Conversion of Co-ordinated Threonine into 3-Carboxyisothiazoline

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The synthesis, crystal structure, and evidence for the mechanism of formation of a 3-carboxyisothiazoline complex of cobalt(III) from chelated threonine are described.

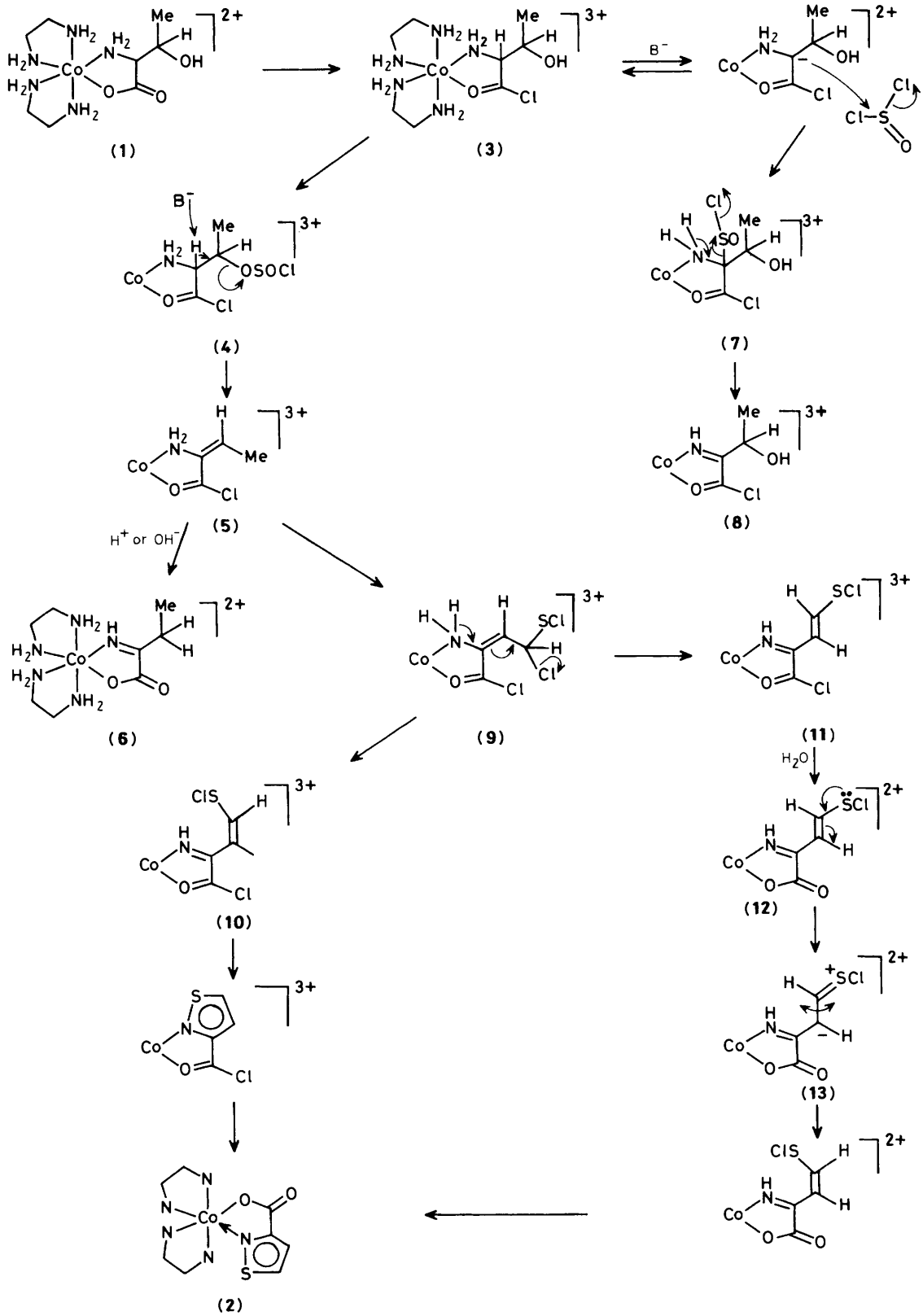
Recently we have been investigating the reactivity of amino-acids bound to the cobalt(III) ion towards thionyl chloride. These reactions can involve thionyl chloride as an oxidant, a chlorinating agent, or as a dehydrating agent and a surprising result has arisen from treatment of chelated threonine with this reagent.

Treatment of Δ-bis(ethylenediamine)threoninatocobalt(III) trifluoromethanesulphonate (**1**) with thionyl chloride in *N,N*-dimethylformamide followed by cation-exchange chromatography resulted in a complex† that has been identified crystallographically as the isothiazoline complex (**2**) shown in Scheme 1.‡ The octahedral complex has a $\Delta(-)_{589}$- configuration about the cobalt atom (Figure 1) and one of the ethylenediamine conformations is disordered. The isothiazoline heterocyclic ring is planar to within 0.008 Å with bond lengths indicative of bond orders greater than one, thereby implying significant charge delocalisation through the ring. Comparison with crystallographic studies of uncomplexed isothiazolines[1] (particularly 4-hydroxymethylisothiazole-3-carboxylic acid[2]) shows that the bond lengths and angles of the isothiazoline ligand are not greatly affected by co-ordination

† Analyses: (i) diperchlorate: found (calc. for $C_8H_{18}N_5CoO_{10}Cl_2S$) C 18.76 (18.98); H 3.61 (3.58); N 13.79 (13.81); Co 11.91 (11.64); Cl 13.97 (14.01); S 5.96 (6.33); (ii) hexafluorophosphate-chloride hydrate: found (calc. for $C_8H_{18}N_5CoO_2PF_6ClS\cdot H_2O$) C 18.94 (19.00); H 3.89 (3.99); N 13.57 (13.85); Co 11.39 (11.65); P 6.64 (6.13); F 22.27 (22.54); Cl 7.32 (7.01); S 5.79 (6.34).

^{1}H n.m.r.: two coupled protons (J_{HH} = 5.5 Hz) at δ 9.35 and 7.87 from sodium trimethylsilylpropanesulphonate acid and a broad envelope at approximately δ 2.9 due to the ethylenediamine methylene protons.

‡ *Crystal data*: $CoCl_2SO_{10}N_5C_8H_{18}$, 0.25 H_2O; orthorhombic; a = 6.489(1), b = 14.281(2), c = 18.853(2), space group $P2_12_12_1$, M = 510.65; D_x = 1.82 (±0.02), D_c = 1.839 g cm^{-3}; Z = 4; μ = 13.88 cm^{-1} (Mo-K_α). For the 1637 reflections collected with a Philips PW 1100/20 diffractometer with $I > 3\sigma(I)$, the R_F is 0.037 and the R_{wF} is 0.047. 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.



Scheme 1

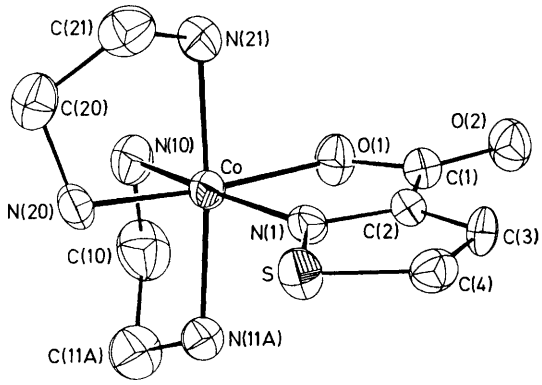


Figure 1. A view of the $[Co(C_2H_8N_2)_2(C_4H_2NO_2S)]^{2+}$ cation with labelling for selected atoms. Thermal ellipsoids enclose 50% probability levels. Only one orientation of the disordered ethylenediamine group is shown and hydrogen atoms have been deleted for clarity. Relevant bond lengths: Co–N(1), 1.948(4); N(1)–S, 1.666(5); N(1)–C(2), 1.335(8); C(2)–C(3), 1.384(8); C(3)–C(4), 1.365(9); C(4)–S, 1.688(6); mean Co–N, 1.95 Å.

to cobalt(III) and a specially interesting facet is the capture of the sulphur atom in this process.

The initial step in the formation of the isothiazoline product from chelated threonine is probably reaction of the carboxylate functionality to give the chelated acid chloride (**3**). Similar reactions are presumed to be involved in the formation of chelated amino-acid esters from amino-acid complexes on treatment with thionyl chloride in alcoholic solvents.[3] Chelation of amino-acids to cobalt(III) makes the proton(s) on the α-carbon quite acidic[4] and formation of the acid chloride activates the system still further.

Two routes for the reaction of thionyl chloride are envisaged (Scheme 1). Thionyl chloride reacts with the alcohol to give the inorganic ester (**4**). This reaction may well occur on a similar time scale to that for the formation of the chelated acid chloride. This ester undergoes a base-catalysed elimination to give (**5**) and then (**6**), by a rearrangement with much precedent in the literature,[5] (α-H is considerably more acidic than γ-H for the reasons pointed out above and will therefore be preferentially eliminated). Alternatively, the acid chloride is deprotonated (possibly by SO_2Cl^- arising from acid chloride formation) and the resulting carbanion attacks thionyl chloride to give the chlorosulphite (**7**) and then the imine (**8**) in a reaction similar to that reported by Büchi and Lukas.[6]

Treatment of the threoninato-complex (**1**) with three equiv. of thionyl chloride results in the formation of a precipitate. The ^{1}H n.m.r. spectrum of this sample displayed a mixture of four species, one of which appeared to be the enamine (**5**). The chemical shifts of the β-methyl and vinyl protons [δ 2.0(d), δ 6.76(q)] are typical of the *E*-isomers of such amino-acid derivatives[7] and treatment with either acid or base gave the imine (**6**). The stability of this enamine complex was unexpected as many unsuccessful attempts have been made to trap analogous species resulting from acid- or base-catalysed eliminations of chelated β-substituted amino-acid complexes.

The β-methyl group of this enamine is highly activated and the reactivity of thionyl chloride towards such active methyl compounds is well known.[8] Indeed, both isothiazolines and benzisothiazolines have been synthesised using a variety of similarly activated compounds with thionyl chloride.[9—11] Reaction of this enamine with thionyl chloride should give the γ-chloro-γ-chlorosulphenyl complex (**9**) which on elimination of HCl would yield the alkenes (**10**) and (**11**) as shown in Scheme 1. The *cis*-alkene would then cyclise immediately to give the observed isothiazoline complex (**2**). This complex, the *trans*-alkene (**11**), and starting material are the other three species observed in the ^{1}H n.m.r. spectrum of the precipitate described earlier.

The *trans*-alkene (**12**) has also been isolated (contaminated with *ca.* 20% final product) and solutions of this mixture slowly react to give the isothiazoline complex. This can be viewed as being achieved *via* the charge-separated tautomer (**13**) which would allow rotation around the C–C bond, giving, on cyclisation of the resulting *cis*-alkene, the isothiazoline complex.

This reaction illustrates the use of thionyl chloride as a dehydrating agent in conditions that do not result in rearrangement of the enamine product. It implies that use of the serinato-complex as a substrate for the reaction should produce a dehydro-alanine complex, a useful precursor to a variety of β-functionalised amino-acids. Moreover, use of other β-hydroxy-amino-acid complexes should result in a variety of substituted isothiazolines. We are currently exploring the synthetic utility of such methodology and its implications.

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