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The effect of steric hindrance in the synthesis of corrolates via the cobalt catalyzed cyclization of 2-(α-hydroxyalkyl)pyrroles ☆

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Abstract

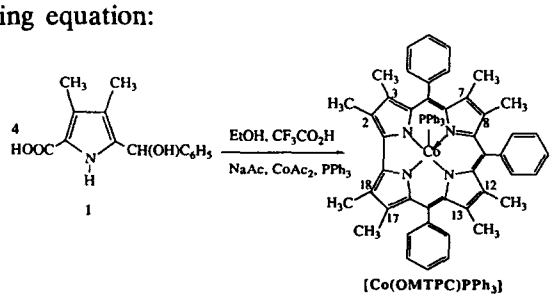
2-(α-Hydroxyalkyl)pyrroles react in the presence of cobalt ions leading to the formation of corrolates or porphyrinates as a function of the 2-substituents. The nature of the cyclic tetrapyrrole obtained can be related to the steric hindrance of the substituent present in the starting pyrrole. The presence of cobalt ions is essential to drive the reaction towards the formation of the contracted corrole macroring. When 3-ethyl-4-methyl-2-(α-hydroxybenzyl)pyrrole-5-carboxylic acid is used as starting material an etio-like cobalt corrolate, i.e. with alternate methyl and ethyl groups on the β-pyrrolic positions, has been obtained as demonstrated by detailed analysis of the NMR spectrum of the complex. A possible reaction pathway explaining the formation of such a species is reported.

Keywords: Cobalt complexes; Corrole complexes; Tetrapyrrole complexes; Cyclization; NMR spectroscopy

1. Introduction

Metal complexes of tetrapyrrolic macrocycles are the subject of numerous studies because of their similarity with the naturally occurring systems and their various catalytic applications. Among them cobalt corrolates may be considered model compounds for coenzyme B_{12}; a rich redox chemistry is possible for these compounds and several variations of the peripheral substituents of the macrocycle can be performed making feasible the modulation of the redox and electronic properties of the resulting complexes [1–3].

During our investigations on the chemistry of metallocorrolates [4–8] we have discovered [3] that the complex [(triphenylphosphine)(5,10,15-triphenyl-2,3,7,8,12,13,17,18-octamethylcorrolato)cobalt(III)] ([Co(OMTPC)PPh_3]) can be prepared by direct cyclization of 2-(α-hydroxybenzyl)pyrrole (**1**) according to the following equation:



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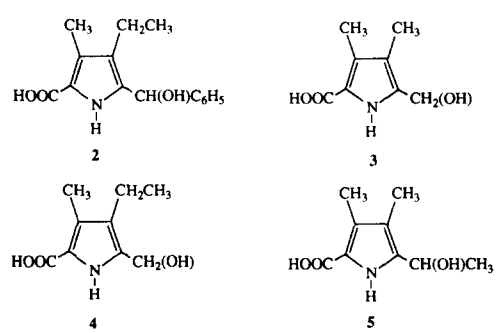
The reaction occurs only in the presence of cobalt and the corresponding porphyrin is the product obtained if other metal ions are used.

The hypothesis formulated for the reaction mechanism involved the formation of a porphyrinogen-like species followed by a cobalt-catalyzed ring contraction reaction.



2 3 4 5

In order to clarify the reaction mechanism and to test the possibility of extending such a simple synthetic route to corrolates with different substitution patterns we have now synthesized pyrroles **2–5** and examined their behavior in the presence of cobalt ions.

2. Experimental

Electronic spectra were recorded on a Philips PU8700 spectrophotometer. Fast atom bombardment (FAB) and

☆ This paper is dedicated to the memory of Professor Ugo Croatto.

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electron impact (EI) mass spectra were obtained on a VG Quattro spectrometer; 3-nitro-benzyl alcohol was used as a matrix in the FAB experiments.

A Bruker AM 400 spectrometer was used to obtain the ^1H NMR spectra as $C_6{}^2H_6$ solutions. All chemical shifts are given in ppm from tetramethylsilane (TMS).

NOE experiments were performed in the rotating frame mode (ROESY) [9,10]. A mixing time of 300 ms was applied in order to obtain the dipolar magnetization transfer. The spectra were measured in phase sensitive mode using TPPI [11]. 512 experiments were carried out accumulating 128 scans over 2K of memory. Processing of data was performed on a Digital graphic workstation using the TRITON NMR processing program [12]. A real 1024×1024 matrix was obtained. A polynomial baseline correction was applied in both dimensions. Detection of cross peaks was performed in the unsymmetrized spectrum. The symmetrization procedure was applied for cosmetic reasons in order to reduce the strong T_1 noise, just to report the results in Fig. 2.

All solvents (Carlo Erba Reagenti) were reagent grade and were used without further purification.

3,4-Dimethyl-2-(α-hydroxybenzyl)pyrrole-5-carboxylic acid (**1**) and 3,4-dimethyl-2-(α-hydroxyethyl) pyrrole-5-carboxylic acid (**5**) were prepared according to literature procedures [2].

3-Ethyl-4-methyl-2-(α-hydroxybenzyl)pyrrole-5-carboxylic acid (**2**) and 3,4-dialkyl-2-hydroxymethyl-pyrrole-5-carboxylic acid (**3, 4**) were prepared following the same procedure using as starting materials ethyl-3-ethyl-4-methylpyrrole-5-carboxylate [13] and 3,4-dialkyl-2-formylpyrrole-5-carboxylic acid [14], respectively.

2,3,7,8,12,13,17,18-Octamethyl-5,10,15,20-tetraphenylporphyrinogen was prepared according to the method of Smith and co-workers [15].

[Co(OMTPC)PPh_3] was prepared following the published procedure [3].

2.1. Cyclization reactions

(i) **2** (0.5 g, 1.93 mmol) was dissolved in hot absolute ethanol (200 ml); trifluoroacetic acid (1 ml) was then added and the dark red solution was refluxed for 15 min. An excess of sodium acetate (2 g, 24.4 mmol), cobalt(II) acetate (0.5 g, 1.91 mmol) and triphenylphosphine (0.5 g, 2.00 mmol) were added and the solution was refluxed for 24 h. The solvent was vacuum evaporated and the residue extracted with diethyl ether, then chromatographed on basic alumina (Merck, type T), using diethyl ether as eluent. The first red band eluted contained [Co(TMTETPC)PPh_3] which was recrystallized from diethyl ether/n-pentane 1:3 (98 mg, yield 20%). *Anal.* Calc. for $C_{67}H_{62}N_4PCo$: C, 79.43; H, 6.17; N, 5.53. Found: C, 79.95; H, 6.05; N, 5.75%.

λ_{max} (diethyl ether): 380, 416sh, 575 (ε: 59 500; 44 000; 10 300 respectively). MS: *m/z* (%): 1012 (29%) [M^+]; 750 (70%) [$M-PPh_3{}^+$].

(ii) **3** (0.3 g, 1.77 mmol) was reacted as described in (i). The residue obtained after evaporation of the solvent was insoluble in diethyl ether. It was therefore dissolved in THF and chromatographed on basic alumina (Merck, type T), using THF as eluent. The first fraction eluted contained octamethylporphyrin (10 mg, yield 5%), the spectral properties of which were identical to those reported in the literature [16].

(iii) **4** (0.35 g, 1.91 mmol) was reacted as described in (i). The solvent was vacuum evaporated and the residue extracted with diethyl ether, then chromatographed on basic alumina (Merck, type T), using diethyl ether as eluent. The first fraction eluted contained etioporphyrin I (12 mg, yield 5%) (λ_{max} (CH_2Cl_2): 398, 497, 533, 566, 620 nm; δ (C^2HCl_3): 10.08 (s, 4H), 4.10 (q, $J=7$ Hz, 8H), 3.65 (s, 12H), 1.88 (t, $J=7$ Hz, 12H), −3.68 (br, 2H) ppm); the second fraction contained its Co(II) complex (55 mg, yield 21%) (λ_{max} (CH_2Cl_2): 398, 497, 533, 566, 620 nm). Both compounds were identified on the basis of their spectral properties which were identical to those reported in the literature [17,18].

(iv) **5** (0.35 g, 1.91 mol) was reacted as described in (i). No evidence for cyclization was obtained.

3. Results and discussion

Pyrrole **2** was synthesized in order to verify the hypothesis of the initial formation of a porphyrinogen-like species followed by a cobalt catalyzed ring contraction reaction: with such a starting material, in fact, an etio-like corrolate (i.e. [(triphenylphosphine)(5,10,15-triphenyl-2,7,12,17-tetramethyl-3,8,13,18-tetraethylcorrolato)cobalt(III)], from now on indicated as [Co(TMTETPC)PPh_3], with alternate methyl and ethyl groups on the β-positions) would be the expected product.

The 400 MHz ^1H NMR spectrum of the complex obtained by direct cyclization of pyrrole **2** is shown in Fig. 1. Assignments have been performed on the basis of a variety of arguments and are summarized, with spectral data, in Table 1. All resonances show the strong shift caused by the macrocycle ring current [19] and, as in the case of other cobalt corrolates [2,3], the shift shown by the resonances due to the protons of the axial triphenylphosphine ligand also demonstrates the shielding effect of the aromatic macrocycle. A comparison of the chemical shift of the *ortho*-protons of the phenyl rings of the axial ligand in the spectrum of [Co(OMTPC)PPh_3] (5.00 ppm) with the value observed in the spectrum of [Co(TMTETPC)PPh_3] (5.32 ppm) indicates that in this latter complex the axial phosphine ligand is at a larger distance from the

Table 1
400 MHz ^{1}H NMR data for [Co(TMTETPC)PPh$_3$] in deuterated benzene

Label	δ (ppm)	Multiplicity	Intensity [a]	Assignment
A	7.96	m		
B	7.75	m		
C	7.46	m	15H	*meso*-Ph
D	7.40	m		
E	7.05	m		
F	6.84	t (J=7 Hz)	3H	*p*-PPh$_3$
G	6.66	t (J=7 Hz)	6H	*m*-PPh$_3$
H	5.32	t (J=7 Hz)	6H	*o*-PPh$_3$
I	3.83	m	1H	18-CH$_2$(Et)
J	3.43	m	1H	18-CH$_2$(Et)'
K	3.24	s	3H	2-CH$_3$
L	2.85	m	1H	3-CH$_2$(Et)
M	2.73	m	3H	3-CH$_2$(Et)'+8 (or 13)-CH$_2$(Et)
N	2.63	q (J=7.4 Hz)	2H	13 (or 8)-CH$_2$(Et)
O	2.37	s	3H	17-CH$_3$
P	2.35	s	3H	12 (or 7)-CH$_3$
Q	2.32	s	3H	7 (or 12)-CH$_3$
R	1.65	t (J=7.4 Hz)	3H	18-CH$_3$(Et)
S	1.26	t (J=7.4 Hz)	6H	3-CH$_3$(Et)+8 (or 13)-CH$_3$(Et)
T	1.19	t (J=7.4 Hz)	3H	13 (or 8)-CH$_3$(Et)

[a] Intensity as the number of protons.

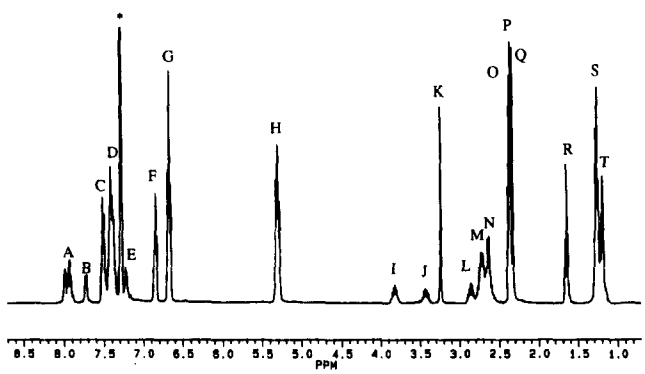


Fig. 1. 400 MHz ^{1}H NMR spectrum of [Co(TMTETPC)PPh$_3$] in deuterated benzene. An asterisk marks the solvent residual signal. Labels refer to the assignments reported in Table 1.

macrocycle plane, probably because of steric constraints introduced by the peripheral substituents.

A high degree of rigidity of the molecule is indicated by the presence of two distinct signals for the methylenic protons of the 18-ethyl group (resonances I and J). The assignment of these resonances is based on their chemical shift values: positions 2 and 18 in the corrole skeleton are in fact those where the highest electron density exists [20] and the only ones that do not experience the shielding effect of the *meso*-phenyl substituents, consequently they are expected to be those resonating at lower field values. Following the same line of reasoning, and comparing the spectrum with that of [Co(OMTPC)PPh$_3$] [2], resonance K, a singlet centered at 3.24 ppm, can be assigned to the 2-methyl group. Selective decoupling demonstrated that resonances I and J are coupled with resonance R that can then be assigned as due to the methyl protons of the 18-ethyl group.

From the definition of the substituents at positions 2 and 18 follows that of the 3 and 17 positions: an ethyl group must be the 3-substituent and a methyl group the one in position 17. In order to identify the corresponding resonances a ROESY experiment was carried out and Fig. 2 shows the upfield region of the spectrum which was essential in defining the geometry of the complex. This experiment allowed the attribution of resonance O to the 17-CH$_3$ and of resonances M and S to the 3-ethyl group.

Having assigned the resonances due to the substituents present in positions 2,3,17 and 18 it is now necessary to define the substitution pattern of the 'right side' of the molecule, i.e. position 7,8,12,13. Four possible schemes can be written: (a) 7,12-Me$_2$-8,13-Et$_2$; (b) 7,13-Et$_2$-8,12-Me$_2$; (c) 7,13-Me$_2$-8,12-Et$_2$; (d) 7,12-Et$_2$-8,13-Me$_2$. Scheme (b) is however impossible because the presence of two methyl groups in positions 8 and 12 is not compatible with the presence of a phenyl group at the adjacent *meso*-position (i.e. 10). In the same fashion schemes (c) and (d) are not compatible with the presence of the 15-Ph group since it has been determined that a methyl is present at position 17. Scheme (a) is then the only possible substitution pattern in agreement with all the experimental data and corresponds to the structure of [Co(TMTETPC)PPh$_3$].

Decoupling experiments and the presence of NOEs demonstrate that the methylenic group generating resonance M and the second methyl group that gives rise

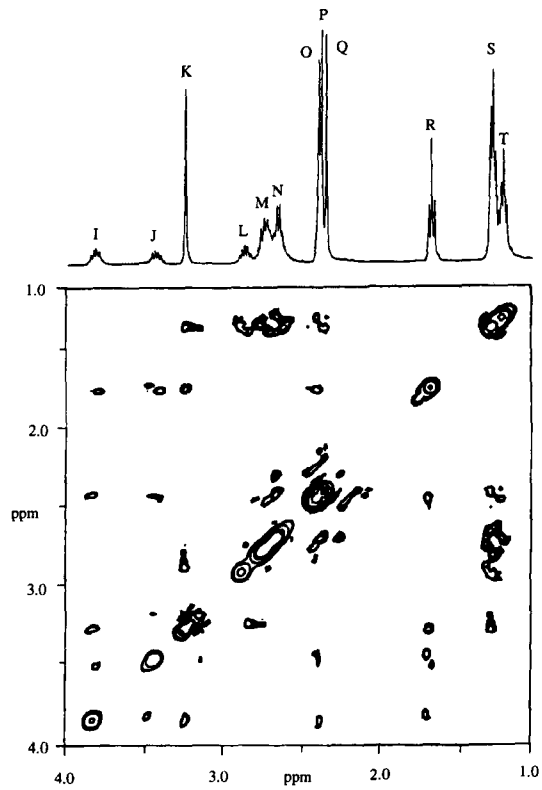


Fig. 2. Aliphatic region of the ROESY spectrum of [Co(TMTETPC)PPh$_3$].

to resonance S correspond to one ethyl group that is adjacent to a methyl which gives rise to resonance Q and that resonances N and T correspond to the second ethyl group adjacent to the methyl group corresponding to resonance P.

Because of the symmetry of the molecule it is impossible to distinguish between the assignments of resonance P as due to the 12-CH_3 and resonance Q to the 7-CH_3 or vice versa. The substitution pattern of the complex is however completely defined and supports the initial hypothesis of a ring contraction reaction that would transform the porphyrinogen skeleton into that of corrole.

Thus, 2,3,7,8,12,13,17,18-octamethyl-5,10,15,20-tetraphenylporphyrinogen was prepared according to the published procedure [15] and reacted with cobalt acetate in the presence of triphenylphosphine. In a first experiment the reaction was carried out in conditions identical to those used to prepare [Co(OMTPC)PPh$_3$] [3] and [Co(TMTETPC)PPh$_3$], and in a second experiment in the presence of the minimum amount of dichloromethane necessary to obtain an homogeneous solution, since the porphyrinogen was only slightly soluble in ethanol.

The addition of trifluoroacetic acid and/or sodium acetate did not modify the results: in all cases the reaction products were 2,3,7,8,12,13,17,18-octamethyl-5,10,15,20-tetraphenylporphyrin and the corresponding chlorin identified by their electronic spectra (λ_{max} = 446 and 421 nm, respectively), which were identical to those reported in the literature [21], with no evidence of the formation of cobalt corrolate from the porphyrinogen.

An alternative reaction pathway for the cyclization of 2-(α-hydroxybenzyl)pyrroles must therefore be formulated; so the changes in the visible spectrum of the reaction mixture were examined in further detail; pyrrole **1** was used because it was available in larger quantities in our laboratory.

3,4-Dialkyl-2-(α-hydroxybenzyl)pyrroles show only an end-absorption in the visible region of the spectrum (Fig. 3, spectrum a); upon addition of trifluoroacetic acid a band at 513 nm appeared, its intensity increased with time and it reached a maximum after 30 min (Fig. 3, spectrum b). As previously reported [3] such a spectrum is different from that of the linear tetrapyrrole which is the typical precursor of the corrole macrocycle, i.e. biladiene-*a,c*; furthermore, the addition of excess base did not generate the spectrum of the bilatriene free base (λ_{max} = 650, 400 nm) [22] but only the appearance of a band at 469 nm was observed (Fig. 3, spectrum c).

Such optical properties are consistent with the formation of a *meso*-phenyldipyrromethene; these species are in fact known to have spectra characterized by a single absorption centered around 515 nm [21].

Porphodimethenes are also reported [21] to have similar electronic spectra, but we may exclude their formation since they are known to derive from porphyrinogens and to exist in equilibrium with the corresponding phlorins (λ_{max} = 750, 430 nm) [23]; the presence of this latter species can be ruled out since no absorption in the low energy region was observed in the optical spectrum of the reaction mixture.

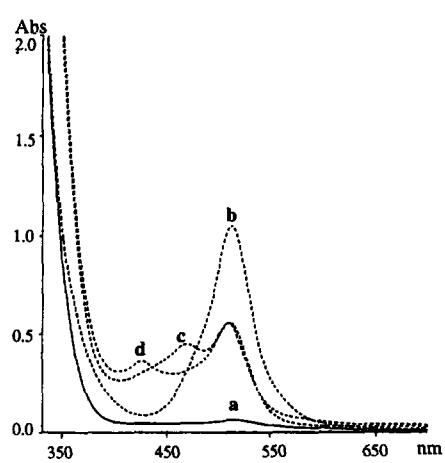
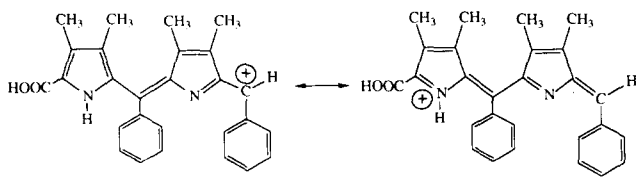


Fig. 3. Electronic spectra of the reaction mixture for the cyclization of pyrrole **1** (diluted 1:20 with absolute ethanol): (a) initial spectrum; (b) after addition of trifluoroacetic acid; (c) after the addition of sodium acetate; (d) after the addition of cobalt acetate and triphenylphosphine.

In the synthesis of sterically hindered porphyrins the formation of dipyrromethenes has been reported to decrease the reaction yield [24]; porphyrins derive in fact from porphyrinogens and it has been suggested that the intermediates preceding the formation of the cyclic tetrapyrrole must be dipyrromethanes rather than dipyrromethenes [25]. However, the acid catalyzed cyclization reactions of 2-(α-hydroxyalkyl)pyrroles to porphyrins occur via elimination of water with formation of carbocationic species which then condense with a second pyrrolic unit [25].

We may then hypothesize for the 513 nm intermediate a structure such as that depicted below (**6**) where two possible resonating forms are shown.



6

Deprotonation of **6** upon addition of a base, such as sodium acetate, explains the spectral changes observed.

Cobalt acetate and triphenylphosphine were then added to the reaction mixture, the visible spectrum (Fig. 3, spectrum d) of which showed the appearance of a peak at 427 nm. It seems reasonable to assume that coordination would bring two dipyrromethene units close to each other achieving the right geometry for the formation of an open-chain tetrapyrrole complex; in fact it has been reported [26] that metal complexes of biladienes have a major absorption at 430 nm. Such a chelate structure may then undergo the cyclization reaction leading to corrole in the presence of cobalt and to porphyrin in the presence of other metal ions.

The specific activity of cobalt in catalyzing the formation of the corrole ring has already been reported [27]; in fact only in the presence of this metal has the cyclization of bipyrrole and dipyrromethane with the formation of corrole been successful. This result emphasizes the importance of cobalt in both stabilizing the intermediate compounds and in conferring a favorable configuration on them.

At variance with what happens with *meso*- or β-unsubstituted biladienes the force that drives our reaction towards the formation of one macroring or the other does not seem to be the preferred coordination geometry of the metal ion but the possibility of obtaining an aromatic planar structure in the final macrocyclic complex.

To further define the effect of peripheral substituents on the cyclization of 2-(α-hydroxybenzyl)pyrrole we then carried out the same reaction using pyrroles **3**–**5** as starting materials. Pyrrole **4** was used to increase the solubility of the macrocycle deriving from the cyclization reaction with respect to that deriving from pyrrole **3** and to decrease the rigidity of the β substituents.

However, in both cases the products of the cyclization reactions were the corresponding porphyrins; in the case of pyrrole **3** we obtained octamethylporphyrin, whilst in the case of pyrrole **4** the main product was the Co(II) complex of etioporphyrin I (i.e. 2,7,12,17-tetramethyl-3,8,13,18-tetraethylporphyrin) together with a small amount (5%) of the metal free macrocycle. These different results can be probably ascribed to the lack of solubility of octamethylporphyrin, preventing the metalation reaction.

The formation of a single isomer of etioporphyrin (i.e. etioporphyrin I) in this case is surprising, because it is known that polymerization of monopyrroles leads to a statistical mixture of all the possible isomers [28]. This result seems to confirm the postulated pathway of the condensation reaction involving coupling of two dipyrromethene units.

With pyrrole **5** no cyclization at all was observed in the same experimental conditions: the relative porphyrin, the highly hindered dodecamethylporphyrin, has never been reported in the literature.

These results indicate clearly the importance of the steric factor in the cobalt catalyzed cyclization reaction: in the presence of *meso*-phenyl substituents the reaction leads to the formation of the corrole ring because it is the less hindered structure. Severe distortions from planarity have in fact been observed for β-alkyl-tetraphenylporphyrin derivatives [15], whilst in the case of corrole the presence of the direct link between two pyrrole rings produces an expansion of the macrocycle core that allows its planarity and hence aromaticity [3].

Acknowledgements

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