Reduction of Tin Porphyrins to Tin Chlorins[1]

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Several new tin porphyrin and chlorin complexes have been prepared and characterized. These appear to retain the tin on reduction to the leuco compounds and re-oxidation. Reduction of the tin porphyrins with dissolving sodium in amyl alcohol gave tin chlorins. The tin chelates were reduced by zinc–pyridine–acetic acid while the corresponding iron and zinc chelates were not. It is suggested that this enhanced ease of reduction is due to the ability of the tin atom to undergo a reversible two-electron change.

Synthetic chlorins have been prepared by the isomerization method of Woodward, *et al.*,[3] and by various reduction procedures. The latter deserve special study to determine the reaction mechanisms involved and the nature of possible directive influences. Hans Fischer and his collaborators reported numerous reductions of porphyrins to chlorins,[4–7] Fischer and Bub[8] made the interesting observation that a leuco compound could be prepared from pheophorbide a_1 which oxidized to a chlorin, mesopheophorbide a, instead of to a porphyrin. Some of these reductions have been reviewed by Wenderoth.[9] More recently synthetic chlorins have been investigated by Ball, Dorough, and Calvin,[10] Dorough and Huennekens,[11] Eisner and Linstead,[12] and Eisner.[13] A critical observation[14] is that under acid conditions, isomerization of leuco compounds may take place, forming porphyrins with altered sequences of pyrrole rings.

The sodium and alcohol method used by Fischer and collaborators was investigated in some detail by Schlesinger, Corwin, and Sargent.[15] We have now applied this to oxochloroporphyrin e_6, its hemin and the hemin of its trimethyl ester and to the corresponding derivatives of 2-vinylchloroporphyrin e_6. The first of these decomposed completely and the second largely decomposed, yielding only a little starting porphyrin but no chlorin. We attribute this decomposition to the instability of these compounds to base.

Based on the observation of Fischer and Bub[8] that leuco chlorins are distinct entities, we suggest that the reduction process of Fischer is in reality a combination of reduction and isomerization, the latter brought about by the strong base used. Hence, an alternative procedure might involve reduction followed by isomerization under the influence of acid.

In an effort to maintain the presence of a metal in the ring system, and thus stabilize the pyrrole ring sequence, we prepared tin 2-vinylchloroporphyrin e_6 trimethyl ester. Reduction of this compound in glacial acetic acid with iron and dry hydrogen chloride yielded the leuco compound. Oxidation with air or quinone immediately produced a tin porphyrin accompanied by a small amount of tin-free porphyrin. That the tin remained in the leuco compound was shown by treatment of the metal-free porphyrin identically in the presence of stannous chloride. The leuco compound was formed but on oxidation to porphyrin showed no trace of tin chelate.

Although the reduction with iron and acid produced no tin chlorins, treatment with dissolving sodium in isoamyl chloride did so. Tin 2-vinylchloroporphyrin e_6 yielded tin mesochlorin e_6 and tin etioporphyrin II yielded tin etiochlorin II.

A supporting observation on the ease with which tin chelates are reduced is the effect of the zinc–pyridine–acetic acid combination used by Kuhn and Winterstein.[16] All free bases at our disposal, both chlorins and porphyrins, yielded reversibly reduced products with gross spectral changes and if the action of the reagent was prolonged or the solutions warmed, leuco compounds resulted. With the iron and zinc chelates, such mild conditions afforded no reduction but with the tin chelate reduction occurred immediately with a dramatic spectral change.

We suggest that in the case of tin chelates, Kuhn's method first reduces the tin from its highest oxidation state to tin(II). By an electron shift, as shown in Fig. 1, one can arrive at a reduced porphyrin system with tin again in its preferred state, tin (IV). The unique feature of the tin is the ease of a two-electron change which makes such an isomerization possible. Among the chemical, electrolytic and photoreduction methods which we have

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(2) Abstracted from the doctoral dissertation of O. D. Collins, III, The Johns Hopkins University, Baltimore, Maryland, 1958; American Cyanamid Fellow, 1955–56; DuPont Teaching Fellow, 1956–57.

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(10) R. H. Ball, G. D. Dorough, and M. Calvin, *J. Am. Chem. Soc.*, **68**, 2278 (1946).

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(13) U. Eisner, *ibid.*, 3461 (1957).

(14) H. Fischer and A. Rothhaas, *Ann.*, **484**, 85 (1930). See also D. Mauzerall, *J. Am. Chem. Soc.*, **82**, 2601 (1960).

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(16) R. Kuhn and A. Winterstein, *Ber.*, **65**, 646, 1737, 1742 (1932).

investigated, the sodium and amyl alcohol reduction of tin chelates is the only one to produce chlorins from these chlorophyll-related porphyrins in reasonable yields.

Experimental

Starting Materials.—Chlorin e_6 trimethyl ester[17] was purified by chromatography on 90% Magnesol and 10% cellulose powder.

Oxochloroporphyrin e_6 trimethyl ester was prepared by a modification of the method of Fischer, Riedmair, and Hasenkamp.[18] Purification was performed chromatographically on Magnesol–cellulose.

2-Vinylchloroporphyrin e_6 trimethyl ester was prepared by a modification of the method of Fischer, Oestreicher, and Albert.[19] Purification was performed chromatographically using Magnesol–cellulose.

Mesochlorin e_6 trimethyl ester[20] was prepared by the controlled hydrogenation of chlorin e_6 trimethyl ester.[21]

Tin 2-Vinylchloroporphyrin e_6 Trimethyl Ester.[22]—Ten milligrams of the porphyrin was heated in 2.5 cc. of pyridine with 25 mg. of stannous chloride for 20 min. on a steam bath. After being cooled to room temperature, the solution was added to 50 cc. of ether. The ether solution was washed three times with 6% hydrochloric acid to remove pyridine and unchanged porphyrin, together with unchanged stannous chloride. After being washed twice with water, the ether solution was evaporated to one tenth of its original volume and dried with anhydrous calcium sulfate. After filtration the solution was evaporated until the first solid appeared and was then refrigerated to crystallize. The preparation was recrystallized from hexane and then from acetone–hexane.

Anal.[23] Calcd. for $C_{37}H_{38}O_6N_4SnCl_2$: C, 53.92; H, 4.65. Found: C, 54.28; H, 4.82.

Spectrum: λ_{max} mμ: (a) 609 (minor peak); (b) 592; (c) 549; (d) 418; (e) 396 (minor peak). ϵ_{max}: (b) 6.12×10^3; (c) 1.53×10^4; (d) 3.27×10^5. Concentration, 1.03×10^{-5} mole/l. in dioxane.

Tin Chlorin e_6 Trimethyl Ester.—The preparation of this tin chelate was identical with that of tin 2-vinylchloroporphyrin e_6-trimethyl ester.

Solvent 1. Spectrum: λ_{max} (mμ) (a) 641.2; (b) 596.8; (c) 566.2; (d) 522.5; (e) 488.5; (f) 412.0. ϵ_{max}: (a) 1.668×10^3; (b) 1.04×10^2; (c) 2.72×10^2; (d) 2.06×10^2; (e) 5.38×10^2; (f) 5.81×10^4. Concentration, 7.645×10^{-5} mole/l. in dioxane.

Anal. Calcd. for $C_{37}H_{40}O_6N_4SnCl_2$: C, 53.79; H, 4.88; Sn, 14.30. Found: C, 53.49; H, 4.95; Sn, 14.03.

Tin Mesochlorin e_6 Trimethyl Ester.[21]—The preparation was identical to those of the two preceding compounds.

Spectrum[24]: λ_{max} mμ: (a) 632.5; (b) 591.7; (c) 559.0; (d) 518.8; (e) 486.0; (f) 408.0. ϵ_{max}: (a) 187×10^3; (b) 1.33×10^2; (c) 3.86×10^2; (d) 2.40×10^2; (e) 7.67×10^2; (f) 6.81×10^4. Concentration, 5.601×10^{-5} mole/l. in dioxane.

Anal. Calcd. for $C_{37}H_{42}O_6N_4SnCl_2$: C, 53.87; H, 5.09. Found: C, 53.56; H, 5.47.

Tin Etioporphyrin II.—Seven hundred milligrams of etioporphyrin II was boiled with 700 mg. of stannous chloride, 150 cc. of glacial acetic acid, and 3.2 mg. of sodium acetate. The tin porphyrin precipitated within 10 min. and was filtered off and washed repeatedly with water. The chelate is very insoluble in most solvents and only slightly soluble in boiling ethylene dichloride, pyridine, and dimethylformamide. The diacetate was refluxed 19 hr. under nitrogen in 50 cc. of purified dioxane with 2 g. of sodium bromide. The solid porphyrin was filtered off and washed with acetone and then cold water; m.p. 280° dec. Qualitative test for bromide was positive. Karl Fischer analysis indicated at least 1.5 moles of water.

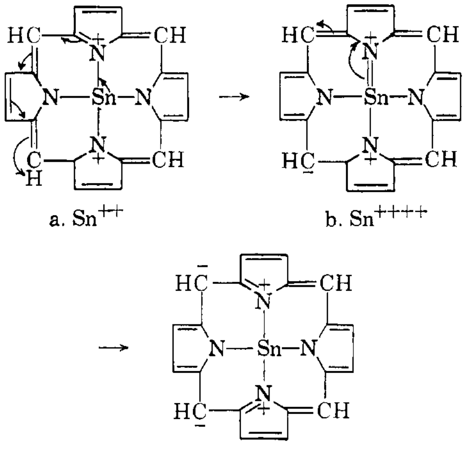
a. Sn^{++} b. Sn^{++++} c. Sn^{++++}

Figure 1

Anal. Calcd. for $C_{32}H_{36}N_4SnBr_2 \cdot 2H_2O$: C, 48.58; H, 5.09; N, 7.08. Found: C, 48.75; H, 5.35; N, 6.95.

Spectrum (diacetate): λ_{max} (mμ): (a) 623; (b) 577; (c) 540; (d) 502. Intensities: (a) IV; (b) II; (c) I; (d) III.

Sodium–Alcohol Reduction of Tin Etioporphyrin II.—Tin etioporphyrin II (700 mg.) was dissolved in 70 cc. of isoamyl alcohol and boiled with 5.0 g. of sodium for 15 min. under oxygen-free nitrogen. Hot absolute alcohol (52 cc.) was added followed by 35 cc. of cold 37% hyrochloric acid after the mixture had been cooled with ice. The mixture was dissolved in 8:1 ethylene dichloride–chloroform and oxidized by brief contact with tetrachloro-*o*-benzoquinone. The unchanged quinone was immediately removed by treatment with aqueous bisulfite. The solvents were evaporated after thorough washing. The dried residue was chromatographed on Magnesol–cellulose with pure ethylene dichloride to give a blue portion sticking at the top and an elutable unidentified red band with absorption at 561 and 524 mμ. The column was then eluted with 1:1 methanol–acetone to give two blue tin chlorin bands followed by two red tin porphyrins. The chlorins and porphyrins were cut apart and each eluted with a mixture of pyridine and ethylene dichloride. The two tin chlorins were rechromatographed on the same system to remove the last traces of tin porphyrin. The second blue chlorin was in larger quantity by far and after it was refluxed in acetic acid with sodium acetate, it agreed spectrally with tin etiochlorin II prepared by sodium–alcohol reduction of etiohemin II and subsequent tin introduction. The bromide was made as before but hydrolyzed during extensive crystallization attempts. The dihydroxide finally precipitated from chloroform–petroleum ether as a blue-black crystalline powder; yield 30 mg., m.p. > 290° dec.

Anal. Calcd. for $C_{32}H_{38}N_4Sn \cdot 2(OH^-) \cdot 2H_2O$: C, 57.60; H, 6.64; N, 8.40. Found: C, 57.99; H, 6.11; N, 8.52.

Spectrum (diacetate): λ_{max} (mμ): (a) 621; (b) 576; (c) 545; (d) 510. Intensities: (a) I; (b) II; (c) IV; (d) III.

Control Reduction of Etiohemin II.—The procedure was the same as that for the tin complex with the following ex-

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(19) H. Fischer, A. Oestreicher, and A. Albert, *ibid.*, **538**, 128 (1939).

(20) H. Fischer and E. Lakatos, *ibid.*, **506**, 152 (1933).

(21) The authors wish to thank Mr. John Davison for this preparation.

(22) The authors wish to thank Mr. Roberto Arellano for this preparation.

(23) All analyses were performed by Mr. Joseph Walter whose assistance is gratefully acknowledged.

(24) Courtesy of Dr. G. F. Kleinspehn.

ceptions: Twenty milligrams of etiohemin II was dissolved in 4 cc. of boiling isoamyl alcohol and 300 mg. of sodium was added. In the final chromatography, a mixture of 20 parts hexane, 10 parts ethylene dichloride, and 3 parts of absolute methanol was used; yield 31% of etiochlorin II, determined spectroscopically.

When 20 cc. of isoamyl alcohol was used in the reduction with 400 mg. of sodium, the yield dropped to 2%.

When the reaction was run as in the first procedure, but with the addition of 1.5 g. of dried Amberlite IRC-50 in its acid form, tetrachloro-*o*-benzoquinone oxidized the reduced product to bright red etioporphyrin II with only traces of etiochlorin.

Zinc–Pyridine–Acetic Acid Reduction.—Several milligrams of porphyrin or chlorin were dissolved in 3 or 4 cc. of pyridine (damp) and several milligrams of zinc dust were added. One drop of acetic acid was added and the reaction vessel flushed with nitrogen. Gentle warming produced an immediate color change and loss of the original spectral bands. Chlorin e_6 triester became bright red with no band absorption but only general absorption below 580 mμ. 2-Vinylchloroporphyrin e_6 triester became brown with general absorption below 519 mμ and then green with additional absorption at long wave lengths. Iron and zinc complexes of 2-vinyl chloroporphyrin triester were ununchanged but tin 2-vinylchloroporphyrin triester changed from its normal hue to reddish purple with two broad bands, a weak one at 609 mμ, and a strong one at 537 mμ.

These colored products were all oxidized back to their respective starting materials immediately upon the addition of oxygen or quinones. If the reaction mixtures stood for many minutes or were further warmed, all became colorless and finally would not oxidize to recognizable products.

Reduction of Tin 2-Vinylchloroporphyrin e_6 Trimethyl Ester. (a) To Chlorins.—The triester (500 mg.) was hydrolyzed in a mixture of 20 cc. of pyridine and 35 cc. of 15% aqueous potassium hydroxide which was blanketed with nitrogen and shaken for 36 hr. at room temperature. Tin was introduced to the free acid as outlined and the tin chelate treated with sodium–isoamyl alcohol as above, and drowned in ether containing about 10% ethylene dichloride. The ethereal solution was at first brown but as the acid was washed out with water, the ether layer became green. The solvents were vacuum stripped after esterification with diazomethane and the residue was chromatographed on 10% cellulose–Magnesol with a mixture of 20 parts hexane, 10 parts ethylene dichloride, and 3 parts absolute methanol. Two chlorin bands were visible, the first of which represented about 10–15 mg. of material whose spectrum in dioxane was qualitatively and quantitatively identical with that of tin mesochlorin e_6 trimethyl ester and the second of which was in smaller quantity (3–4 mg.). The spectrum of this second band in dioxane differed slightly from that of the major band.

(b) To Leuco-Porphyrins.—The tin chelate from 10 mg. of the vinylchloroporphyrin ester was dissolved in 10 g. of glacial acetic acid in a three-necked, 50-cc. flask fitted with nitrogen inlet, reflux condenser, and dry hydrogen chloride inlet. The mixture was heated to 80° and powdered iron was added while the contents of the vessel were blanketed with nitrogen. Hydrogen chloride was then bubbled through the mixture. After 20 min. at 120° the liquid was nearly colorless. It was cooled under nitrogen and drowned in 50 cc. of water. The water was extracted with ether containing a small amount of ethylene dichloride. After the ether was washed acid-free, it was pale yellow and showed no band spectrum. Tetrachloro-*o*-benzoquinone instantly oxidized the solution to maroon. Chromatography of the esterified product on Magnesol with a mixture of 20 parts ethylene dichloride and 4 parts acetone showed three bands. The first yellow band showed no spectrum; the red band following this showed the spectrum of metal-free 2-vinyl porphyrin. Near the top of the column was the purple tin complex.

(c) Control Reduction of Free Porphyrin in the Presence of Stannous Chloride.—The reaction was run exactly as above except that free porphyrin was used instead of the tin complex and 50 mg. of stannous chloride was added after the hydrogen chloride addition had begun. Chromatography of the products yielded a brown band as well as the red band of the porphyrin ester but no chelate band.

Additions of Phenyllithium to *cis*- and *trans*-Dibenzoylstyrenes[1,2]

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Phenyllithium adds 1,2 twice to the carbonyl groups of *trans*-dibenzoylstyrene, giving the *trans*-glycol. It adds similarly but stepwise to the *cis* isomer, giving first the γ-hydroxy ketone in its cyclic hemiketal form, and in the second stage the *cis*-glycol.

Because of the very considerable proportions of 1,4-addition of phenyllithium to *cis*- and *trans*-dibenzoylethylenes,[2c] to *cis*-chalcone[4] and to the *cis*- and *trans*-α-phenylchalcones,[5,6] it was predicted, incorrectly, it now transpires, that both *cis*- and *trans*-dibenzoylstyrenes I and III also would undergo 1,4-addition to a considerable extent.

The main crystalline product of the reaction between phenyllithium and *trans*-dibenzoylstyrene (I) was the *trans*-pentaphenyl glycol II (40%). This was the result of two successive 1,2-additions to the carbonyl groups. No one of the several easily isolable 1,4-addition products was isolated.

The structure of the *trans*-glycol II was shown by analysis, the very strong and normal type infrared hydroxyl absorptivity at 2.86 mμ, and the absence of carbonyl group absorptivity in the 6-μ region.

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[1] Work supported by a contract with the Office of Ordnance Research, U.S. Army, and a research grant from the National Science Foundation.

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