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TWO OBSERVATIONS ON A MODEL OF THE BIOSYNTHESIS OF UROPORPHYRINOGEN III

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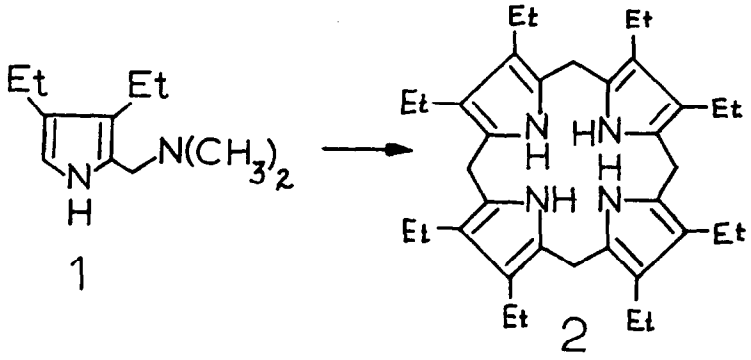
We wish to report several observations made on the mechanism of cyclization of pyrrole 1 to octaethylporphyrinogen 2 (eq 1) that we feel are relevant to questions surrounding the biosynthesis of the great ring of porphyrins and the biosynthesis of corrins.

On standing at room temperature in freeze-thaw degassed acetic acid solution, 1 spontaneously cyclotetramerizes with formation of ocatethylporphyrinogen (2), equation 1. The time of half formation of 2 is approximately 6 hr. Octaethylporphyrinogen may be isolated by recrystallization as a white crystalline substance, m.p. 218-219.5 (dec), in 40-60% yield and is quite stable as long as air is rigorously excluded from its surroundings. The structure of 2 follows from 1) its NMR[1] spectrum showing the ethyl groups as a



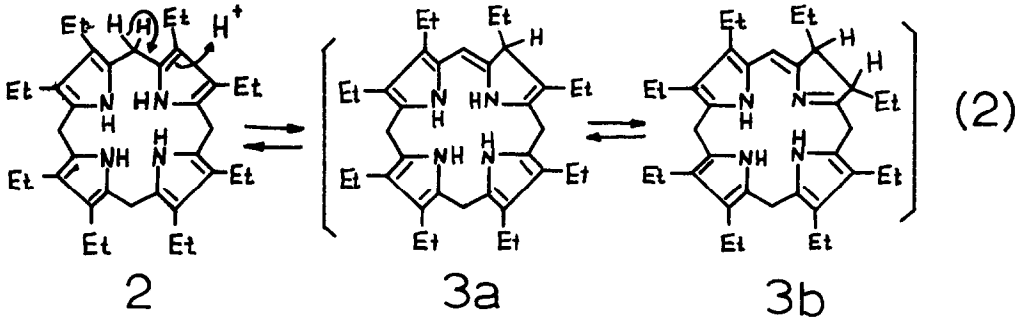
(1)

triplet and quartet at δ1.10 and 2.39 respectively, the bridging methylene groups as a singlet at δ3.70, and NH at δ6.9 in the proper ratios, 2) quantitative oxidation of 2 in dilute benzene solution by air to octaethylporphyrin[2],[3]

and 3) its elemental analysis. We feel that the facile cyclization of this "barebones" model of porphobilinogen is an important demonstration of the only secondary role played by the functional groups of porphobilinogen (PBG) in the biosynthesis of uroporphyrinogen III[5,6]. It also clearly demonstrates that "template effects"[7,8] need not play an important role in guiding the enzymatic cyclotetramerization of PBG.

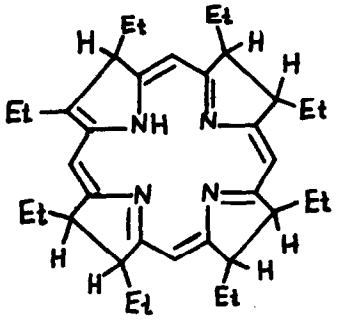
Furthermore, we observe that octaethylporphyrinogen (2) is very susceptible to exchange of its bridging methylene hydrogens with solvent acetic acid. Dissolution of 2 in acetic acid-d rapidly produces 2-d_8, the NMR signal due to the bridge methylene hydrogens disappearing completely. Treatment of 2-d_8 with acetic acid-d_0 results in the rapid reappearence of NMR signals due to the methylene hydrogens of 2. Porphyrinogen can be recovered and characterized from these reactions. Although no direct comparison has been made, this process, having a half life to approximately 15 min. at 25°, is apparently comparable in rate with the acid ctalyzed exchange of the γ and δ hydrogens of chlorins[9,10]. Under conditions of rapid deuterodeprotonation of 2 tertiary amine 1 is stable: it exchanges H-5 only slowly with acetic acid-d_1.

One may propose an acid catalyzed tautomerization scheme for this reaction (eq 2) involving transient production of the pyrrylidine pyrroline



(2)

enamine-imine pair 3a and 3b. In this respect it is interesting to note the proposed intermediacy of "corphins"[11] (as 4) in the biosynthesis of the corrin ring system. The mechanistic relationship between 3a-3b and 4 is obvious and lends credence to this proposal.



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