary benzylic type alcohols to hydrocarbons. The alternate route, i.e., hydrogenation of an alkene intermediate, afforded the same product but with much poorer yield (~20%). These procedures work well on all of the keto porphyrins. Thus monoketone **5** afforded the methyl-*gemini*-octaethylchlorin (MeOEC) in more than 90% yield. It should be mentioned that this route to alkylated chlorin and isobacteriochlorins is made even more attractive by the recently developed large-scale pyrrole and OEP synthesis with which hundreds of grams of OEP can now be prepared very inexpensively (Wang & Chang, 1979).

^{1}H NMR. The three dimethyl-*gemini*-octaethylisobacteriochlorins (**1**–**3**) thus prepared consist of diasteric isomers. ^{1}H NMR spectra (180 MHz) of **1**–**3** are shown in Figure 1, and the peaks are assigned in Table I. Also included is the spectrum of the methyl-*gemini*-octaethylchlorin (**4**) for comparison. The diasteric nature of the DMOEiBC's can be seen readily by the bifurcation of the meso protons. Previous ^{1}H NMR spectra of diastereomeric OEiBC prepared by the sodium isoamylate reduction method also exhibit similar splittings of the meso protons (Inhoffen et al., 1969; Bonnett et al., 1967), revealing the influence of the substituents of the reduced pyrrole rings. Such splitting is not coupled to any other protons and is largest for the α-H flanked by the two reduced pyrrole rings and smallest, or not present at all, for the γ-H located farthest from the asymmetric centers.

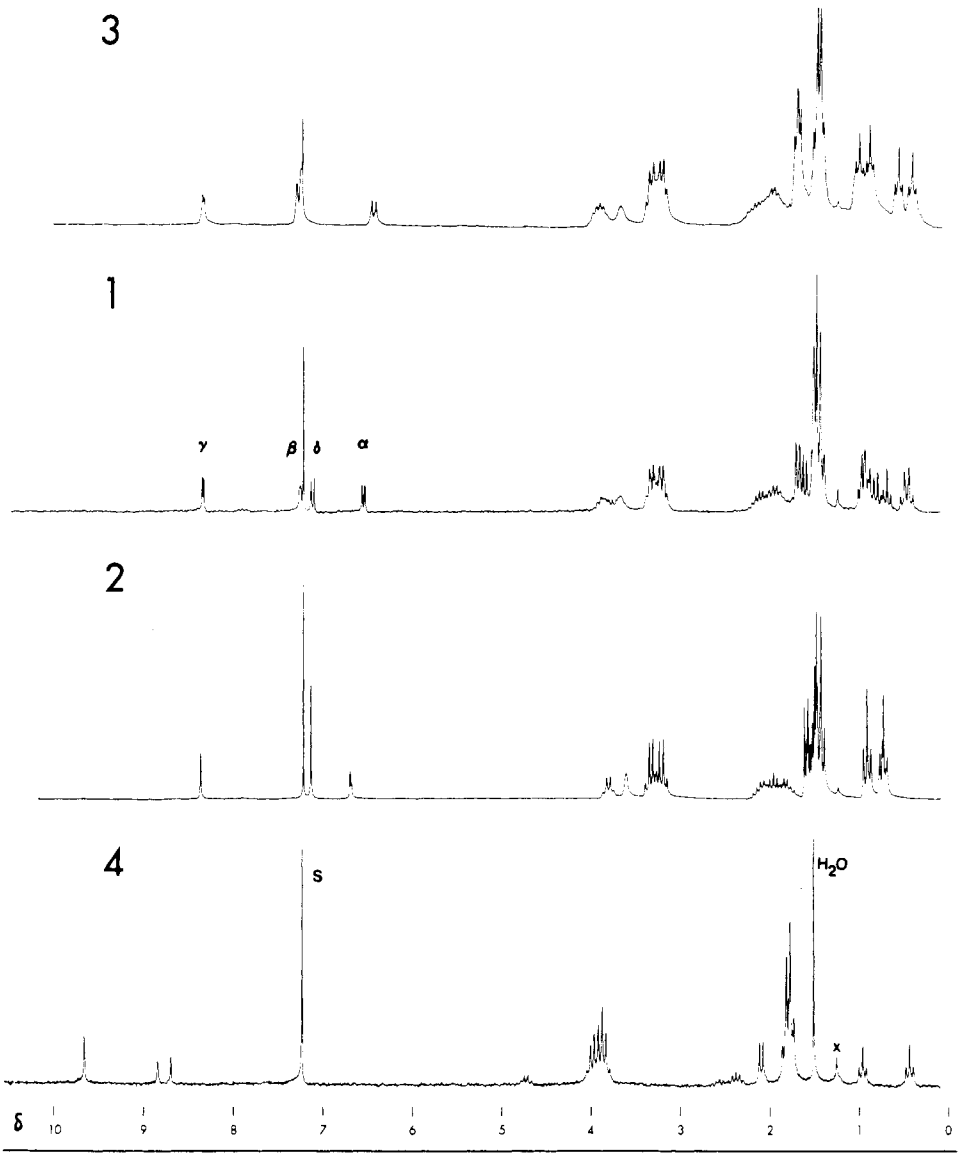


FIGURE 1: 180-MHz proton NMR spectra for **3** (1,4-DMOEiBC), **1** (2,4-DMOEiBC), **2** (2,3-DMOEiBC), and **4** (MeOEC). Concentration: 10^{-3} M in $CDCl_3$. S indicates the solvent peak and X is an impurity. Me_4Si peaks and the N–H signal of **4** are not shown.

Table I: ^1H NMR (δ) Assignments for DMOEiBC's and MeOEC (180 MHz, $CDCl_3$)

	DMOEiBC			4
position	2 (2,3-)	1 (2,4-)	3 (1,4-)	(MeOEC)
meso	8.38, γ	8.35, γ	8.35, γ	9.69
protons	7.15, β, δ	7.28, β	7.29, β, δ	8.87
	6.70, α	7.13, δ	6.44, α	8.71
		6.56, α		
pyrroline H	3.80 q	3.86 q	3.89 q	4.73 q
methyl	1.60 d	1.67 d	1.69	2.10 d
		1.60 d		
ethyl	3.26	3.26	3.26	3.92
(sat.)	1.42	1.42	1.45	1.78
ethyl	1.93	1.99	2.02	2.48
(unsat.)	0.90, 0.72	0.37–0.98	0.4–0.9	0.97,
	(2t)	(m)	(4t)	0.44
				(2t)
NH	3.59	3.65	3.65	−2.2 (not shown)

Molecular models of DMOEiBC further suggest that the two geminal ethyl groups do not have much freedom of rotation and that they cannot assume any symmetric orientation in reference to the ring. This results in multiplication of the NMR peaks of the geminal ethyl groups. Another factor which may contribute to the complexity of the spectrum is the warping of the pyrroline rings. Recent X-ray structural studies of ZnTPiBC revealed that at least one of the reduced rings, is slightly twisted out of plane (Spaulding et al., 1980).

The inner N–H protons of the isobacteriochlorins were found at about δ 3.6. This is a remarkable shift from the δ −4 of OEP and δ −2.2 of MeOEC. Similar shifts (at δ 2∼3) have been observed for sirohydrochlorin (Scott et al., 1978) and OEiBC (Inhoffen et al., 1969). This downfield shift is believed to be an indication of the reduced diamagnetic ring current of the saturated porphyrin ring (Bonnett et al., 1967). The possible out-of-plane geometry of the N–H bonds in isobacteriochlorins may also contribute to reduce the ring-current effect.

Absorption Spectra. Visible spectra of DMOEiBC's are shown in Figure 2. It should be noticed that while the band maxima and the overall spectral features of all isobacteriochlorin derivatives are very similar, one notable difference between alkylated (including sirohydrochlorin) and unalkylated tetrahydro derivatives is that the intensity of the red band at ∼635 nm as well as the red Soret shoulder at ∼400 nm is much lower for the alkylated compounds. Table II provides

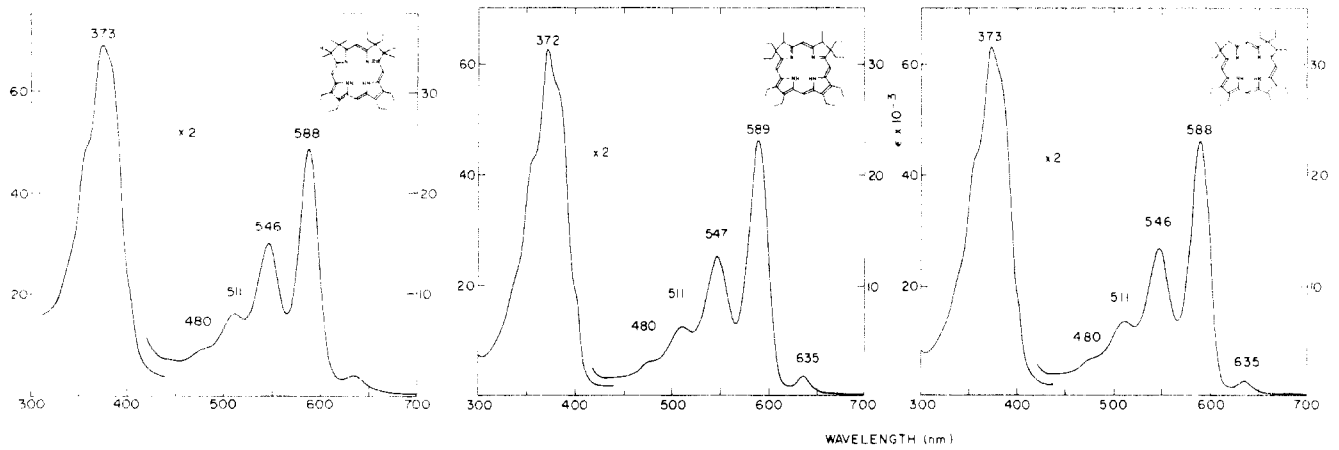


FIGURE 2: Absorption spectra of the three DMOEiBC's (**1**–**3**) in methylene chloride at 22 °C.

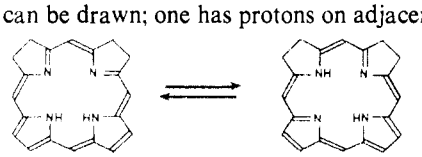
Table II: Spectral Characteristics of Isobacteriochlorins

compd	A_{588}/A_{635}	ref
2,4-DMOEiBC	17	this work
2,3-DMOEiBC	13	this work
sirohydrochlorin	16	Deeg et al. (1977)
	10[a]	Murphy et al. (1973)
OEiBC	3.5	Eisner (1957)

[a] Rough estimation, because the base line of the spectrum was not zeroed.

some comparison of the ratio of the red band vs. the most intense band in the visible region. It is further observed that while this ratio varies only slightly with different solvents (±10%), it is extremely sensitive to temperature. For example, at 60 °C the red band of 2,3-DMOEiBC is about 20% more intense than at room temperature, but at liquid nitrogen temperature this peak disappears altogether (Figure 3) whereas the band at 588 nm increases in intensity enormously. These results seem to suggest that the 635-nm peak, as well as the 400-nm peak, belongs to a species which is different from the species which exhibits the intense 588-nm band. Judging from the clean spectral transitions displayed by Figure 3, it may be concluded that isobacteriochlorins in solution may consist of at least two forms which are in rapid equilibrium and that these two forms have different ground-state energy. The population of these two forms can be modulated by the pyrrole ring substituents. A reasonable conjecture concerning the identity of these forms would be that they are valence tautomers.

Tautomeric Structures of Isobacteriochlorin. The conjugation pattern of isobacteriochlorin has been a subject of considerable curiosity (Oester, 1971). At least two tautomeric structures can be drawn; one has protons on adjacent pyrroles



and the other, on diagonal rings. In the cis tautomer, the placement of hydrogens on adjacent pyrrole nitrogens would introduce severe steric strains which can be partially relieved by bending the N–H bonds out of the plane such that one would point above and the other below. In the trans tautomer, the conjugation is formally interrupted, yet the isolated nitrogen can still participate in the greater ring conjugation by assuming partial positive characters. It is rather difficult to assess the relative energy levels of these two valence tautomers

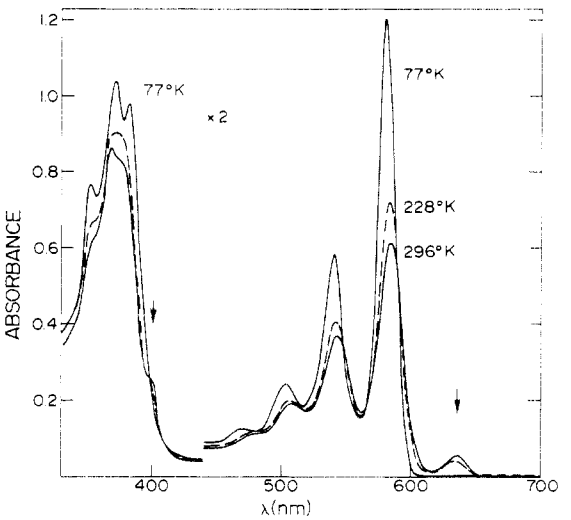


FIGURE 3: Temperature dependence of the absorption spectrum of **2** (2,3-DMOEiBC). Spectra were recorded in 2-methyltetrahydrofuran solvent, which forms a clear glass at liquid nitrogen temperature.

because both would suffer some degree of loss of the porphyrin-type resonance stabilization. However, the observation that alkyl groups could influence the population of the two forms may suggest a clue. If we assume that the nitrogen of the reduced ring can be made slightly more electron rich by alkyl substituents, the likelihood of having the trans tautomer would be increased. This would place the 635- and 400-nm bands to the cis tautomer and the intense 588-nm band to the trans tautomer.

Further evidence of the tautomerism of isobacteriochlorin can be found in the IR spectra. Figure 4 shows the IR absorptions of 2,3-DMOEiBC and the corresponding methylated MeOEC. Attention is brought to the N–H stretching region (3200–3400 cm^{-1}). In contrast to porphyrins and chlorins which have only one N–H stretching frequency, the isobacteriochlorin exhibits two peaks. The recently synthesized geminal octamethylisobacteriochlorin (Montforts et al., 1979) is also reported to have two peaks. The presence of two ν_{N-H} can be interpreted as either (A) they are from the two nonequivalent nitrogens in the trans tautomers or (B) they reflect the presence of both cis and trans tautomers.

If (A) were true then we would have to accept the fact that the two ν_{N-H} differ by an energy $\sim$100 cm^{-1}. This seems too large a difference when one considers that pyrrole (3400 cm^{-1}), OEC (3340 cm^{-1}), and OEP (3310 cm^{-1}) all have very close ν_{N-H} values (Mason, 1958). The alternative is that the peaks are from individual tautomers, and we may even predict that

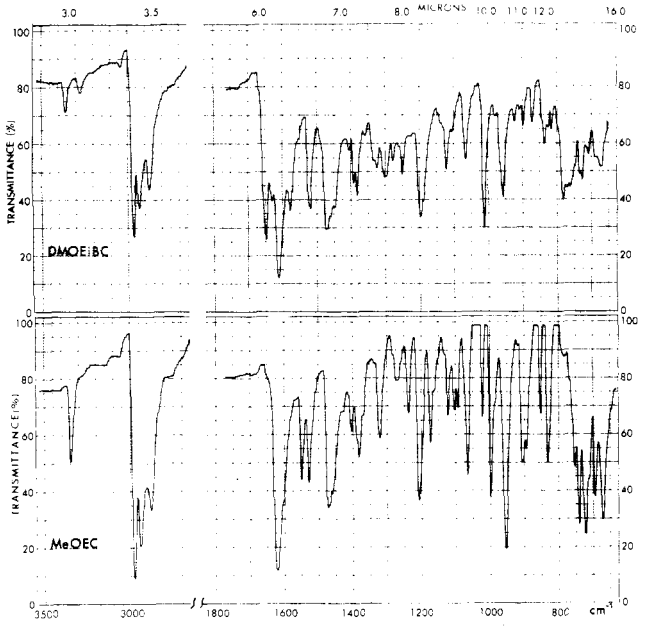


FIGURE 4: IR spectra of 2,3-DMOEiBC (**2**) and MeOEC (**4**). Samples were formulated in KBr pellets.

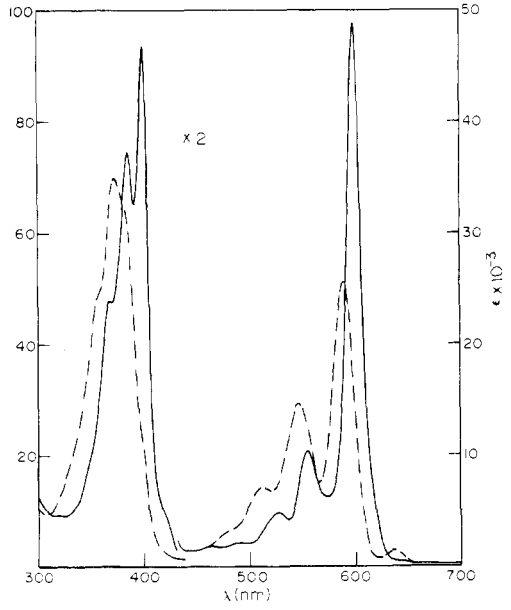


FIGURE 5: Zinc insertion to DMOEiBC. To a sample of 2,4-DMOEiBC (**1**) in 3 mL of CH_2Cl_2 (--) was added one drop of saturated methanol solution of zinc acetate. The solution was kept at 40 °C for 5 min and the spectrum (—) was recorded at 22 °C.

the 3365-cm^{-1} signal belongs to the trans form, in accordance with the ν_{N-H} of chlorins and porphyrins. The ratio of the 3365-cm^{-1} vs. 3270-cm^{-1} band is also temperature dependent. At elevated temperatures, the intensity of the 3270-cm^{-1} band increases at the expense of the 3365-cm^{-1} band. This is consistent with our postulate that more of the cis tautomer would form as the temperature goes up. It should be emphasized, however, that this is only a tentative assignment; more data are needed for a definitive picture.

Metal Complexes. Several metal complexes were prepared to further explore the fitness of the DMOEiBC's as sirohydrochlorin models. The isobacteriochlorins have very high affinity for divalent cations such as Zn^{2+} and Cu^{2+}. Figure 5 shows the spectral transition from free base to the Zn complex. The spectrum of Zn(2,4-DMOEiBC) is nearly identical with that of zinc sirohydrochlorin (Murphy et al., 1973; Deeg et al., 1977). Addition of H_2SO_4 to Zn(2,4-DMOEiBC) in methanol results in expulsion of the metal ion and formation of the protonated species (611, 570, 490, 409, 396 and 378 nm).

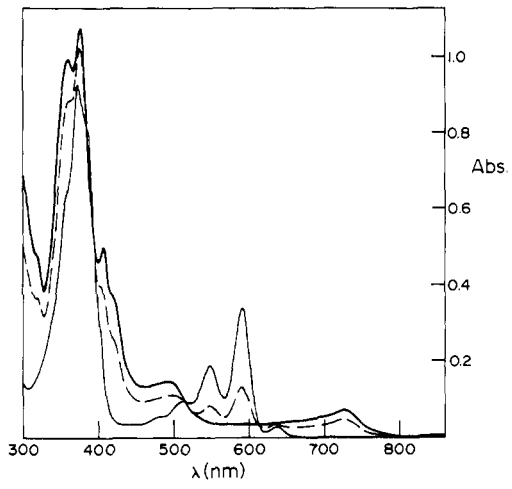


FIGURE 6: Cation radical $(DMOEiBC)^{+\cdot}$ generated by iodine oxidation. A solution of 2,3-DMOEiBC (**2**) in CH_2Cl_2 (light solid line) was titrated with I_2 in CH_2Cl_2 through the use of a 10-μL microsyringe; 0.6 equiv of I_2 (--) and 1.2 equiv of I_2 (heavy solid line).

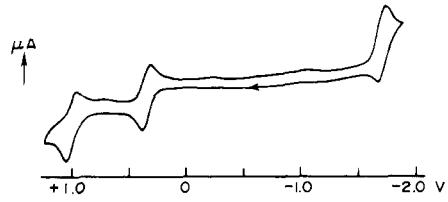


FIGURE 7: Cyclic voltammogram of 2,4-DMOEiBC (**1**). The waves (left to right) are 2+/1+ (+0.95 V), 1+/0 (+0.37 V), and 0/1- (−1.72 V) processes, respectively. The CV experiment was performed in butyronitrile using tetra-*n*-butylammonium perchlorate as supporting electrolyte and a SCE as reference electrode; scan rate, 200 mV/s.

The iron complex of 2,4-DMOEiBC has also been synthesized. The ferrous complex binds CO and exhibits spectral properties very similar to those of the corresponding siroheme derivatives (Chang & Fajer, 1980).

Stability and Oxidation of DMOEiBC. One of the salient features of our alkylated isobacteriochlorins is that, like sirohydrochlorin, they cannot be dehydrogenated to chlorins or porphyrins. This can be evidenced by the experiment that addition of 2 mol equiv of dichlorodicyanobenzoquinone (DDQ) to the 2,4-DMOEiBC in benzene solution produces nothing but a slight spectral maxima shift. In contrast, the same amount of DDQ would convert TPiBC in benzene instantaneously and quantitatively into TPC; eventually the excess DDQ oxidizes TPC into TPP. The resistance against photooxidation is also much higher for the alkylated compounds. It is noticed, however, that the zinc DMOEiBC as well as the protonated form is more labile and would decompose rapidly in the presence of oxygen and light, but the photooxidation product is not a chlorin. Further study is under way to elucidate this reaction.

When iodine is used as the oxidant, a completely different reaction takes place. Figure 6 illustrates the spectral changes that occurred on iodine oxidation. The product is a cation radical:

$$DMOEiBC \rightarrow DMOEiBC^{+\cdot} + e$$

This cation radical has been fully characterized by electrochemical studies as well as by EPR and ENDOR spectroscopy (Richardson et al., 1979a, 1979b). The cyclic voltammogram

of DMOEiBC (Figure 7) reveals three well-defined, reversible, one-electron redox reactions. In addition to the monocation radical which can be obtained at +0.37 V, a dication radical can also be generated at +0.95 V. These oxidation potentials are much less positive compared to those of porphyrins and chlorins (Chang & Fajer, 1980). $DMOEiBC^{+\cdot}$ is very stable, as evidenced by the fact that the radical species generated from iodine oxidation under air (Figure 6) is identical with that obtained in a vacuum electrolytic apparatus (Richardson et al., 1979a) and remains stable in solution for days. In contrast, reaction of I_2 and TPiBC under similar conditions does not yield pure $TPiBC^{+\cdot}$, and the radicals convert into protonated TPC within a short period of time.

Conclusion

The discovery of sirohydrochlorin marked the beginning of a new venture for porphyrin researchers. Many questions concerning the nature of sirohydrochlorin and siroheme and their biological functions are waiting to be answered. The successful preparation of the faithful sirohydrochlorin model compounds described here undoubtedly will speed the progress in this research. Our present results already indicate that isobacteriochlorin undergoes oxidation reactions much easier than does the corresponding chlorin or porphyrin. While doing so, it requires the alkyl substituents on the reduced pyrrole rings to help maintain the integrity of the molecule. This is a unique property of sirohydrochlorin, and perhaps it is important for siroheme functioning. Other studies on electrochemistry and ligand coordination of iron DMOEiBC are under way to further probe the role of sirohydrochlorin in nature.

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