HETEROCYCLES, Vol. 6, Nos. 9, 10, 1977

HETEROCYCLIC CHEMISTRY RELATED TO PORPHYRINS

Burchard Franck*, Gregor Fels, Günter Ufer, Rolf Steinkamp, Christian Wegner and Gerhard Bringmann

Organisch-Chemisches Institut der Universität Münster

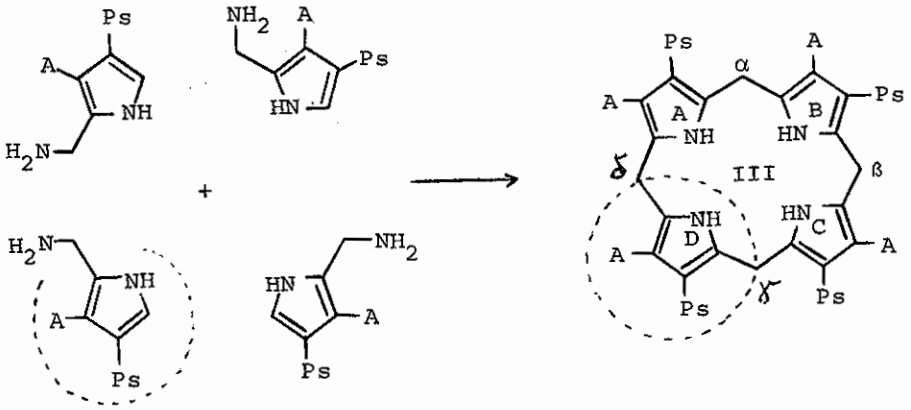
Orleansring 23, D-44 Münster, West Germany

The porphyrin system is a heterocyclic natural product skeleton with many-sided chemical and biological properties. Thus, similar as in the case of alkaloids and steroids, the development of biomimetic porphyrin syntheses deserves special interest. This can be done, as in our investigations, with the following sequence:

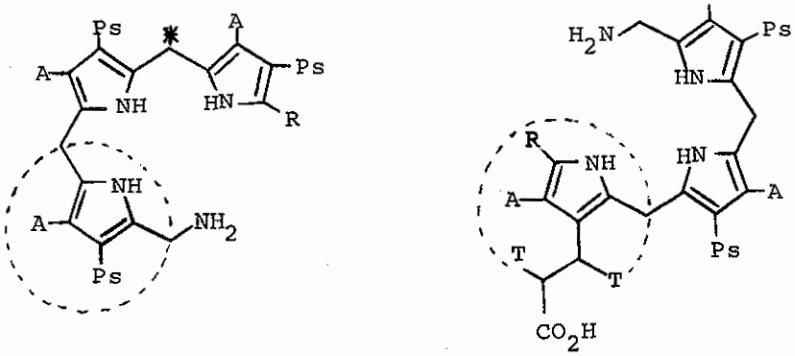
1. Determination of biogenetic mechanisms and precursors
2. Selection of biogenetic steps, promising for synthetic purposes
3. Finding optimum applications and conditions.

Investigations on Heme Biosynthesis

As evident from incorporation experiments with labelled precursors, heme and related cyclic tetrapyrroles are biosynthesized from four molecules of the monopyrrol porphobilinogen (1) via uroporphyrinogen III (2) under rotation of one pyrrole unit (within the dotted circle)[1-3]. In order to investigate how and when the "pyrrole-inversion" occurs during biosynthesis, the two isomerie tripyrroles (3a) und (4a) and their



(1) (2)



(3) (4)

a: R = H
b: R = CO_2H

A = $-CH_2-CO_2H$
Ps = $-CH_2-CH_2-CO_2H$

carboxy derivatives (3b) und (4b), labelled specifically with ^{14}C and ^{3}H respectively, were chosen, synthesized and fed to heme forming enzyme systems in competition experiments. Therewith the

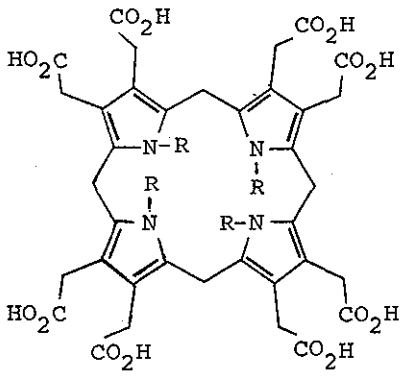
carboxy derivatives (3b) and (4b), being inert to the enzyme system, made possible a reliable determination of the otherwise problematic "chemical blank"[4], caused by non-enzymic condensation of heme precursors during feeding experiments. Subsequent isolation and chemical degradation of the labelled heme revealed that the tripyrrole (3a) is transformed directly, under partial scrambling of the ^{14}C-label, into heme. These results provide extensive insight into the course of "pyrrol inversion" in porphyrin biosynthesis and explain the hitherto contradictory results[4,5] of several research groups.

Biomimetic Porphyrin Syntheses

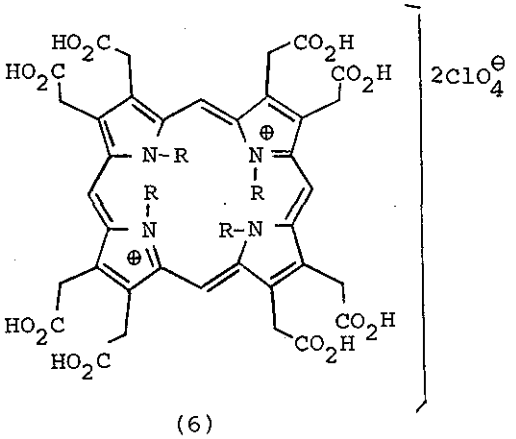
Among the reactions of porphyrin biosynthesis the cyclotetramerisation of porphobilinogen (1) to porphyrinogens (e.g. 2) is most important for the development of biomimetic syntheses. Being a mannich base and a vinylogous enamine, porphobilinogen (1) behaves as a reactive, bifunctional compound, and condenses in vitro acid or base catalyzed with 60 - 80 % yield to give a mixture of uroporphyrinogen isomers in which uroporphyrinogen III (2) predominates[8]. By taking advantage of this efficient biomimetic reaction it was possible to obtain known and novel porphyrinogens very conveniently and with high yields by condensation of 12 different porphobilinogen derivatives. The porphyrinogens or porphyrins crystallysed directly from the reaction mixture when the sidechains of the precursors were identical, and no isomers possible.

By this procedure the highly strained N,N,N,N-tetraalkyl-porphyrinogens (5a-5c) could be obtained from the corresponding N-alkyl-norporphobilinogens[7] with the yields given below. In contrast to normal porphyrinogens (5a-5c) are

resistant to mild oxidation and need $Ce(SO_4)_2$ for transformation to the bisquaternary porphyrins (6a-6c).

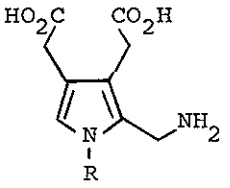


(5)



(6)

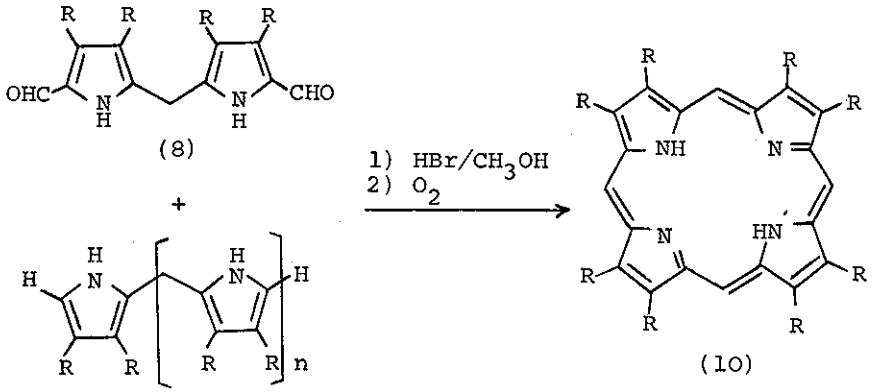
a: R = CH_3 68%
b: R = C_2H_5 31%
c: R = CH_2-C_6H_5 4%



(7)

The cyclotetramerisation of porphobilinogen derivatives proceeds so much selective that dimers and trimers as well as higher cyclic or noncyclic oligomers could not be detected as intermediates. This could be explained by conformational analysis of the oligopyrrole precursors[6].

Further impressive evidence for the strongly preferred porphyrin formation came from attempts to synthesize cyclic penta- and hexapyrroles directly by condensation of the tri- and tetrapyrroles (9b) and (9c) with the dialdehyde (8). In spite of the very mild reaction conditions only a porphyrinogen (10) was obtained, accompanied by elimination of pyrrole units.



a: n = 1
b: n = 2
c: n = 3

R = CH_2-CH_2-CO_2H

Thus the porphyrins appear as a natural product chassis, whose formation is extremely favoured by kinetic and thermodynamic control. This is possibly one of the reasons why they were selected during the evolution as a ligand for enzymatically active metals. In addition this provides ideal possibilities for biomimetic syntheses of biologically active as well as exotic porphyrins (e.g. N,N,N,N-tetraalkyl-porphyrinogens).

References

1. E.I.B. Dresel and J.E. Falk, Biochem. J. 1956, 63, 80.

2. B. Franck, D. Gantz, F.-P. Montforts and F. Schmidtchen, Angew. Chem. internat. Edit. 1972, 11, 421.

3. A.R. Battersby, G.L. Hodgson, E. Hunt, E. McDonald and J. Saunders, J. Chem. Soc. Perkin I 1976, 273.

4. A.R. Battersby and E. McDonald in K.M. Smith: Porphyrins and Metalloporphyrins, Elsevier, Oxford 1975, p. 61.

5. A.R. Battersby, E. McDonald, D.C. Williams and H.K.W. Wurziger, J.C.S. Chem. Comm. 1977, 113.

6. B. Franck, A. Rowold, Ch. Wegner and H.G. Eckert, Philos. Trans. R. Soc. London, Ser. B 1976, 273, 181.

7. B. Franck and Ch. Wegner, Angew. Chem. internat. Edit. 1975, 14, 424.

8. G.H. Cookson and C. Rimington, Biochem. J. 1954, 57, 476.