An Attempted Preparation of a Simple Tetrahydroporphine[1]

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We have for some time been interested in the properties of two simple porphyrins, $\alpha,\beta,\gamma,\delta$-tetraphenylporphine and $\alpha,\beta,\gamma,\delta$-tetraphenylchlorin.[2] In an effort to extend our studies to include a representative of the third type of porphyrin ring (see Fig. 1), we have attempted to convert tetraphenylchlorin to tetraphenyl-tetrahydroporphine by catalytic hydrogenation.[3] The preparation and properties of two compounds (designated alpha and beta) which may be isolated from such a hydrogenation are reported here.

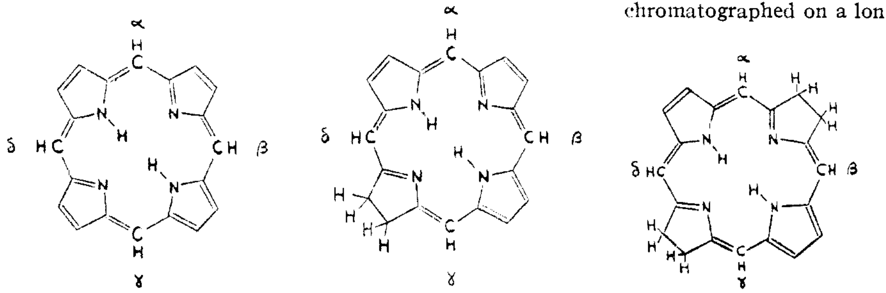

Fig. 1.—Porphyrin rings: a, porphine; b, chlorin (dihydroporphine); c, tetrahydroporphine.

Experimental

Preparation of the Compound Alpha.—One hundred cc. of a 2×10^{-4} M ether solution of $\alpha,\beta,\gamma,\delta$-tetraphenylchlorin is stirred gently under hydrogen at a pressure of 1 atmosphere with 0.1 cc. of gravity packed Raney nickel prepared according to Pavlic and Adkins.[4] The time of stirring varies with the activity of the catalyst, and may range from one-half hour for freshly made catalyst to 4 hours for 3 month old catalyst. Catalyst in amounts appreciably larger than that given above causes the chlorin to be reduced to leuco compounds quite rapidly; stirring for periods in excess of those given results in a decreased yield. Evidence of reaction is the appearance of a very intense peak in the near infrared at 7425 Å. When this peak, which is due to alpha, appears to be at an optimum, the alpha is separated from the reaction mixture by filtering off the Raney nickel, and extracting the ether filtrate with 8 to 10 100-cc. aliquots of 5 N hydrochloric acid. This removes the chlorin from the ether solution, but leaves alpha. The extraction is best done in a minimum of light. The ether solution is washed with water, with 6 N ammonium hydroxide, and with water again. It is then dried over anhydrous sodium sulfate, and finally evaporated to dryness under vacuum. The solid residue is taken up in a minimum of trichloroethylene, and chromatographed on a column tightly packed with talc (an aspirator vacuum is applied to the bottom of the column). After 5 to 10 minutes development with trichloroethylene, the column shows three distinct color separations as follows (from the bottom of the column upwards): a tan band which contains alpha, a green band which contains mostly unreacted chlorin, and a thin blue-gray band which contains some beta and some chlorin. A long chromatographic development of the mixture results in considerable conversion of alpha to chlorin; a very short column (2.5 cm. long by 1.0 cm. in diameter) is therefore used in order that the alpha will have progressed sufficiently in 5 to 10 minutes to begin eluting from the column. Alpha also deteriorates upon standing in trichloroethylene, but pyridine added to the solution inhibits this decomposition. The yield on the basis of the amount of chlorin used in the experiment is about 2%; on the basis of chlorin actually reacted (subtracting out the chlorin recovered), 4%.

Alpha may be converted readily to a magnesium derivative by the action of ethylmagnesium iodide in ether solution.

Preparation of the Compound Beta.—Although beta is formed in the above reduction, greater yields are obtainable if the hydrogenation is conducted in a purified dioxane solution. Twenty ml. of a dioxane solution of tetraphenylchlorin (about 10^{-3} M) is reduced in a manner similar to that described above. The amount of catalyst employed is 0.2 cc. of gravity packed Raney nickel. The reaction time again depends on the activity of the catalyst, and varies from one-half hour for freshly prepared material to 4 hours for 3 month old catalyst (much longer reaction periods result only in loss of chlorin). The Raney nickel is filtered, and the dioxane evaporated to dryness under vacuum. The residue is taken up in a minimum of trichloroethylene, and chromatographed on a long talc column (1 cm. × 10 cm.), developing for several hours with the same solvent. Even though the compound decomposes slowly under the conditions of the chromatographic separation, a long development is necessary if a fairly pure sample of beta is to be obtained. A typical column after a three-hour development consists essentially of only two bands, a green chlorin band toward the bottom of the column, and above and next to the chlorin band, a blue band which contains beta. The beta band is cut out from the extruded column, repacked in a small sintered-glass filter, and eluted with pyridine. The beta thus obtained contains from 5 to 10% chlorin, and is obtained in a yield of only about 2%.

Discussion

Alpha has been identified tentatively as a tetrahydroporphine. The identification is based on the following reasoning: (1) It has long been recognized[5] that porphyrin ring compounds exhibit very characteristic absorption spectra. Thus compounds containing either a porphine or a chlorin ring absorb in two regions of the visible in such a characteristic and uniform way as to permit their easy differentiation by spectral means from other organic structures, and even to permit their separate identification. Tetrahydroporphines absorb in the same two regions of the visible as porphines and chlorins and, in addition, absorb strongly in the near infrared, a region where neither porphines nor chlorins absorb. In Fig. 2 are shown the spectrum of the magnesium derivative of alpha and the spectrum of the naturally occurring magnesium tetrahydroporphine, bacteriochlorophyll. The close resemblance of these two spectra, the fact that alpha is prepared by the reduction of a chlorin, and the knowledge that of all organic structures there are few with electronic transitions in the infrared, together constitute strong presumptive evidence that alpha is a tetrahydroporphine.

(2) It has been observed[6] that simple chlorins may be quantitatively converted to the corresponding porphine by photochemically effecting the

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[1] Sixth in a series on fundamental properties of porphyrin ring systems. Article five: This Journal, **74**, 3977 (1952).

[2] For the system of nomenclature employed, see *ibid.*, **73**, 4315 (1951), footnote 2; **74**, 3974 (1952), footnote 2.

[3] W. Schlesinger, A. H. Corwin and L. Sargent, *ibid.*, **72**, 2867 (1950), have reported the preparation of a simple tetrahydroporphine by the reduction of etiohemin II with sodium and alcohol.

[4] A. A. Pavlic and H. Adkins, *ibid.*, **68**, 1471 (1946).

[5] F. Haurowitz, *Ber.*, **68**, 1795 (1935); E. Rabinowitch, *Rev. Modern Phys.*, **16**, 226 (1944); H. C. Longuet-Higgins, C. W. Rector and J. R. Platt, *J. Chem. Phys.*, **18**, 1174 (1950).

[6] M. Calvin, *et al.*, This Journal, **70**, 699 (1948); **71**, 4025 (1949).

transfer of two hydrogens to a suitable quinone. When alpha and 1,2-naphthoquinone are illuminated in a deoxygenated solvent with light of wave length longer than 6900 Å., the alpha band at about 7500 Å. completely disappears, and a new colored product is formed which agrees spectrally point for point from 8000 to 4000 Å. with a known sample of tetraphenylchlorin (see Fig. 3). Illumination with wave lengths higher than 6900 Å. presumably prevents any photochemical oxidation of the chlorin which is formed, since the chlorin does not absorb at these wave lengths. The fact that 1,2-naphthoquinone, which is known to be capable of removing two hydrogen atoms from adjacent saturated β-pyrrole carbons in a porphyrin, brings about the conversion of alpha to a chlorin is evidence in agreement with a tetrahydroporphine structure for alpha.

(3) Alpha is most reluctant to form acid salts or metal derivatives as reported for other tetrahydroporphines, a result which is in agreement with simple resonance theory.[7]

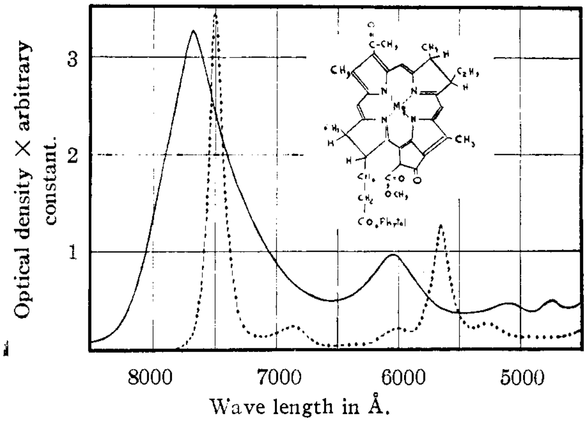


Fig. 2.—Absorption spectra: dotted line, magnesium derivative of alpha in benzene; solid line, bacteriochlorophyll in ethyl alcohol (after French, ref. 4). The currently accepted structure of bacteriochlorophyll is shown in the inset.

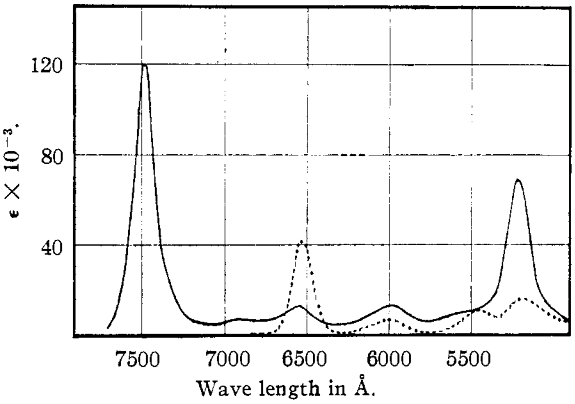
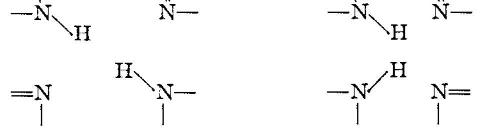


Fig. 3.—Absorption spectra in benzene: dotted line, tetraphenylchlorin free base; solid line, alpha free base. The extinction coefficient of the alpha is calculated on the assumption that one mole of chlorin is formed for each mole of alpha used up in the conversion of alpha to chlorin by 1,2-naphthoquinone (see discussion).

(4) The spectra of porphine and chlorin free bases show very marked changes with changes in temperature. The spectra of alpha, however, is unaffected by temperature changes (other than the usual band sharpening at low temperatures (see Fig. 4)). The spectral shifts observed with porphine and chlorin free bases have been interpreted on the basis of changes in the equilibrium concentrations of very similar N–H tautomers of the type[8]



In the case of a tetrahydroporphine, such isomers are not of nearly identical energy as they are for porphines and chlorins but are of much different energy due to the fact that a hydrogen cannot be bonded to a reduced pyrrole ring without requiring either a disruption in the conjugated single–double system or a separation of charge in the molecule. A tetrahydroporphine should therefore exist essentially as a single species over a wide range of

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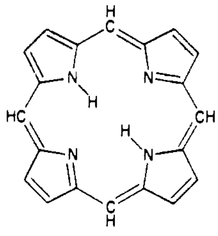
[7] For example, consider the equilibrium, $PH_2 + 2H^+ \rightleftarrows PH_4^{++}$. In the case of the porphine, two resonance forms of type I and eight of type II may be written for the free base, and 12 resonance forms of type III may be written for the acid salt. In the free base, the contribution of type II forms to the resonance hybrid results in a negative



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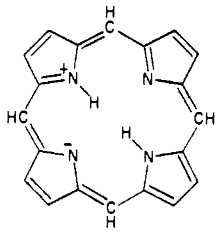
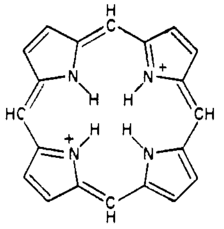


II



III

charge on the two center nitrogens which will accept the protons, facilitating their acceptance. In the acid salt, the two positive charges on the nitrogens are distributed among all four nitrogens, thus decreasing the tendency of any one nitrogen to lose its proton. Both of these effects operate in the direction of increasing the base strength. In the case of tetrahydroporphine, low energy forms of type II may not be written, and only two low energy resonance forms for the acid salt may be written, both of which carry single positive charges on the two nitrogens which are in the reduced pyrrole rings. Relative to the porphine, then, the tetrahydroporphine has less of a tendency to pick up a proton, and the acid salt more of a tendency to lose a proton. (This argument may be made on the basis of resonance energies rather than on the basis of the charge displacements resulting from resonance; the two treatments are in reality the same.) The base strength of the chlorin is predicted to lie between the two extremes of the porphine and the tetrahydroporphine.

A similar resonance treatment predicts the equilibrium $PH_2 \rightleftarrows P^{=} + 2H^+$ to lie further to the left in the case of the tetrahydroporphine as compared to the porphine, with the chlorin again occupying an intermediate position.

[8] G. D. Dorough and K. T. Shen, THIS JOURNAL, **72**, 3939 (1950).

temperature. The spectral behavior of alpha with changing temperature is therefore indicative of a tetrahydroporphine structure.

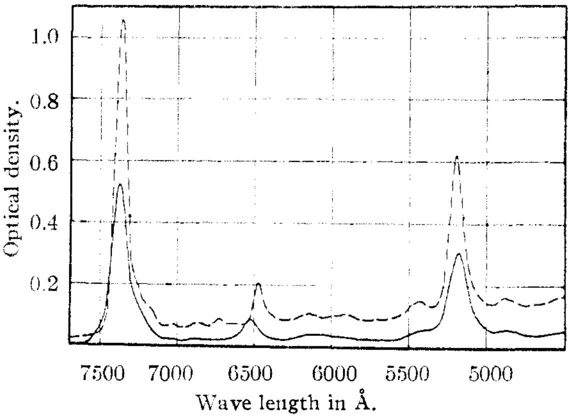


Fig. 4.—Spectra of alpha free base at different temperatures: solid line, room temperature; dotted line, liquid nitrogen temperature. (Uncorrected for contraction of solvent. The factor is 0.76. Notice that the peak at 6500 Å., which is due to a small amount of chlorin impurity, shifts with temperature. The solvent for this experiment was an ether, isopentane, alcohol mixture in the ratio of 5:5:2.)

To summarize, alpha has a spectrum like that of a known tetrahydroporphin, is at a reduction level more reduced than a chlorin, can be oxidized to the chlorin by a reagent which attacks saturated pyrrole rings in reduced porphyrins, and possesses chemical and physical properties either recorded for or to be expected of tetrahydroporphines. Alpha therefore appears to be a tetraphenyltetrahydroporphine.

A complete identification of alpha would require some type of quantitative analysis which would show that it possessed two more hydrogens than tetraphenylchlorin, and some sort of information which would permit one to place the extra hydrogens on either adjacent or opposite pyrroles. We have no information which could be considered to meet the latter requirement, other than the somewhat tenuous evidence that bacteriochlorophyll is reduced on opposite pyrroles, and that alpha is spectrally similar to bacteriochlorophyll. (The spectral characteristics of a tetrahydroporphine with adjacently reduced pyrroles are unknown.) The former requirement might be met by the usual analysis for the percentage of the elements, although the C and H values of tetraphenyltetrahydroporphin do not differ very much from those of the corresponding chlorin. (For tetraphenylchlorin: C, 85.68; H, 5.24. For tetraphenyltetrahydroporphin: C, 85.41; H, 5.54.) However, since alpha is obtainable in only very low yields from a starting product which itself is not too readily available, we were not able to procure enough alpha for a conventional microanalysis. Several attempts were made to follow the reaction of 1,2-naphthoquinone and alpha quantitatively on a 15–30 microgram scale, the assumption being that if a 1:1 ratio of alpha reacted to naphthoquinone used could be demonstrated, this would be strong evidence that alpha was a tetrahydroporphine. The experiments were not successful due to difficulties involved with oxygen removal and quinone volatility.

The identification of beta has proven to be very elusive. Like alpha, beta may be photoöxidized to tetraphenylchlorin with 1,2-naphthoquinone, which would suggest that beta might also be a tetrahydroporphine (*e.g.*, a tetrahydroporphine with adjacent pyrroles reduced is a possibility). However, the other properties of beta such as its spectrum, its ability to form readily acid salts and metallo-derivatives, and the behavior of its spectrum when the temperature is changed are similar to the properties of a chlorin. One possibility is that the catalytic hydrogenation has effected a reduction of a benzene ring to a cyclohexadiene ring to give a compound which would have the properties of a chlorin and yet be more reduced than a chlorin. The absorption spectra of the free base and the zinc derivative of beta are given in Fig. 5. The molar extinction coefficient of the free base was calculated from a quinone oxidation experiment on the assumption that one mole of chlorin is formed for each mole of beta oxidized. The value was 29,000 at 5910 Å. in benzene solution at room temperature.

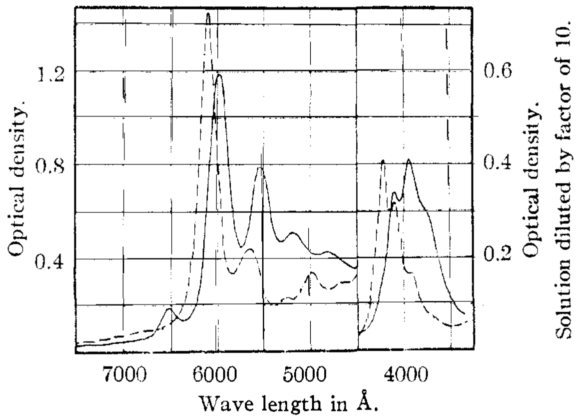


Fig. 5.—Absorption spectra in benzene: dotted line, zinc-derivative of beta; solid line, beta free base. The small peak at about 6500 Å. is due to chlorin impurity.

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The Diffusion Coefficient of Cupric Glycinate

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Cupric glycinate is one of the few non-ionic water-soluble colored molecules. Since it showed promise as a colorimetric standard for calibrating diffusion cells we have determined the diffusion coefficient, *D*, in sintered glass diffusion cells[3] using KCl as a standard.[4] The membrane surfaces were stirred by magnetic stirrers encased in polythene. The denser solution was on top to facilitate stirring of the more remote parts of the cells.

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(1) Borden Co., Chemical Division, Bainbridge, N. Y.

(2) Based on material in the thesis of Henn Soonpää filed in the University of Oregon Library; M.S., 1953.

(3) J. W. McBain and C. R. Dawson, *Proc. Roy. Soc. (London)*, **A118**, 32 (1935).

(4) A. R. Gordon, *Ann. N. Y. Acad. Sci.*, **46**, 301 (1945).