Conversion of Chelated Hydroxy-L-proline into Pyrrole-2-carboxylate

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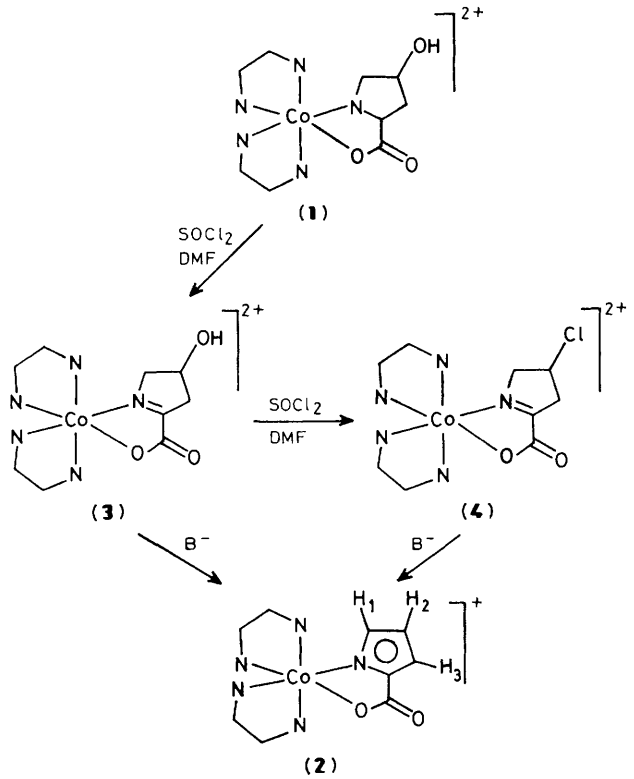
Oxidation of chelated hydroxy-L-proline by thionyl chloride gives substituted dihydropyrroles, which undergo subsequent base-induced elimination to give chelated pyrrole-2-carboxylate complexes.

In connection with our studies of the reactivity of amino acid complexes towards thionyl chloride, the hydroxy-L-prolinate complex (**1**) promised to be a particularly interesting substrate. Recent work has shown that thionyl chloride reacts with α-amino acid complexes to give α-imino acid complexes.[1] Alcohols react with thionyl chloride to give either alkyl chlorides[2] or alkenes.[3] For the hydroxy-L-prolinate complex, both reaction routes are likely to occur; we considered that this could give rise to new dihydropyrroles and possibly, after elimination of HCl, the pyrrole-2-carboxylate complex (**2**).



Scheme 1

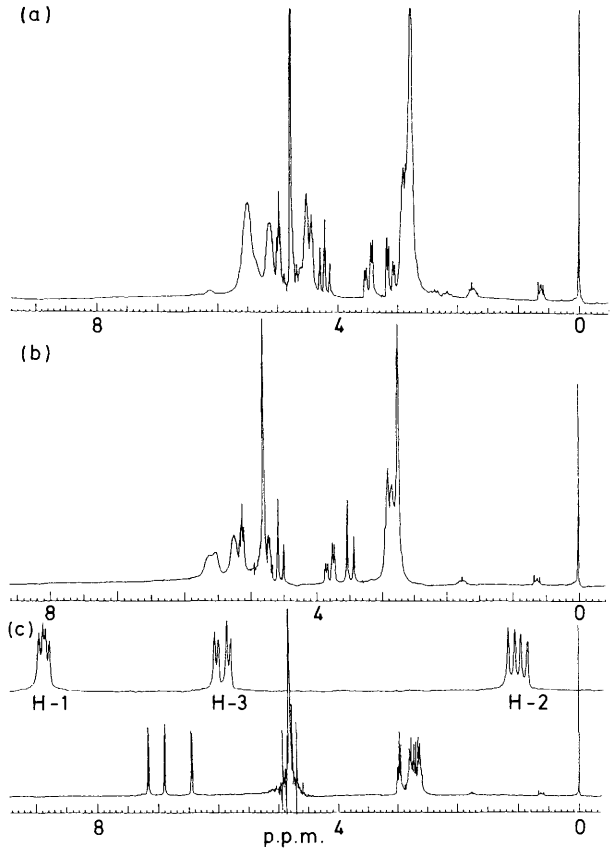


Figure 1. ^{1}H N.m.r. spectra of (a) the hydroxy complex (**3**); (b) the chloro complex (**4**) (one enantiomeric pair of diastereoisomers); and (c) the pyrrole-2-carboxylate complex (**2**).

The trifluoromethanesulphonate salt of the complex (**1**) was dissolved in *N*,*N*′-dimethylformamide and cooled in ice–salt before addition of a large excess of thionyl chloride. Cation-exchange chromatography after quenching in a large volume of water yielded a single band. The ^{1}H n.m.r. spectrum of this material showed it to be predominantly a dihydropyrrolecarboxylato complex, obtained as a mixture of diastereoisomers, together with a small amount of a compound exhibiting similar splitting patterns. The ^{1}H n.m.r. spectrum of the product after recrystallisation [Figure 1(a)], along with elemental analysis results,† allows the identification of this compound as the hydroxydihydropyrrolecarboxylato complex (**3**).

Repeating the reaction at room temperature again gave a single product, the ^{1}H n.m.r. spectrum of which was identical with that of the impurity in the initial experiment. Crystals of an enantiomeric pair of diastereoisomers were obtained from a concentrated perchlorate solution of this complex. The ^{1}H n.m.r. spectrum [Figure 1(b)] enables a tentative identification of this compound as the chlorodihydropyrrolecarboxylato complex (**4**); this was confirmed by elemental analysis.‡

The mechanism of oxidation of α-amino acid complexes to the corresponding imines has been discussed previously;[1] the formation of the complex (**3**) is a further example. The implication of isolating the hydroxy complex (**3**) in the initial experiment and exclusively the chloro complex (**4**) under the more vigorous conditions is that the chlorination is a subsequent, slower step.

Treatment of these dihydropyrrole complexes with base (sodium carbonate) results in a quantitative yield of the pyrrole-2-carboxylate complex (**2**). The ^{1}H n.m.r. spectrum is shown in Figure 1(c) and all this chemistry is summarised in Scheme 1. The three mutually coupled protons in the aromatic region implied the pyrrole structure and a single-crystal *X*-ray structure determination has confirmed this implication (Figure 2).§ The pyrrole ring is planar to within 0.003 Å and the carbon–carbon bond lengths of around 1.39 Å are typical of aromatic compounds.

^{1}H N.m.r. spectra of the complex (**2**) in acid D_2O show that the aromatic protons exchange. This implies a substantial reactivity towards electrophiles. An assignment of each of the aromatic proton resonances was made on the basis of coupling constants [Figure 1(c)].[4] In acid solution the resonances for H-1 and H-3 move downfield by *ca.* 0.15 and 0.2 p.p.m., respectively. The H-2 signal is less affected, moving by only *ca.* 0.05 p.p.m. Further, these protons exchange at different rates (H-2 > H-3 ≫ H-1); for example at pD *ca.* 0.5 H-2 is almost completely exchanged after 5 min whereas H-1 requires several hours to reach the same point.

† Found (calc. for $C_9H_{22}N_5Cl_2CoO_3\cdot 0.5H_2O$): C, 27.7 (27.9); H, 5.8 (6.0); N, 17.8 (18.1); Cl, 18.4 (18.3); Co, 15.3% (15.2%).

‡ Found (calc. for $C_9H_{21}N_5Cl_3CoO_{10}\cdot H_2O$): C, 20.0 (19.9); H, 4.0 (4.3); N, 12.9 (12.9); Cl, 19.6 (19.6); Co, 10.9% (10.9%).

§ *Crystal data* for (**2**): $CoClN_5O_2C_9H_{19}\cdot 2H_2O$, monoclinic; a = 11.765(1), b = 7.4784(6), c = 17.840(2), β = 17.87(1)°, space group $P2_1/n$, M = 359.70, D_c = 1.537 g cm^{-3}; μ = 109.0 cm^{-1} (Cu-K_α). For 2229 reflections collected (Picker FACS-I diffractometer) with $I > 3\sigma(I)$, R_F is 0.043 and R_{wF} 0.056. Atomic co-ordinates, bond lengths and angles, and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre. See Notice to Authors, Issue No. 1.

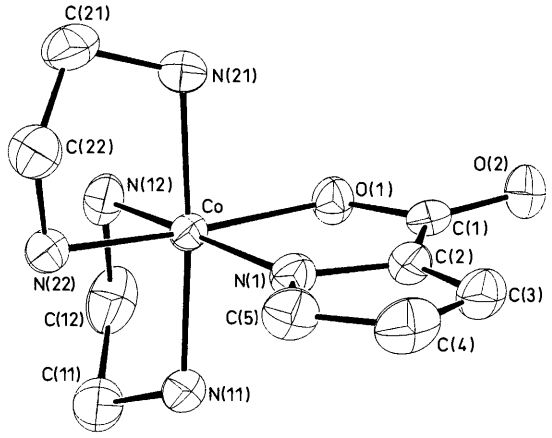


Figure 2. Structure of the pyrrole-2-carboxylate complex (**2**). Relevant bond lengths: Co–N(1), 1.904(3); Co–O(1), 1.923(2); O(1)–C(1), 1.301(4); C(1)–O(2), 1.252(4); C(1)–C(2), 1.441(5); C(2)–C(3), 1.384(5); C(3)–C(4), 1.389(6); C(4)–C(5), 1.395(6); C(5)–N(1), 1.351(5); mean Co–N (ethylenediamine ligands): 1.95 Å.

For the free ligand the ^{1}H n.m.r. spectrum is similar to that of the complex in the aromatic region. The resonances are 0.15—0.2 p.p.m. upfield from those of the complex, and the coupling constants involving H-1 are slightly larger.¶ After 24 h at pD 0.5, H-2 in pyrrole-2-carboxylic acid had still not fully exchanged, and H^1 and H-3 appeared not to have undergone any exchange at all. Therefore, as a rough estimate, the complex is at least 150 times more reactive towards electrophilic attack than the free ligand. This correlates well with the ^{1}H n.m.r. chemical shift data, which imply that the complex has a stronger ring current and therefore more π-electron density, giving rise to the greater susceptibility towards electrophilic attack. This is not especially surprising, since the metal ion replaces a proton on the pyrrole nitrogen atom and the polarising effect of Co^{3+} is considerably less than that of H^+.[5] However, the increased reactivity towards electrophilic reagents upon co-ordination raises interesting prospects for synthesis.

¶ For the free ligand, 2.44 and 1.47 Hz for coupling with H-2 and H-3, respectively, to be compared with 1.95 and 1.22 Hz for the complex.

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