Chemistry of Corphinoids: Synthesis of a Nickel(II) Complex Containing the Chromophore System of Coenzyme F430

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In a model study, the structural features characteristic of the chromophore of coenzyme F430 are generated regio- and diastereo-selectively in a two-step reduction–addition sequence from a nickel(II) dihydrocorphinate precursor.

Recently, structure (**1**)[1] was deduced for factor F430,[2] the nickel-containing coenzyme[3] that is part of the system of enzymes catalysing the production of methane from carbon dioxide and hydrogen in methanogenic bacteria. Factor F430 is the first known biologically functional porphinoid with nickel as the central metal ion.[2b,c] Its uroporphinoid ligand system contains an extra carbocyclic ring and, as a tetrahydro derivative of a corphin,[4] it combines structural elements of both the corrins and the porphins. Recent observations made in our laboratory on synthetic nickel(II) complexes structurally related to F430[5] and on the coenzyme itself[6] point to the view that the structure of F430 represents another instructive example of Nature's variations of the structural theme of uroporphinoids, whereby the reactivity of the central metal ion is tuned to a specific coenzymic task.[7] Here we report the synthesis of the nickel(II) complex (**3**), a compound which we value as a chemical model for F430. The cyano group at the *meso* position between rings C and D serves as a substitute for F430's electrophilic acyl substituent at this position.

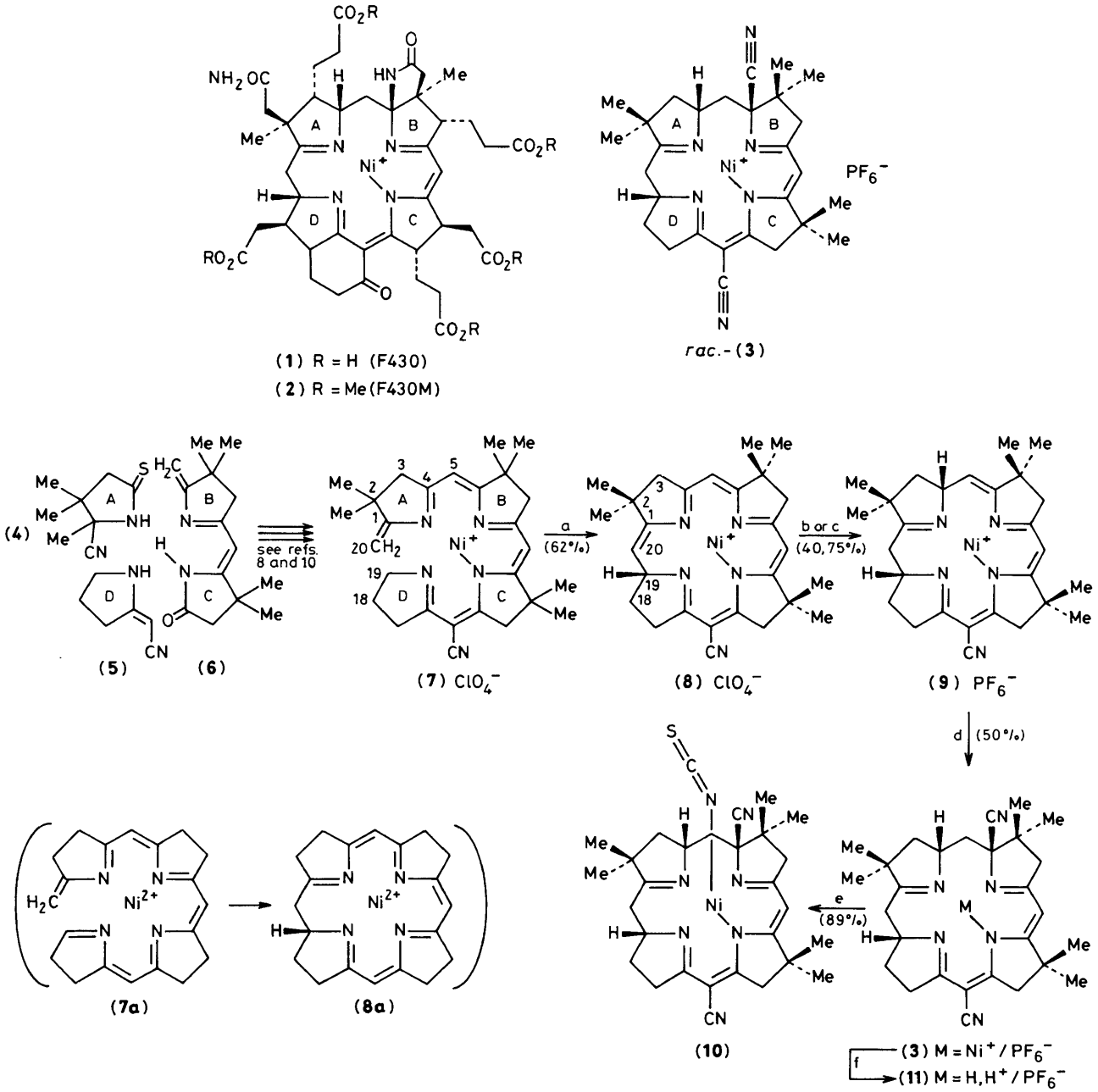
The synthesis of (**3**) (Scheme 1) is an extension of earlier work from our laboratory.[8,9] Electrochemical oxidation of the nickel(II)–1-methylene-1,19-secocorrinate (**7**)† in anhydrous acetonitrile–acetic anhydride–acetic acid (10:1:1) under argon at room temperature gives, after work-up with sodium acetate, the crystalline cyclisation product (**8**) in > 60% yield.[11,12] The product shows the u.v.–visible spectrum of a dihydrocorphinate[5] and its ^{1}H n.m.r. spectrum (in $CDCl_3$) documents the (C-19) → (C-20) ring closure by showing one of the three vinyl proton signals (δ 5.30) to be a doublet (*J* 2.5 Hz) which is coupled with a (>CH–N=) methine proton multiplet (δ 5.04). The oxidative cyclisation (**7**) → (**8**) is mechanistically complex.‡ We view the central step to be the valence tautomerisation (**7a**) → (**8a**). The cyclic system (**8a**) (presumably as hexaco-ordinate complex) survives the oxidizing conditions thanks to the low nucleophilicity of its non-enaminoid chromophore system; its deprotonation on work-up with sodium acetate produces (**8**).

In close analogy to a previously described example,[5] the electrochemical reduction of (**8**) (reaction conditions b) leads regio- and diastereo-selectively to the *cis*-4,18,19,20-tetrahydrocorphinate (**9**) as the main reaction product. The spectral changes (u.v.–visible, ^{1}H n.m.r.) that accompany the conversion (**8**) → (**9**) are characteristic and closely parallel those observed in the earlier example, where the constitution and configuration of the reduction product were established by *X*-ray analysis.[5] The diastereoselectivity of the reduction amounts to about 15:1 in favour of the *cis*-isomer (**9**). What we assume to be the *trans*-diastereoisomer was observed by t.l.c. analysis and recognized as such by its u.v.–visible spectrum. Similarly, only small amounts of a constitutionally isomeric 1,18,19,20-tetrahydrocorphin derivative (u.v.–visible; see also ref. 5) were detected.

The tetrahydrocorphinate ion (**9**) is rather unstable (especially in the presence of base) and, among the various noncrystalline salt forms, the hexafluorophosphate was the easiest to handle. On treatment with excess of NaCN in the presence of AcOH in dimethyl sulphoxide (DMSO), the

† Starting material for our earlier studies on the A/D-secocorrin → corrin-cycloisomerisation;[8] for its preparation from the precursors (**4**), (**5**), and (**6**) see refs. 8 and 10.

‡ *Cf.* the mechanism of the *electrochemical* A/D-secocorrin → corrin-cycloisomerisation[11,9] by which (**7**) gives the corresponding nickel(II)–1-methyl-1,19-*trans*-corrinate [40% besides 48% recovered (**7**), see ref. 11, p. 213]. Both the reaction medium and the reaction temperature of the process (**7**) → (**8**) are critical: operating at 0 °C leads to the 19-acetoxy-derivative of (**7**) instead of (**8**),[12] whereas the (1 → 19)-oxide derived from the 19-hydroxy-derivative of (**7**) is produced almost quantitatively when the electrochemical oxidation is carried out in (moist) acetonitrile at room temperature.[9a]



Scheme 1. Reaction conditions (for details see refs. 11 and 15; t.l.c. on SiO_2 + 1% $NaClO_4$); a, 8.4 × 10^{-5} mol of (**7**) in 50 ml of MeCN, 0.1 M $LiClO_4$ + 9.2 ml of AcOH–Ac_2O, 1 : 1, argon, Pt electrode, +1.20 → +1.30 V, 1.6 Faraday/mol after 3 h; work-up: NaOAc, CH_2Cl_2, H_2O, $NaClO_4$; t.l.c. (EtOAc–toluene, 5 : 1), cryst. from MeOAc; b, 4.50 × 10^{-5} mol of (**8**) in 25 ml of MeCN, 0.1 M $LiClO_4$ + *ca.* 4.5 × 10^{-5} mol of AcOH, Hg-pool electrode, −1.07 → −1.15 V (≤ 5 mA), 1.8 Faraday/mol after 2 h; t.l.c. (toluene–EtOAc, 7 times developed); c, 5.7 × 10^{-5} mol of (**8**) in 3 ml of $(CH_2Cl)_2$ + 0.5 ml of AcOH + Zn dust, 50 °C; crude product obtained after work-up with aqueous $NaClO_4$–CH_2Cl_2 (t.l.c.: one main component, $\varepsilon_{415\ nm}$ 75%) directly treated as in d; d, 2.4 × 10^{-5} mol of (**9**) in 1.5 ml of DMSO + 3.5 × 10^{-3} mol of NaCN + 1.7 × 10^{-3} mol of AcOH, 70 °C, 7.5 h; t.l.c. ($CHCl_3$–EtOAc–Et_2O, 10 : 1 : 2); anion exchange: shaken in CH_2Cl_2 with aqueous NaCN (neutral covalent cyano complex), and then with 0.1 M acidified aqueous solution of KPF_6; cryst. from CH_2Cl_2–MeOAc; e, (**3**) in CH_2Cl_2 shaken with 0.1 M aqueous KNCS, room temp. cryst. from CH_2Cl_2–EtOAc in glove-bag; f, 3.3 × 10^{-5} mol of (**3**)·(Cl^-) in 1.5 ml of conc. HCl + 40 μl of propane-1-thiol degassed in ampoule, 65 °C, 24 h; t.l.c. (EtOAc–toluene, 5 : 1, in glove-bag); cryst. as PF_6^- salt from MeOAc–hexane in glove-bag.

(crystalline) HCN adduct (**3**) was obtained. Besides decomplexed (fluorescent) material,§ it was the only product which could be isolated and, specifically, no diastereoisomer was observed. Preparatively, (**3**) was most conveniently prepared directly from the dihydrocorphinate (**8**) without purification of the tetrahydro intermediate (**9**) and by carrying out the reduction step (**8**) → (**9**) with Zn–AcOH in CH_2ClCH_2Cl instead of electrochemically (reaction conditions c; diastereoselectivity 7 : 1 in favour of *cis*-isomer). The overall yield of chromatographically purified and crystallized product (**3**) by this two-step procedure was 35%.

§ Treatment of the mixture of fluorescent greenish by-products (4 spots on t.l.c., $\lambda_{max.}$ 445 nm) with $NiCl_2$ in MeOH–AcOH containing NaOAc gave material which closely resembled (**3**) in its u.v.–visible spectra.

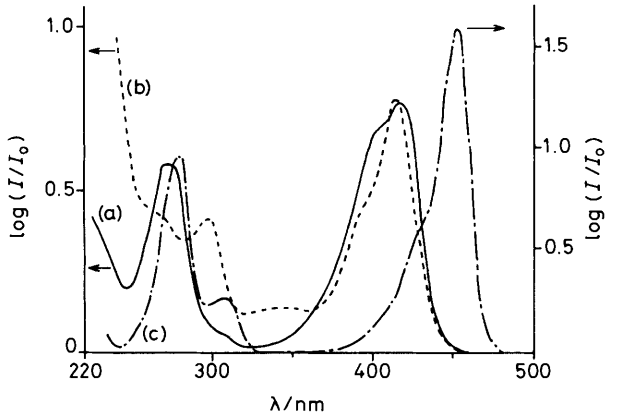


Figure 1. U.v.–visible spectra: (a), (**3**) in MeOH (2.90×10^{-5} M); (b) (**3**) in CH_2Cl_2 (4.26×10^{-5} M); (c), (**11**)·PF_6^- in CH_2Cl_2 (2.93×10^{-5} M).

The structure assignment for the F430 model complex (**3**) (see spectral data¶) is corroborated by an *X*-ray structure analysis (see below). The u.v.–visible spectrum of (**3**) in MeOH (Figure 1a) closely resembles the spectrum of F430M (**2**).[1] In this solvent, both complexes are paramagnetic [μ 2.50 and 1.84[6] μ_B for (**3**) and (**2**), respectively] and, therefore, contain a penta- or hexa-co-ordinated nickel(II) ion. Fortunately (for n.m.r. spectroscopy), both complexes are diamagnetic in non-nucleophilic solvents (*e.g.* anhydrous CH_2Cl_2) and, accordingly, their metal ion is tetraco-ordinated in such solvents. Figure 1b illustrates the pronounced influence of the solvent's nucleophilicity on the electronic spectrum of (**3**). The propensity of the nickel(II) in (**3**) for axial co-ordination is documented by the essentially quantitative reaction of (**3**) with rhodanide ion to form the beautifully crystallising, paramagnetic isothiocyanato complex (**10**) whose remarkable solid state structure is described in the following communication.[13]

Removal of the nickel(II) ion from (**3**) without destruction of the ligand system is difficult. The labile metal-free ligand could be isolated in low yield as the crystalline hexafluorophosphate (**11**) after heating of (**3**) with propanethiol[14] in conc. HCl with strict exclusion of oxygen. To the characteristics of the protonated ligand salt (**11**) belong a dominant sharp absorption band at 450 nm (see Figure 1c) and a strong fluorescence emission band at 468 nm. Re-complexation of (**11**) to (**3**) proceeds without difficulty [$Ni(OAc)_2$, MeCN, 65 °C].

Two aspects of this work appear to be of special relevance to the structure of coenzyme F430. First, the complex (**3**) models the coenzyme structure with respect to both the characteristic constitution of the chromophore and the specific (relative) configuration at the three chirality centres of the inner macrocycle. Both these structural features are generated regio- and diastereo-selectively in a two-step reduction–addition sequence from a dihydrocorphinate precursor. It will be of interest to discover whether the biosynthesis of coenzyme F430 will turn out to be 'chemomimetic' in the sense that it mimics this intrinsically 'natural' chemical mode of chromophore formation. Secondly, the nickel(II) ion in the *tetrahydrocorphinoid* model complex (**3**) is on the brink of being able to interact covalently in the direction perpendicular to the ligand plane. Equally charged nickel(II) complexes of the chromophore-related *corrin-ligand* do not show any (recognizable) reactivity in the axial direction.[8c,9b] This aspect of axial reactivity of corphinoid nickel(II) complexes is dealt with further in the following communication.

We thank Dr. W. W. McWhorter and Dr. E. Zass for their help in preparing the final manuscript. The work was supported by the Swiss National Science Foundation.

Received, 21st June 1984; Com. 866

¶ Selected spectral data (for complete data see refs. 15 and 11): (**8**): m.p. 237 °C (decomp.); $\lambda_{max.}$ (EtOH) 267 (log ε 4.19), 305 (4.25, sh.), 320 (4.35, sh.), 332 (4.40), 394 (3.77), 422 (3.82), and 466 nm (3.90, br.); ^{1}H n.m.r. δ($CDCl_3$) 6.26 (s, 10-CH), 5.91 (s, 5-CH), and 5.30 (d, *J* 2.5 Hz, 20-CH), see also text; *m/z* 483 ($M^+ - HClO_4$, 28%); (**9**): $\lambda_{max.}$ (EtOH) 289 (4.16), 298 (4.14, sh.), 324 (3.64, sh.), 341 (3.61), 364 (3.55, sh.), 424 (4.17), 441 (4.12 sh.), and 474 nm (3.63, sh.); δ($CDCl_3$) 5.68 (s, 10-CH), 5.10 (d, *J* 2 Hz, 5-CH), 4.79 (m, 4-CH), 3.43 (m, 19-CH), and 2.90 (m, 20-CH_2); *m/z* 486 ($M^+ - PF_6^-$, 100%); (**3**): m.p. 273 °C; $\lambda_{max.}$ (MeOH, Figure 1a) 270—276 (4.30), 309 (3.25, sh.), 402 (4.37, sh.), and 417 nm (4.42); $\lambda_{max.}$(CH_2Cl_2, Figure 1b) 268 (3.99, sh.), 297 (3.99), 348 (3.51), 393 (4.03, sh.), and 412 nm (4.26); δ(CD_2Cl_2) 5.68 (s, 10-CH), 4.36 (m, 4-CH), and 3.47 (m, 19-CH); *m/z* 513 ($M^+ - PF_6^-$, 100%); (**10**): m.p. 253 °C; $\lambda_{max.}$(CH_2Cl_2) 276 (4.31), 298 (3.76, sh.), 400 (4.25, sh.), and 419 nm (4.41); $\nu_{max.}$ ($CHCl_3$) 2100 cm^{-1} (N=C=S); M_r (CH_2Cl_2) 589 ± 15 (*c* 2.6×10^{-3} M); (**11**): $\lambda_{max.}$ (CH_2Cl_2, Figure 1c) 279 (4.52), 307 (3.97), 426 (4.30, sh.), and 450 nm (4.73); δ(CD_2Cl_2) 9.98 (br., 2 NH), 5.54 (s, 10-CH), 4.52 (m, 4-CH), and 4.38 (m, 19-CH); *m/z* 457 ($M^+ - PF_6^-$, 100%).

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