Condensation of Formaldehyde with Chelated Glycine and Ethylenediamine: a New Macrocycle Synthesis; *X*-Ray Structures of [α-Hydroxymethylserinebis(ethylenediamine)cobalt(III)]$^{2+}$ and [α-Hydroxymethylserine-1,4,8,11-tetraaza-6,13-dioxacyclotetradecanecobalt(III)]$^{2+}$ Ions

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Summary Condensation of formaldehyde with glycinatobis(ethylenediamine)cobalt(III) ion yields in turn [α-hydroxymethylserinebis(ethylenediamine)cobalt(III)]$^{2+}$ and the macrocycle [α-hydroxymethylserine-1,4,8,11-tetraaza-6,13-dioxacyclotetradecanecobalt(III)]$^{2+}$, the structures of which have been established by *X*-ray structural analysis.

The condensation of aldehydes with chelated glycine to generate a number of the α-substituted amino-acids is well known.[1,2] The amino-acid products were usually identified by chromatography after decomposition of the complex but few of the intermediate complexes have been characterised. Two recent studies[2,3] of such complexes obtained by condensing CH_2O and MeCHO with bis(glycinato)copper(II) have shown the complexity of such condensations. Oxazolidine rings link the glycine N and α carbon atoms and the complexes apparently decompose in acid to give serine and threonine in accord with the previous publications[1,4]

The present work arose from attempts to determine the sequence of intermediates in the formation of such complexes using a more kinetically robust system, namely the glycinatobis(ethylenediamine)cobalt(III) ion. Here there was no prospect of the ligands leaving the metal ion in the lifetime of the reactions and the organic chemistry must take place on the complex; the same restriction does not exist with the labile Cu^{II} complexes.

Condensation of formaldehyde (1·8 M) with $[Co(en)_2gly]$-

Cl_2 (en = $H_2NCH_2CH_2NH_2$) (0·3 M) in aqueous solution saturated with Li_2CO_3 yields several products after chromatography on Sephadex SP 25. After 5 min reaction at 25 °C, three major products were detected on the column. The second band eluted was unchanged cobalt glycinate ion and the remaining two fractions were isolated as $ZnCl_4^{2-}$ or $S_2O_6^{2-}$ salts. Analytical data for fraction (i) indicated that two formaldehyde units had condensed, and a single crystal *X*-ray structural analysis of the dithionate salt, which recrystallised from water as the monohydrate, established the structure of the dipositive cation as [(α-hydroxymethylserine)bis(ethylenediamine)cobalt(III)]$^{2+}$.

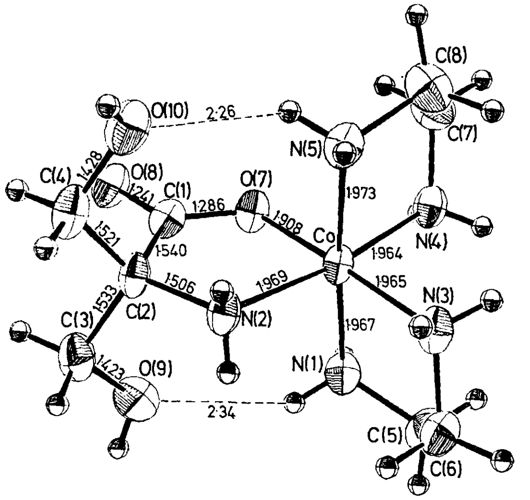

Figure 1 Stereochemistry of the [Co(α-$HOCH_2$-serine)$(en)_2$]$^{2+}$ cation with principal bonds lengths (Å) (e.s.d's range from 0·003 to 0·006 Å). The dashed lines denote significant hydrogen-bonded contacts.

Crystal data: $C_8H_{24}CoN_5O_4S_2O_6.H_2O$, monoclinic, a = 12·061(6), b = 12·368(6), c = 15·846(8) Å, β = 126·61(6)°, space group $P2_1/c$, D_m = 1·75(1), D_c = 1·72 g cm^{-3} for Z = 4. Intensity data were measured on a STOE automatic Weissenberg diffractometer using graphite crystal-monochromated Mo-K_α radiation. The structure was solved by Patterson and difference Fourier syntheses and refined by full-matrix least-squares on 3243 independent reflections with $I \geqslant 3\sigma(I)$ to a current R factor of 0·033.

The structure of the complex cation (Figure 1) shows that both formaldehyde molecules have condensed at the α-carbon of the glycinate to give α-hydroxymethylserine.

Analytical data for the third major fraction eluted from the column, isolated as the $ZnCl_4^{2-}$ salt, indicated that six formaldehyde units had condensed. The nature of this dipositive cation was again established by *X*-ray structural analysis, and shown to be [α-hydroxymethylserine-1,4,8,11-tetra-aza-6,13-dioxacyclotetradecanecobalt(III)]$^{2+}$. *Crystal data:* $C_{12}H_{28}CoN_5O_6ZnCl_4.H_2O$, monoclinic, a = 8·513(1), b = 15·973(1), c = 17·500(2) Å, β = 108·46(1)°, space group $P2_1/c$, D_m = 1·83(1), D_c = 1·83 g cm^{-3} for Z = 4. Reflection data were collected on a Picker FACS-1 diffractometer using graphite crystal-monochromated Cu-K_α radiation. The structure was solved by direct methods (MULTAN) and refined by block-diagonal least-squares on 2430 reflections with $I \geqslant 3\sigma(I)$ (corrected for absorption, μ = 120·18 cm^{-1}) to an R factor of 0·040.

The structure (Figure 2) shows that the hydroxymethylserine complex has condensed further with the aldehyde, not at the glycine centre, but at the ethylenediamine N atoms to produce a macrocycle, 1,4,8,11-tetra-aza-6,13-dioxa-tetradecane (dioxacyclam). The cyclic system contains two five-membered ethylenediamine-type chelates both with δ conformations and two six-membered chelates with basically chair conformations.

This latter type of condensation appears to be applicable to other bis(ethylenediamine) complexes and [(oxalato)(dioxacyclam)cobalt(III)] chloride.$3H_2O$ has been characterised. The quadridentate oxalato-complex is stable in acid and neutral solution but in very basic aqueous solutions (pH > 12) it immediately turns brown and decomposes within minutes to a red solution. The initial reaction is reversible and appears to be deprotonation (pK *ca.* 12). The cation $Co(en)_3^{3+}$ also undergoes the same type of condensation and some of the products have been separated but not yet characterised.

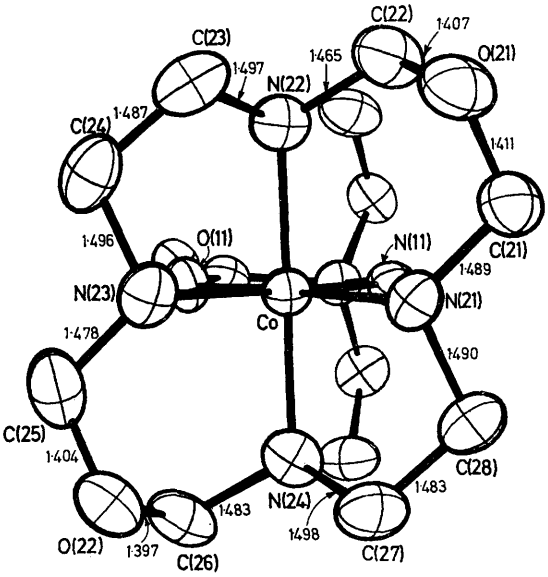

Figure 2 Stereochemistry of the [Co(α-$HOCH_2$-serine)(6,13-dioxacyclam)]$^{2+}$ cation. Principal bond lengths (Å) other than those shown; Co–O(11), 1·903; Co–N(11), 1·971; Co–N(21), 1·958; Co–N(22), 1·998; Co–N(23), 1·978; Co–N(24), 1·970.

The initial hydroxymethylserine complex presumably undergoes further condensation by adding the aldehyde at the N centres to form the tetracarbinolamine complex. Elimination of water at two carbinolamines to give the bisimine-biscarbinolamine complex followed by addition of the carbinol units at the imine carbon atoms yields the dioxacyclam macrocycle.

The process is interesting from an organic and inorganic synthetic point of view. It clearly points to similar methods for synthesising macrocycles using such complexes and it should be applicable to numerous metal–ammine systems.

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