Synthesis of New Tetraphenylporphyrin Molecules Containing Heteroatoms Other than Nitrogen. I. Tetraphenyl-21,23-dithiaporphyrin

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Abstract: A new and general synthesis of tetraphenylporphyrin analogs is described. The tetraphenyl-21,23-dithiaporphyrin was prepared in a pure form. Its electronic spectrum, as well as preliminary X-ray measurements, suggests that the central sulfur and nitrogen atoms are somewhat out of the plane of the molecule, facilitating attainment of a smaller angle between the phenyl groups and the porphin plane than is found in tetraphenylporphyrin. The chemical shift of the β-pyrrole hydrogens as found in the ^1H NMR spectrum at room temperature is almost identical with that found for tetraphenylporphyrin at −80°. Protonation is seen to occur at the nitrogen atoms and the optical spectrum of the conjugate acid is qualitatively similar to that of the conjugate acid of tetraphenylporphyrin.

The porphin skeleton plays an important role in many biological and catalytic systems.[1,2] Tetraphenylporphyrin is a thermally stable ligand, which can be synthesized according to established methods. We have shown before that its metal complexes are catalysts for oxidative dehydrogenation[3] and symmetry forbidden reactions.[4]

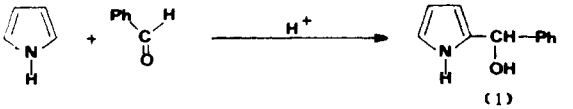
The great advantage of using these molecules as catalysts is that their structure can be modified in a controlled way and correlations between catalytic activity and structure can be followed. Catalytic activity has been shown to be dependent on the central metal atoms,[3] as well as on substituents in the *p*-phenyl positions,[5] and correlations with physical properties of the catalyst in solution could be found.

An attractive modification in the molecule would be to change the immediate environment around the central metal atom, which means to replace the nitrogen atoms by other heteroatoms. In this paper we report the synthesis of tetraphenylporphyrin (TPP) with two opposite NH groups being exchanged for sulfur. In the future we shall report the synthesis of molecules containing other heteroatoms and the catalytic activity of these systems.

A general synthesis (Scheme I) for tetraphenylporphyrin has been given by Adler and coworkers,[6] and the conditions for optimal yield and purity have been studied.[7]

The only example of a dithiaporphin in the literature is the synthesis by Broadhurst and Grigg,[8] who used a [3 + 1] cyclization (Scheme II). This approach was not found to be suitable for the synthesis of the tetraphenyl derivative, however, and therefore we worked out another synthetic scheme, which appeared to be applicable not only for the disulfur compound, but for other heteroatoms as well.

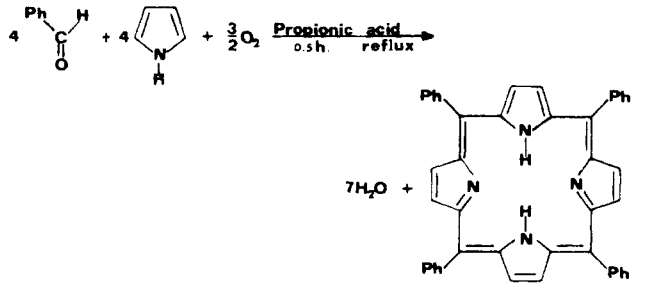
The Synthesis. To arrive at a good synthetic method, it is best to consider the mechanism of the ordinary acid-catalyzed reaction between benzaldehyde and pyrrole first, and to see whether this reaction can be modified to suit our purpose. The first step is commonly assumed to be the acid-catalyzed addition of pyrrole to benzaldehyde.



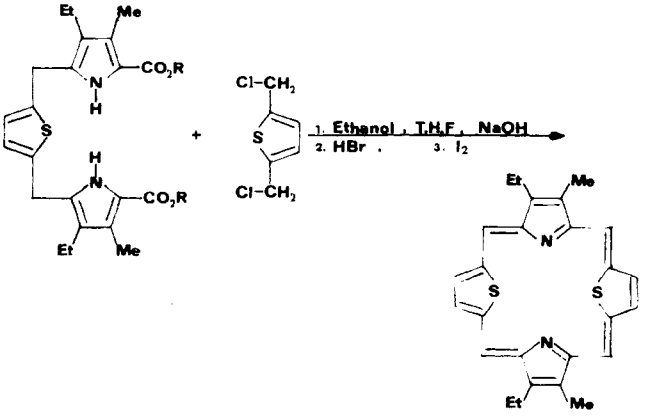
(I)

It is not yet clear, how intermediate I reacts further, but we can envisage four possibilities (shown in Scheme III). If we assume V to be an intermediate, which reacts with pyrrole under oxidizing conditions to give porphyrin, it should be possible to synthesize new porphyrin-molecules by the general reaction shown in Scheme IV, where Y in VI stands for a heteroatom other than nitrogen.

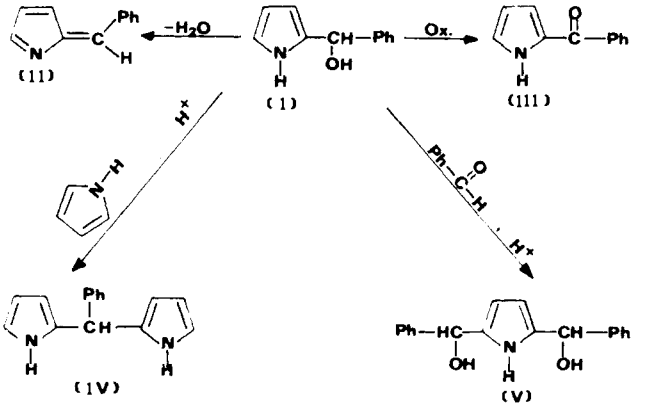
Scheme I



Scheme II

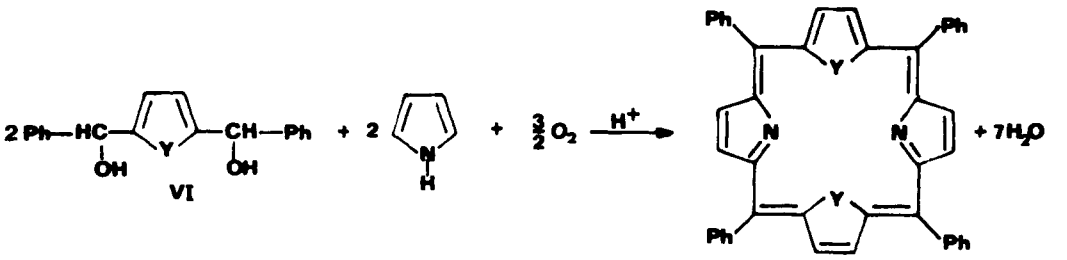


Scheme III

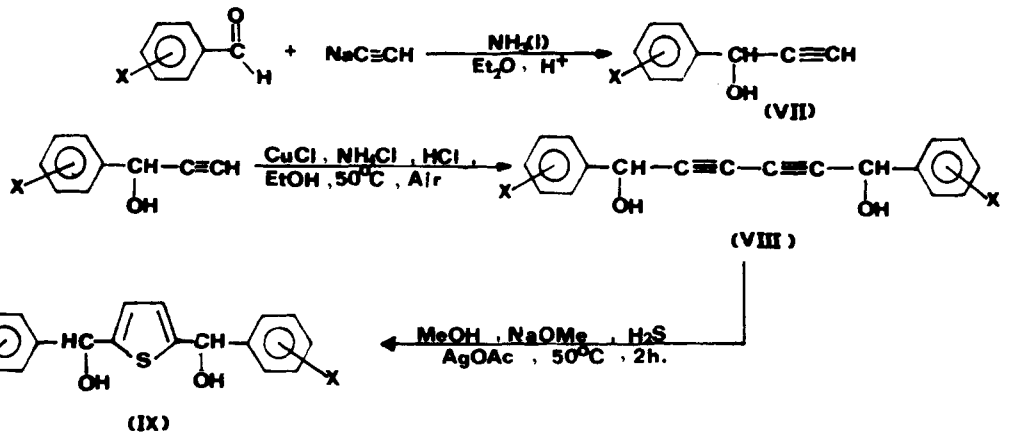


The problem is now reduced to the synthesis of the dialcohol VI. It did not seem feasible to start from the bare heterocycle and therefore we developed Scheme V, which appeared to be generally applicable. 2,5-Bis(phenylhydroxy-

Scheme IV



Scheme V



methyl)thiophene (IX, X = H) has been prepared before[9] in 14% yield. According to the Scheme V it can be prepared in 25% yield in an easy and convenient way.

The assumption that such a dialcohol can give porphyrin by an acid-catalyzed reaction with pyrrole appears to be justified and Table I gives the porphyrin yields as a function of temperature, solvent, and acidic catalyst. The yields were calculated from the optical spectra. We see that only the solvents chloroacetic acid/benzene, chloroacetic acid/toluene, and propionic acid gave reasonable yields, which depended on the duration of the reaction. To find the reaction time for maximum yield, we followed the optical density at 435 nm as a function of time for these three solvent systems and the result is given in Figure 1. A change of solvent from benzene to toluene under otherwise identical conditions gives almost double the yield; therefore an increase in reaction temperature seems to benefit porphyrin yield. From Figure 1 we see that the yield as a function of reaction time goes through a maximum and the material apparently decomposed when heated too long under these drastic conditions. The dependence of porphyrin yield on temperature can only be explained after further elucidation of the mechanism, but some pertinent interesting phenomena can be reported at this stage.

In all cases, besides the porphyrin, another compound was found, green in color, having a strong absorption at 450 nm. In benzene and a 1:1 benzene–methanol mixture, more of this green compound was found than in the high temperature systems. If, however, the reaction mixture containing the green material was exposed to ordinary daylight for 48 hr, only porphyrin was found.

We explain the formation of the light-sensitive green compound as due to a competition between cyclization and dehydrogenation. The product of dehydrogenation would be the dithia analog of bilatriene *abc*,[10] 1-(phenylmethylene)-5,10,15-triphenyl-20,22-dithiabilatriene *abc*.

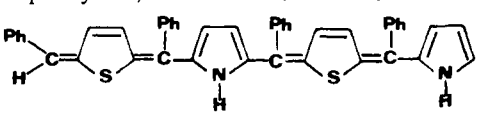


Table I. Influence of Various Factors on the Synthesis of Tetraphenyl-21,23-dithiaporphyrin[a]

Solvent(s)	Acid	Acid concn, %	Time, hr	Yield, %
10% benzene in methanol	HBr in HOAc	1 (v/v)	20	0.2
10% benzene in methanol	HBr in HOAc	2 (v/v)	20	0.25
50% benzene in methanol	HBr in HOAc	2 (v/v)	20	
Benzene	$ClCH_2CO_2H$	1 (w/w)	20	4.0
Benzene	$ClCH_2CO_2H$	2 (w/w)	20	4.7
Benzene	$ClCH_2CO_2H$	2 (w/w)	1.5	6.0
Toluene	$ClCH_2CO_2H$	2 (w/w)	1	10.0
Propionic acid			0.5	8.5
Propionic acid			1	9.0
Acetic acid			0.5	

[a] All of the experiments were performed under reflux conditions, on solutions of 0.34 mmol of IX and of pyrrole in 100 ml of solvent.

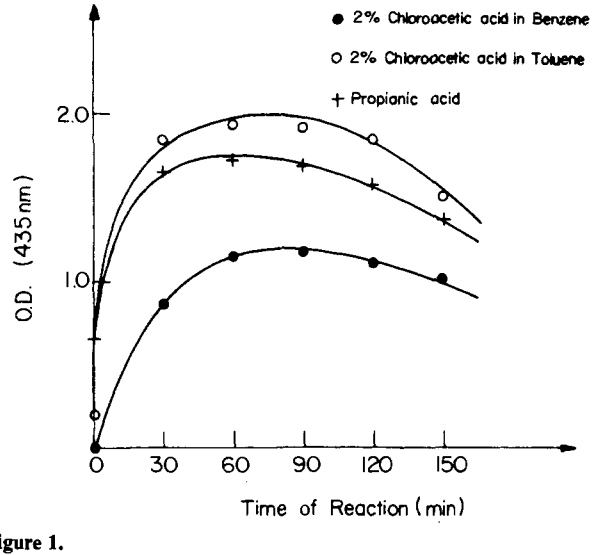


Figure 1.

Table II. Optical Spectra of Porphins and Porphyrin

	Soret, λ_{max}, nm (ϵ)[a]	Q bands, λ_{max}, nm (ϵ)[a]			
		IV	III	II	I
Tetraphenyl-21,23-dithiaporphyrin ($CHCl_3$)	435[a] (297,500[b])	515 (29,625)	548 (7250)	635 (2220)	699 (4625)
Tetraphenylporphyrin[b]	419 (464,000)	485 (3800), 515 (18,700)	548 (8600)	592 (5500)	647 (3900)
21,23-Dithiaporphin[c] (Pyridin)	402 (64,900)	494 (11,030)	521 (4140)	613 (1140), 621 (1006)	645 (252), 674 (640)
Aethioporphyrin I[c]	400.5 (135,030)	500 (11,900)	583 (8340)	571 (5460)	627 (4360)

[a] ϵ was calculated from measurements at several concentrations. No change was found with dilution. [b] Reference 13. [c] Reference 8.

It is a very reactive, light-sensitive compound and could not be isolated. We were, however, able to isolate the green compound in the synthesis of tetraphenyl-21,23-diselenoporphyrin, about which we shall report at a later stage. Upon exposure to light for 15 min, it was converted into the porphyrin.

The visible spectrum of the 1-(phenylmethylene)-5,10,15-triphenyl-20,22-diselenobilatriene *abc* in 5% benzene in hexane has peaks at 425, 452, 595 and 630 nm and shoulders at 565 and 714 nm. The optical densities are 1.42, 1.66, 0.85, and 0.7 and 0.8 and 0.3, respectively.

This polyene has 20 π electrons and its cyclization is forbidden thermally, but allowed photochemically.[11] Therefore, our assumption at this stage is that the green compound is the product of dehydrogenation, which under the influence of light cyclizes into the porphyrin.

The dithiaporphyrin cannot be purified by chromatography on silica gel or neutral alumina, but repeated purification on basic alumina and subsequent recrystallization from chloroform–pentane gives pure dark violet crystals, which dissolve in chloroform or benzene with a red orange color and in trifluoroacetic acid with a green color.

Electronic Spectra. In Table II the optical spectrum is given of the tetraphenyldithiaporphyrin. For comparison the spectra of tetraphenylporphyrin itself, of the dithiaporphin synthesized by Broadhurst and Grigg and of that of its nitrogen analog, aethioporphyrin I, are also included.[12] As is the custom with porphyrin spectra, a distinction is made between the intensive Soret band in the near-ultraviolet and four Q bands in the visible spectrum. Although we do not want to give a detailed interpretation of the spectrum, some trends are discernible, which can give information about the configuration of the tetraphenyldithiaporphyrin in solution.

We can observe in Table II several effects due to the introduction of two sulfur atoms in either TPP or aethioporphyrin I. (a) The absorption frequency of the Soret band is hardly affected in aethioporphyrin I, while tetraphenyldithiaporphyrin shows a bathochromic shift of 16 nm as compared to tetraphenylporphyrin itself. (b) The extinction coefficients of Q bands II, III, and IV show roughly the same dependence on sulfur introduction for both porphyrins. For Q band I, on the other hand, an increase in intensity is found for tetraphenylporphyrin and a rather drastic decrease in the case of aethioporphin I. (c) In both porphyrins the introduction of sulfur causes bathochromic shifts of Q bands I and II, while bands III and IV are much less affected.

It is generally known that the conjugate acids of tetraphenylporphyrin-type molecules show a typical green color, which is not found for the dications of porphyrins that do not carry aromatic groups in the meso positions. This has been explained by Stone and Fleischer[14] as being due to the fact that in the dications of tetraphenylporphyrin-like molecules, a greater resonance interaction with the phenyl groups occurs than in the free base. By X-ray measurements it is found that, in free base tetraphenylporphyrin, the phenyl groups make an angle of at least 70° with the plane of the porphin moiety, while the four nitrogen atoms are within the plane of the molecule. The phenyl groups cannot become more coplanar, because of steric interaction between the *o*-phenyl hydrogen and the β-pyrrole hydrogen. Because of the presence of two extra protons the nitrogen atoms are turned out of the plane of the molecule in the dication and the pyrrole units are tilted. Therefore, there is less steric hindrance in the dication and the phenyl groups can turn toward a smaller angle with porphin plane.

The spectral results of the greater resonance interaction in the conjugate acid are a bathochromic shift of the Soret band, an increase in intensity of the Q I band and a bathochromic shift of Q bands I and II. These are exactly the effects we find when tetraphenylporphyrin is converted into its dithia compound and which are, with the exception of the bathochromic shifts of the Q I and II bands, not found for the aethioporphyrin I.

This suggests that, in the tetraphenyldithiaporphyrin, more resonance interaction occurs with the phenyl groups than in tetraphenylporphyrin itself. In tetraphenylporphyrin the distance between adjacent nitrogen atoms is 2.05 Å,[15] the Van der Waals radius of nitrogen is 1.5 Å. Sulfur, on the other hand, has a radius of 1.85 Å; so steric crowding is to be expected. This is also in accordance with preliminary X-ray measurements, which show the sulfur atoms to be out of plane by 0.09 Å and the nitrogen atoms by 0.24 Å. The angle between the phenyl rings and the porphin moiety is found to be 61°. We have argued before,[5,16] and it has been calculated by Wolberg,[17] that in solution an average smaller angle between the phenyl groups and the porphin plane can be expected than in the solid state. This is also supported by the fact that, according to ^1H NMR measurements, the phenyl groups start to rotate in solution between 20–100°.[18] Therefore, it is reasonable that the tetraphenyldithiaporphyrin shows trends in its solution spectrum which are typical for the conjugate acids of tetraphenylporphyrin molecules, because the two sulfur and nitrogen atoms are somewhat turned out of the molecular plane.

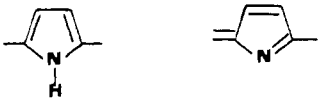
In Table III the spectra of the conjugate acids of tetraphenyldithiaporphyrin, tetraphenylporphyrin itself, and dithiaporphin are compared with those of their free bases. In all three cases a simplification of the Q band structure occurs on protonation. In spite of the fact that the conjugate acid of tetraphenylporphyrin has considerable nonplanarity[14] while most of the metallotetraphenylporphyrins are planar, the resemblance of their optical spectra was ascribed to an increase in symmetry, as compared to the free base. In the dithia derivatives no change of symmetry occurs on protonation. The decrease in complexity of the optical spectra in the above cases has, therefore, to be ascribed to other reasons.

The conjugate acids of tetraphenyldithiaporphyrin and tetraphenylporphyrin show the bathochromic shifts of the Q bands, which we have seen are typical for these porphyrins. In tetraphenyldithiaporphyrin this shift is considerably larger, however, than for tetraphenylporphyrin. We take this as an indication that in the conjugate acid of tetraphenyldithiaporphyrin there is more resonance interaction with the phenyl groups than there is in the conjugate acid of tetraphenylporphyrin. Whether this is true can only be proven, however, by X-ray measurement of the structure of tetraphenyldithiaporphyrin conjugate acid.

The spectra of the metal complexes are informative in this respect. We succeeded in preparing all of the metal complexes of tetraphenyldithiaporphyrin with the first row d^5-d^{10} transitions metal ions. Their solutions are all green in color and a typical spectrum, that of (tetraphenyldithiaporphyrin)iron(III) (ClO_4^- as the anion), is λ_{max} 464 (ϵ 210,000) (Soret band), 702 (38,600) and 744 (36,600) (Q bands). This spectrum is qualitatively similar to that of the conjugate acid, except that all three bands show an even greater bathochromic shift. This seems to suggest that, because of steric crowding, the metal ion cannot enter the molecule and, being at one side of the plane, causes an even greater distortion because of specific interaction with either the two sulfur or the two nitrogen ligands.

Proton Nuclear Magnetic Resonance Spectra. Proton nuclear magnetic resonance spectra were measured in deuterated chloroform ($CDCl_3$) for the free base in and in deuterated trifluoroacetic acid (DTFA) for the diprotonated form. The data are presented in Table IV. In the free base a single sharp peak is obtained (δ 8.65 ppm) for four β-pyrrole hydrogens and another single sharp peak (9.64) for the four β-thiophene hydrogens. These two singlets do indicate a twofold axis of symmetry, which is in accordance with the proposed structure of the molecule.

Tetraphenylporphyrin shows only one peak for the β-pyrrole hydrogens at 8.72 ppm, as if the molecule has a fourfold axis of symmetry. This has been explained by Storm[20] as being due to a rapid tautomeric equilibrium, and by measuring the ^1H NMR spectrum as a function of temperature he could get two peaks at −80°. This was explained by the assumption that the tautomeric equilibrium is frozen at this temperature and that we have two pyrrole type rings (i and ii). A peak at 8.90 ppm was ascribed to the β hydrogens of ring type i and another at 8.61 ppm to the β hydrogens of ring type ii.



(i) (ii)

Because in tetraphenyldithiaporphyrin the NH groups are exchanged by S, no tautomerism is possible, and we have only pyrrole type ii. Our value of 8.65 ppm fits nicely that of 8.61 ppm as found by Storm and confirms his hypothesis as well as our structure.

Comparing the chemical shifts in $CDCl_3$ and DTFA, we see a deshielding effect, which is due to the two positive charges in the diprotonated form. We find a change of 0.41 ppm for the β-pyrrole hydrogens against one of only 0.08 ppm for the β-thiophene hydrogens, which shows that protonation occurs at nitrogen and not at the sulfur atoms.

The chemical shifts of the phenyl hydrogens are similar in tetraphenylporphyrin and its dithia analog and the differences are too small to give valuable information.

Experimental Section

NMR spectra were determined for solutions in deuteriochloroform (except where otherwise stated) with a Varian HA-60 (60 Hz) and with a Varian HA-100 (100 Hz), using tetramethylsilane as internal reference. Optical spectra were determined for solutions in chloroform and in TFA with a Cary 14 spectrophotometer. Infrared spectra were determined with a Perkin-Elmer 237 spectrophotometer. Mass spectra were obtained by direct insertion into the ion source of an CH 4 instrument.

1-Phenyl-2-propyn-1-ol was obtained from Merck; otherwise it can be synthesized by the usual procedure.[21]

1,6-Diphenylhexa-2,4-diyne-1,6-diol. Coupling of 1-phenyl-2-propyn-1-ol according to the usual procedure[22] gave >85% diyne mixture of stereoisomers: mp 100-101° (lit.[23] 101-102°); NMR ($CDCl_3$) δ 1.64 ppm (s, br, 1 H), 2.37 (s, br, 1 H), 5.56 (m, 2 H), 7.38 (m, 10 H).

2,5-Bis(phenylhydroxymethyl)thiophene. Deaereated absolute ethanol (40 ml), containing sodium methoxide (0.02 mol) and silver acetate (5 mg), was saturated with a rapid stream of hydrogen sulfide, under a slow stream of dry argon; 2,6-diphenylhexa-2,4-diyne-1,6-diol (2.62 g, 0.01 mol), dissolved in 25 ml of absolute deaereated ethanol, was added dropwise, with vigorous stirring, over a period of 30 min. The mixture was warmed on a water bath at 60-70°, under a slow steam of H_2S, for 3 hr. Water (100 ml) was added, and the product was extracted with benzene (3 × 100 ml). The benzene fractions were combined and washed with water (3 × 250 ml) and with saturated sodium chloride solution (250 ml) and dried over sodium sulfate. The benzene was evaporated and the remaining oil was dissolved in a minimum amount of boiling toluene. Crystallization gave 750 mg of white crystals (25%): mp 137-138° (lit.[14] 138-139°); ir (ν_{max} in cm^{-1}) 3450, 3060, 3030, 2922, 2852, 1605, 1490, 1305, 1280, 1250, 1190, 1080, 1014, 950, 920, 815, 760, 700; NMR (CD_3CN) δ 1.42 ppm (s, 1 H), 2.26 (s, br, 1 H), 4.13 (s, br, 1 H), 5.5 (s, 1 H), 7.39 (m, 12 H).

Tetraphenyl-21,23-dithiaporphyrin. 2,5-Bis(phenylhydroxymethyl)thiophene (100 g, 3.38 × 10^{-4} mol) and 22.6 mg of pure pyrrole (3.38 × 10^{-4} mol) were dissolved in 80 ml of dry and distilled toluene containing 2% (w/w) chloroacetic acid. The mixture was refluxed for 1 hr. After cooling the solution was washed twice with 100 ml of 5% ammonia solution and once with water and dried over sodium sulfate. The toluene was evaporated and the crude product was chromatographed three times on basic alumina, with 1:1 chloroform-benzene as eluent. Crystallization was performed in a desiccator containing pentane, from a concentrated chloroform solution; 11 mg (10% yield) was obtained: neither

Table III. Optical Spectra of Porphin and Porphyrin Conjugate Acids

	Soret, λ_{max}, nm (ϵ)[a]	Q bands, λ_{max}, nm (ϵ) II	I
Tetraphenyl-21,23-dithiaporphyrin (TFA)	456 (335,000)	692 (37,040)	739 (33,030)
Tetraphenylporphyrin[b] (HCl)	448 (436,000)	608 (9000)	659 (50,900)
21,23-Dithiaporphin (TFA)[c]	412 (156,000)	535.5 (6800)	592.5 (4470)

[a] ϵ was calculated from measurements at several concentrations. No change was found with dilution. [b] Reference 14. [c] Reference 8.

Table IV. Chemical Shifts in the ^1H NMR Spectra of Tetraphenylporphyrin and Tetraphenyl-21,23-dithiaporphyrin

	δ, ppm		
	β-Pyrrole H	β-Thiophene H	Phenyl H
Tetraphenyl-21,23-dithiaporphyrin ($CDCl_3$)	8.65	9.64	8.22 (*o*) 7.79 (*m, p*)
Dideuteriotetraphenyl-21,23-dithiaporphyrin^{2+} (DTFA)	9.06	9.72	8.63 (*o*) 8.03 (*m, p*)
Tetraphenylporphyrin ($CDCl_3$)	8.72		8.30 (*o*) 7.80 (*m, p*)
Dideuteriotetraphenylporphyrin^{2+} (DTFA)	8.85		8.59 (*o*) 8.08 (*m, p*)

[a] Reference 19.

melting nor decomposition were observed on heating to 350°; ir (in KBr, ν_{max} in cm^{-1}) 3060, 2910, 1630, 1602, 1488, 1240, 1190, 1120, 1013, 798, 782, 728, 750; MS (rel intensity) 648 (M^+) (100), 324 (M^{2+}) (45%). Anal. Calcd for $C_{44}H_{28}N_2S_2$: C, 81.48; H, 4.32; N, 4.32; S, 9.88. Found: C, 80.44; H, 4.43; N, 4.23; S, 9.82.

(Tetraphenyl-21,23-dithiaporphyrin)iron(III) Triperchlorate. Porphyrin (32.4 mg, 5×10^{-5} mol) was dissolved in 100 ml of dry, pure chloroform (Fluka). $Fe(ClO_4)_3$ (3.54 g, 10^{-2} mol) (Non-Yellow, The G. Frederick Smith Chemical Co.) was dissolved in 4 ml of absolute ethanol, 1 ml of triethyl orthoformate was added, and the solution was stirred for 5 min. Then 0.1 ml (excess) of the $Fe(ClO_4)_3$ solution was added to the porphyrin solution, and the solution turned deep green immediately. The solvent was evaporated to dryness under reduced pressure and the residue was dissolved in 250 ml of dry, pure methylene chloride. The green solution thus obtained was concentrated under reduced pressure to 20–25 ml and put in a desiccator containing pentane. Green crystals (31 mg, 60% yield) were obtained.

1-(Phenylmethylene)-5,10,15-triphenyl-20,22-diselenabilatriene *abc*. 2,5-Bis(phenylhydroxymethyl)selenophene (113 mg, 3.38×10^{-4} mol) and 22.6 mg of pyrrole were dissolved in 100 ml of dry pure benzene containing 2% (w/w) chloroacetic acid. The mixture was refluxed for 30 min, and, after cooling to room temperature, was washed twice with 100 ml of 5% ammonia solution and once with water and dried over sodium sulfate. This solution was concentrated to ~5 ml under reduced pressure and separation was performed on a Varian liquid chromatograph, Model 8500. The column was Micropak S.I.-10, *l* 25 cm, i.d. 2.2 mm. The effluent was 40% benzene in hexane, 100 ml/hr. The detector was a Varian spectrophotometer, Model 635, which was also used to run the visible spectra during elution.

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Pyruvamide Semicarbazone Formation. Kinetics, Mechanism, and Pertinence to Pyruvamide-Dependent Histidine Decarboxylase[1]

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Abstract: Pyruvamide semicarbazone formation proceeds by way of readily recognizable carbinolamine intermediates. Rate and equilibrium constants for uncatalyzed, acid catalyzed, and phosphate buffer catalyzed modes of carbinolamine formation and dehydration, and equilibrium constants for pyruvamide hydration, are reported for pyruvamide itself, and for *N*-propylpyruvamide, pyruvanilide, pyruvoylphenylglycine, and *N,N*-dimethylpyruvamide. The fast uncatalyzed and phosphate catalyzed first step for *N*-protopyruvamides appears to proceed in a structurally unique manner via a zwitterionic intermediate stabilized by duple intramolecular hydrogen bonding and/or sigmatropic rearrangement in a bridged eight-centered system which is tantamount to simultaneous concerted intramolecular general acid and general base catalysis of the coordination process. An unusually low-lying transition state and a metastable isoamide intermediate likely are involved. The reaction is strongly general acid catalyzed by $H_2PO_4^-$ and, apparently, general base catalyzed by PO_4^{2-}! The second step, carbinolamine dehydration, is quite slow. Comparison of pertinent rate constants with known kinetic parameters for histidine decarboxylase reveals that reaction of the pyruvamide prosthetic groups with histidine to give the enzyme histidine carbinolamine needs little or no catalysis by the apoenzyme protein, but that dehydration of the carbinolamine must needs be accelerated 10^6-fold.

Pyruvamide residues and related functions appear to be involved in a variety of enzyme catalyzed reactions.[2,3] The most completely authenticated case is the involvement of N-terminal pyruvoylphenylalanine residues of histidine decarboxylase (histidine carboxy-lyase, E.C.4.1.1.22) as prosthetic groups for the decarboxylation of histidine, as demonstrated by Snell et al.[2] Recently[4] we have shown that pyruvamide itself promotes the deamination of amines and the decarboxylation of phenylglycine under very mild conditions and, consequently, have undertaken a study of what promises to be a revealing organic model of an enzyme catalyzed reaction, the transamination and decarboxylation of amines and α-amino acids by pyruvamide and N-substituted pyruvamides.

A likely sequence of reactions[2,4] involving the pyruvamide moiety is shown in general form in eq 1.