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Coordination Catalysis: Comments on the Origin of the Stereoselectivity in the Condenstation of Acetaldehyde with Glycine Coordinated to Cobalt(III)

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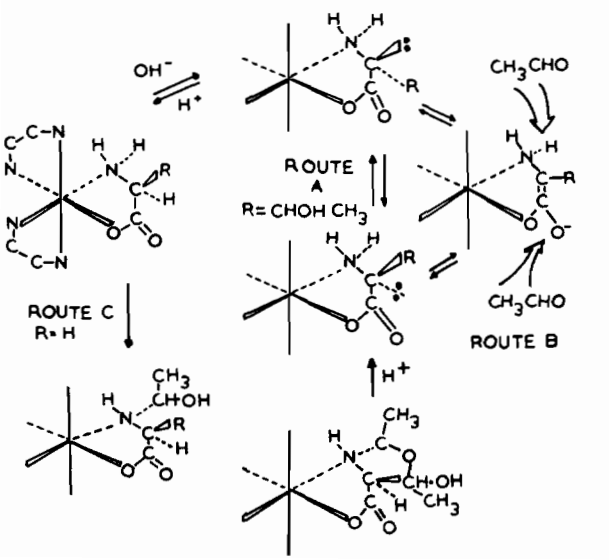
The activation of glycine caused by its coordination to cobalt(III) was first reported by Akabori [1] who described the condensation of acetaldehyde with $[Co^{III}(gly)_3]$ to yield $[Co^{III}(threo)_3]$. Shortly afterwards, a similar reaction was reported by Murakami and Takahashi [2] who employed $[Co^{III}(en)_2gly]^{2+}$ and noted that if the starting material was optically active then the product, threonine, was formed stereoselectively. More recently, similar results have been obtained by Dabrowiak and Cooke [3] who were able to increase the optical yield by careful control of the reaction conditions. Using Λ-(+)-$[Co^{III}(en_2)gly]^{2+}$ they showed that the preferred isomeric product had the 2S configuration both for the threonine (2S.3R) and the allothreonine (2S. 3S), whilst Murakami and Takahashi, using Δ-(−)-$[Co^{III}(en)_2gly]^{2+}$ had noted a preponderance of 2R-threonine.

The mechanism of this reaction is generally accepted to involve a carbanion intermediate, Scheme I, formed by the base catalysed removal of the methylene proton. This has been demonstrated directly through p.m.r. observations [4] of ^1H–^2H exchange of the glycinate methylene protons in alkaline ^2H_2O, and by comparison of the rate of exchange and ligand racemisation [5] in complexes of S-alanine and S-valine. However, despite this, and the evident importance of this reaction as a potential route for the direct preparation of other amino acids from glycine, no convincing explanation of the stereoselectivity has been put forward.



Three possibilities present themselves, Scheme I. The first requires no initial selectivity in the formation of the diastereoisomeric products, but depends on continued exchange at the 2-carbon after the condensation to give the thermodynamically controlled equilibrium (route A). However, the work of Dabrowiak and Cooke seems to exclude this possibility, since they reported that the epimerisation of optically pure S-threonine coordinated to the cobalt appeared to be negligible under similar conditions to those used for the formation of the new carbon–carbon bond. Moreover, work by Buckingham *et al.* [5] has shown that in the case of Λ-(+)-$[Co^{III}(en)_2S\text{-val}]^{2+}$ the base catalysed ligand equilibration led to an equilibrium ratio for Λ-(+)-$[Co^{III}(en)_2R\text{-val}]^{2+}$/Λ-(+)-$[Co^{III}(en)_2S\text{-val}]^{2+}$ of 1.7 with similar results being obtained for other amino acids by Keyes and Legg [6]. Therefore, it is clear that even if epimerisation could occur, the Λ configuration about the cobalt centre would generate the R-configuration at the new chiral centre, rather than the S, and consequently the mechanism cannot account for the observed stereoselectivity in the condensation reaction. Indeed, it would tend to favour a reduction in stereochemical yield.

The second possibility (route B) requires that the incoming aldehyde can "recognise" the configuration of the cobalt and therefore preferentially attacks one face of the glycinate ligand, despite the availability of the alternative mode of entry. However, whilst stereoselective association is well known [7] it is usually associated with ion-pairing and whilst the preferred orientation might be generated by specific hydrogen bonding, this is rather unlikely.

The remaining possibility (route C) requires the reactivities of the two pro-chiral glycinate methylene hydrogens to be intrinsically different. Certainly, in chiral $[Co^{III}(en)_2gly]^{2+}$ the two hydrogens occupy diastereoisomeric positions, but Sargeson and his co-workers [8] have shown that the rates of exchange of these pro-R and pro-S protons are indistinguishable. However, by using N-benzylglycine and thereby introducing a bulky substituent onto the amino acid nitrogen, they were able to generate a distinct stereochemical difference between the two hydrogens, with the pro-S undergoing exchange more readily then to pro-R for the Λ configuration at the cobalt.

The origin of this stereoselectivity can be related back to the further stereospecificity which occurs in the creation of the quaternary nitrogen by coordination of the substituted amino group to the cobalt. Thus it has previously been shown for sarcosine [9], (N-methylglycine) and now for N-benzylglycine [8] that binding of the ligand to cobalt to give the overall Λ-configuration for the chelate ring system enforces the R configuration on the amino acid nitrogen, thereby minimising the non-bonded interactions between the substituent on the nitrogen and the diaminoethane chelate rings. In turn the absolute configuration about the nitrogen then controls the relative lability of the two methylene hydrogens through both steric and electronic effects. Therefore, the presence of a bulky group attached to the nitrogen could lead directly to the observed stereoselectivity at the 2-carbon. Such a substituent could be generated by the reaction of the aldehyde with the nitrogen of the amino acid, prior to condensation of a further molecule of aldehyde at the 2-carbon and indeed such reactions, leading eventually to oxazolidine derivatives, are now known to occur for amino acid complexes of copper (II) [10, 11] and a similar reaction, though with different product occurs with cobalt (III) [12]. These intermediates are generally labile, particularly to acid and hence are usually destroyed during the work-ups and so not recognised, but they may be isolated by careful treatment of the reaction mixture and have been subjected to X-ray crystallographic analysis.

The formation of the cyclic oxazolidine type of structure in fact goes one stage further since this intermediate may be related to the cyclic amino acid proline. The complex $[Co^{III}(en)_2S\text{-prol}]^{2+}$ exhibits two sorts of stereospecificity which are relevant here [13]. Formation of the complex from *trans*-$[Co^{III}(en)_2Cl_2]Cl$ which is necessarily optically inactive, yields Λ-(+)-$[Co^{III}(en)_2S\text{-prol}]^{2+}$ stereospecifically, *i.e.* the configuration of the proline generates an assymetric centre at the cobalt [13], therefore the converse must be true and if the configuration about the cobalt is Λ, proline-like ring structures should be generated with the S configuration. Moreover, exchange of the 2-C methine hydrogen in coordinated S-proline is stereospecific [6], that is to say it occurs without loss of configuration at the chiral centre in the ligand. Clearly therefore, if the Λ-(+)-$[Co^{III}(en)_2gly]^{2+}$ should react to produce a cyclic oxazolidine intermediate, with proline-like structure, it should do so as to create the S configuration at the 2-carbon centre and whilst it persists this structure should effectively "lock" the ligand into this configuration, preventing racemisation even if further 2C–H exchange occurs.

Overall, then, the stereoselective formation of threonine from glycine via chiral $[Co^{III}(en)_2gly]^{2+}$ can be seen as a remarkable train of stereoselective events. Selection of the absolute configuration about the cobalt first generates a preferred configuration for a labile N-substituted intermediate, which in turn leads to the appropriate selectivity in the activation of the methylene hydrogens of the glycinate ligand. Condensation of a further aldehyde moiety at this centre, followed by an intramolecular cyclisation leads to an oxazolidine type structure similar to the cyclic amino acid, proline. The formation of the new carbon–carbon occurs stereoselectively, first because of the chiral preference in the formation of the carbanion and second because of the preferred configuration of the oxazolidine ring. The cyclic intermediate then provides stabilisation against further racemisation.

The series of reactions not only account for the observed stereoselectivity but also serve to illustrate both the change in ligand reactivity and the subtle and elegant interactions at different levels of molecular disymmetry in coordination compounds.

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