High-yield synthesis of a chiroporphyrin by hydrogen bond-directed cyclisation

Céline Pérollier,[a] Jacques Pécaut,[a] René Ramasseul,[a] Robert Bau[b] and Jean-Claude Marchon*[a]

[a] *Laboratoire de Chimie de Coordination, Service de Chimie Inorganique et Biologique, Département de Recherche Fondamentale sur la Matière Condensée, CEA-Grenoble, 38054 Grenoble, France. E-mail: jcmarchon@cea.fr*
[b] *Department of Chemistry, University of Southern California, Los Angeles, California 90089-0744, USA*

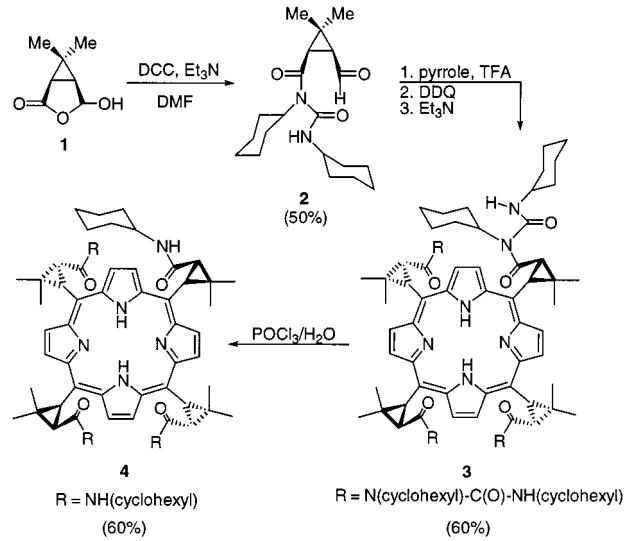
Received (in Basel, Switzerland) 24th May 1999, Accepted 29th June 1999

A new chiroporphyrin is prepared in 60% yield using complementary intramolecular hydrogen-bonding interactions between *N*-acylurea substituents to direct the cyclisation of the tetrapyrrolic intermediate; similar hydrogen-bond assistance by carboxylic acid functions is suggested for cyclisation of hydroxymethylbilane to uroporphyrinogen I.

Esters and disubstituted amides of (1*R*, 3*S*)-(−)-2,2-dimethyl-3-formylcyclopropane-1-carboxylic acid **1** [also called (1*R*, *cis*)-caronaldehyde or biocartol][1,2] are valuable building blocks for the synthesis of porphyrins bearing chiral *meso*-cyclopropyl groups. These chiroporphyrins are obtained as the D_2-symmetric α,β,α,β atropisomer exclusively by classical condensation reaction between the formyl group and pyrrole in modest yield (2–20%). We have shown recently that their manganese(III) complexes are competent catalysts in the asymmetric epoxidation[3] and aziridination[4] of aromatic alkenes. We have also found that the ruthenium(II) and cobalt(III) complexes of tetramethylchiroporphyrin (derived from the methyl ester of **1**) display multipoint binding of axial ligands such as alcohols,[5] amines[6] and amino alcohols:[7] in addition to the metal–ligand interaction, the host–guest bonding array involves two convergent ester carbonyl groups which act as hydrogen bond *acceptors* on each face and are instrumental in ligand enantioselection. In order to obtain a new type of chiroporphyrin bearing both hydrogen bond *donors* and *acceptors*, we have now synthesized the *N*-acylurea **2** by reaction of **1** with DCC, and the corresponding chiroporphyrin. To our surprise, the amphoteric nature of **2** led to an unprecedented high yield of chiroporphyrin **3** (60%), presumably by directing cyclisation of the porphyrinogen intermediate *via* intramolecular hydrogen bonding.

Compound **2** was previously obtained as a side-product (18%) in esterification reactions of **1** catalyzed by DCC–DMAP, and it has been characterised as an *N*-acylurea on the basis of its ^{1}H and ^{13}C NMR spectra.[1] Without competing alcohol or amine reactant, reaction between **1**, 1.2 equiv. of DCC and 1.2 equiv. of Et_3N in DMF, followed by workup and purification by silica gel chromatography (CH_2Cl_2–EtOAc 9 : 1) affords **2** in 50% yield (Scheme 1). The structure assignment was confirmed by X-ray crystallography† (Fig. 1). Notable features of the stereochemistry of **2** are the planarity of the disubstituted amide and urea moieties, and the near orthogonality of the two corresponding planes. The urea is flanked by two sterically bulky cyclohexyl substituents, yet its C11–O12 group is able to interact with the N13–H group of a neighbouring molecule in the crystal, resulting in a chain of strong head-to-tail N–H···O=C–N–H···O=C hydrogen bonds (N13A···O12, 2.889 Å; H13···O12, 1.937 Å; N13A–H···O12, 170.6°) along the *c* axis. There is no hydrogen bond to the amide carbonyl group C8–O9.

After the classical condensation reaction between **2** and pyrrole, subsequent aromatisation of the porphyrinogen intermediate[8] with DDQ and neutralisation with Et_3N, the purple color and nearly clean porphyrin UV–visible spectrum of the reaction mixture came as a surprise. In fact, the D_2-symmetric free base porphyrin **3** was obtained in an unprecedented yield of 60% after purification by silica gel chromatography with CH_2Cl_2–MeOH mixtures. For comparison, a similar condensation reaction carried out on the related *N*-ethyl-*N*-phenyl amide of **1** led only to a 12% yield of chiroporphyrin.[9] Isolation of the abundant porphyrinogen intermediate of **3** was attempted, but this compound was still contaminated with linear oligopyrrole side-products after silica gel chromatography and single crystals could not be obtained. Crystals of the nickel(II)-substituted derivative of **3** were successfully grown from a DMSO solution.



Scheme 1

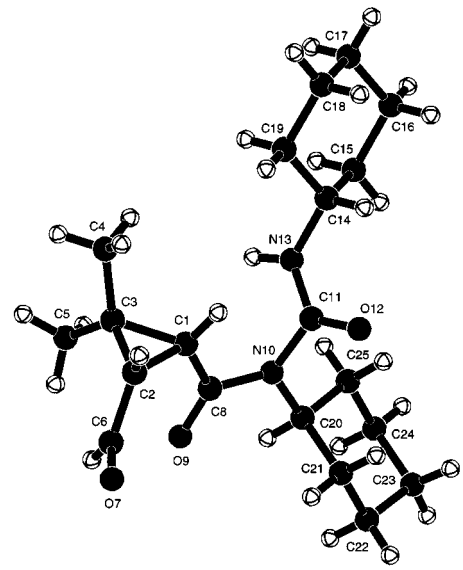


Fig. 1 Molecular structure of **2** showing the planar amide (C1–C8–O9–N10–C11–C20) and urea (N10–C11–O12–N13–C14) moieties, and the near orthogonality of the two corresponding planes (dihedral angle around N10–C11: 76.4°).

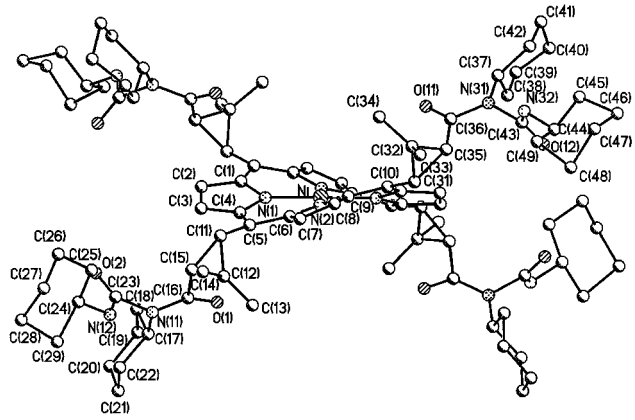


Fig. 2 ORTEP view (30% probability) of the molecular structure of Ni-**3** showing the conformations of the *N*-acylurea substituents with inward oriented amide carbonyl (O1, O11) and urea N–H (N12, N32) groups, and the absence of intramolecular hydrogen bonds.

The X-ray structure of Ni-**3**† (Fig. 2) shows a highly ruffled α,β,α,β porphyrin with inward oriented amide carbonyl and urea N–H groups, and indicates that the distance between two opposite α or β substituents is too large to allow any intramolecular hydrogen bonding interaction. However, examination of a molecular model of the porphyrinogen intermediate suggests that conformations in which the opposite *meso* groups on each face are close enough to allow double hydrogen bonding between the urea N–H donor and amide C=O acceptor groups[10] are accessible. We conclude that the self-complementary nature of the *N*-acylurea substituent of **2** leads to a preorganised, quadruply hydrogen-bonded tetrapyrrole intermediate in which the close proximity of the two reactive end groups directs intramolecular cyclisation[11] and leads to a high yield of porphyrinogen [Fig. 3(*a*)].

The carboxylic acid function is another classical example of self-complementary hydrogen-bonding groups, and it is tempting to speculate that the carboxylic acid substituents on the β-pyrrolic positions of porphobilinogen may serve the function of

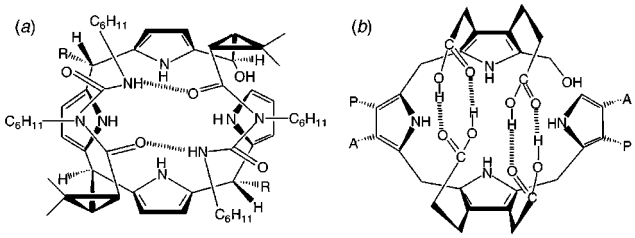


Fig. 3 (*a*) The conformation of the tetrapyrrole intermediate, preorganised by hydrogen bonding between self-complementary *N*-acylurea substituents, which leads to a high yield of porphyrinogen and to a 60% yield of **3**. For the sake of clarity, only the H-bonding pattern on the top face is shown, and each of the two H-bonded *meso* substituents on the bottom face is abbreviated as R. (*b*) Proposed hydrogen-bond assistance by carboxylic acid functions in the cyclisation of hydroxymethylbilane to uroporphyrinogen I. For the sake of clarity, the double hydrogen bond between each of the opposite acetic (A) and propionic (P) substituent pairs on the lower face has been omitted.

directing the spontaneous macrocyclisation of the hydroxymethylbilane tetrapyrrole to uroporphyrinogen I [Fig. 3(*b*)].[12]

Finally, the high yield synthesis of **3** from a readily accessible *N*-acylurea derivative of **1** makes this macrocycle a convenient precursor of other chiroporphyrins, as exemplified by the preparation of the tetra-*N*-cyclohexylamide **4** by $POCl_3$-induced cleavage of the ureido groups,[13] which will be described elsewhere.

Notes and references

† *Crystal data* for **2**: $C_{20}H_{32}N_2O_3$, M_r = 348.5, orthorhombic, a = 10.861(2), b = 20.595(3), c = 8.948(2) Å, U = 2001.5(6) Å^3, T = 163 K, space group $P2_12_12_1$, Z = 4, μ(Cu-Kα) = 0.615 mm^{-1}, 1574 reflections measured, 1425 unique, of which 1273 with $F > 4.0\,\sigma(F)$ were used in all calculations, R_1 = 0.0608 [$I > 2\sigma(I)$], wR_2 = 0.1553, GOF = 1.19. For Ni-**3**: $C_{96}H_{132}N_{12}O_8Ni{\bullet}5C_2H_6SO{\bullet}3H_2O$, M = 2085.53, tetragonal, $a = b$ = 15.091(3), c = 63.54(2) Å, U = 14472(6) Å^3, T = 193 K, space group $P4_32_12$, Z = 4, μ(Mo-Kα) = 0.257 mm^{-1}, 46236 reflections measured, 10825 unique (R_{int} = 0.3052), of which 2864 with $F > 4.0\,\sigma(F)$ were used in all calculations, R_1 = 0.1192 [$I > 2\sigma(I)$], wR_2 = 0.2614, GOF = 1.004, Flack index 0.04(5). The relatively poor quality of the data set collected for Ni-**3**, as judged from the large R_{int} value, probably contributes to the large final R factors. CCDC 182/1314. See http://www.rsc.org/suppdata/cc/1999/1597/ for crystallographic data in .cif format.

1 M. Veyrat, L. Fantin, S. Desmoulins, A. Petitjean, M. Mazzanti, R. Ramasseul, J.-C. Marchon and R. Bau, *Bull. Soc. Chim. Fr.*, 1997, **134**, 703.
2 C. Pérollier, J. Pécaut, R. Ramasseul and J.-C. Marchon, *Bull. Soc. Chim. Fr.*, 1997, **134**, 517.
3 M. Veyrat, O. Maury, F. Faverjon, D. E. Over, R. Ramasseul, J.-C. Marchon, I. Turowska-Tyrk and W. R. Scheidt, *Angew. Chem., Int. Ed. Engl.*, 1994, **33**, 220; C. Pérollier, J. Pécaut, R. Ramasseul and J.-C. Marchon, *Inorg. Chem.*, 1999, in the press.
4 J.-P. Simonato, J. Pécaut, W. R. Scheidt and J.-C. Marchon, *Chem. Commun.*, 1999, 989.
5 M. Mazzanti, M. Veyrat, R. Ramasseul, J.-C. Marchon, I. Turowska-Tyrk, M. Shang and W. R. Scheidt, *Inorg. Chem.*, 1996, **35**, 3733.
6 D. Toronto, F. Sarrazin, J. Pécaut, J.-C. Marchon, M. Shang and W. R. Scheidt, *Inorg. Chem.*, 1998, **37**, 526.
7 J.-P. Simonato, J. Pécaut and J.-C. Marchon, *J. Am. Chem. Soc*., 1998, **120**, 7363.
8 J. S. Lindsey and R. W. Wagner, *J. Org. Chem.*, 1989, **54**, 828.
9 C. Pérollier, *Doctoral Thesis*, Université Joseph Fourier, Grenoble, 1998.
10 For structurally characterised examples of strong dimerisation *via* complementary hydrogen bonding between urea N–H donors and amide C=O acceptors, see: F. H. Beijer, R. P. Sijbesma, H. Kooijman, A. L. Spek and E. W. Meijer, *J. Am. Chem. Soc*., 1998, **120**, 6761.
11 For reviews of hydrogen-bonded self-assembling complexes, see: D. S. Lawrence, T. Jiang and M. Levitt, *Chem. Rev.*, 1995, **95**, 2229; M. M. Conn and J. Rebek, Jr., *Chem. Rev.*, 1997, **97**, 1467. For a previous example of macrocyclisation directed by hydrogen bonding, see: F. J. Carver, C. A. Hunter and R. J. Shannon, *J. Chem. Soc., Chem. Commun.*, 1994, 1277.
12 For a recent review of heme biosynthesis, see: A. R. Battersby and F. J. Leeper, *Top. Curr. Chem.*, 1998, **195**, 143. For structurally characterised uroporphyrinogen derivatives, see: G. Sawitzki and H. G. von Schnering, *Angew. Chem., Int. Ed. Engl*., 1976, **15**, 552; C. Lehmann, B. Schweizer, C. Leumann and A. Eschenmoser, *Helv. Chim. Acta*, 1997, **80**, 1421.
13 S. Avramovici-Grisaru and S. Sarel, *Nouv. J. Chim.*, 1982, **6**, 455.

Communication 9/04134F