The Selective Activation of Amino-acids and Peptides

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Summary The exchange of the methylene-group protons of amino-acid or peptide complexes of copper(II) or cobalt(III) has been investigated and is shown in general to be stereoselective and to occur only for the *C*-terminal residue of the peptides.

CO-ORDINATION to certain transition-metal ions may lead to activation of amino-acids and peptides. We find that in a large number of complexes containing chelated amino-acids, the protons of the methylene or substituted methylene group exchange under alkaline conditions, and this can conveniently be followed by changes in the ^1H n.m.r. spectra, using deuterium oxide as the solvent. It is known[1] that the glycinatobisethylenediaminecobalt(III) cation, $[Co^{III}(en)_2gly]^{2+}$, undergoes exchange in the methylene group of the glycine and more recently it was shown that

in $[Co^{III}(en)_2$L-ala$]^{2+}$ a similar exchange occurs,[2] accompanied by racemisation of the amino-acid. For this last exchange the rate of racemisation was the same as the rate of exchange. We now describe several cases where proton exchange is stereoselective.

We find that similar exchanges are catalysed by copper(II) ion; such activation was predictable since[3] aldehydes could be condensed with glycine in the presence of copper(II), giving substituted β-hydroxy-α-amino-acids.

Bis-glycinatocopper(II), $[Cu(gly)_2]$ is completely deuteriated in less than 12 hr. at pD $\geqslant$ 12, as is $[Cu($L-ala$)_2]$. However, racemisation of the L-alanine is not complete in less than 48 hr., and hence the exchange is stereoselective. Further, no deuterium incorporation occurred in the methyl group of the alanine. Strikingly, however, β-alanine failed to deuteriate in either methylene group, under the same conditions, suggesting that activation requires, adjacent to the methylene group in question, the presence of more than one group capable of transmitting the electron-withdrawing effect of the metal.

Under similar conditions, no exchange occurred with either methylene group of glycylglycine, (as the 1:1 complex with copper in 0·5M-NaOD/D_2O) and this was confirmed by the observation that neither glycyl-L-alanine nor L-alanyl-glycine racemised under these conditions. A possible explanation for this is afforded by the work of Kim and Martell[4] on the Cu^{II}–glycylglycine system in which they found that at high pH complexes such as $[Cu^{II}(OH^-)(GG^{2-})]$ existed. The addition of a hydroxy-group reduces the effective charge of the metal, making it less electron-withdrawing. Neither of these effects occurs with the corresponding bis-dipeptidecobaltate(III) complexes and they are well known to exchange stereoselectively.[5]

We have now investigated this latter system further and find that, depending on the peptide, two types of behaviour occur, shown in the Figure. It has been suggested that if either or both amino-acid residues in the dipeptide be optically active then the complex is formed stereospecifically.[6,7] Thus the two types of behaviour may be explained by suggesting that the "fast" stage is due to the racemisation of the *C*-terminal residue only and the "slow" stage is due to racemisation at the cobalt centre. To confirm this hypothesis we have also prepared a series of complexes of the type $[Co^{III}A_3(\alpha_1\alpha_2)]^+$ (where A = NH_3 or $^1/_3$ dien and $\alpha_1\alpha_2^{2-}$ = dianion of a dipeptide) and have shown that if $\alpha_1\alpha_2^{2-}$ = glygly then exchange occurs in the *C*-terminal residue only, both by deuteriation and the addition of aldehydes. Similarly, $[Co^{III}$(dien)gly-L-ala$]^+$ racemises under these conditions at a rate slower than exchange, *i.e.* the exchange is stereoselective; whereas $[Co^{III}$(dien)L-alagly$]^+$ is optically unaffected under identical conditions. That exchange occurs only in the *C*-terminal residue is a reflection on the abilities of the different co-ordinated groups to transmit the electron-withdrawing effect of the metal. Several attempts were made to prepare the analogous tripeptide complexes $[Co^{III}$(dien)(glyglygly)$]^+$ but the product in every case was $[Co^{III}$(dien)(glygly)$]^+$ formed by hydrolysis of the tripeptide. A similar hydrolysis of dipeptides is well known.[9] If the reaction is repeated with L-ala-glygly then the product is $[Co^{III}$(dien)(L-alagly)$]^+$ indicating that hydrolysis is specific for the *N*-terminal dipeptide.

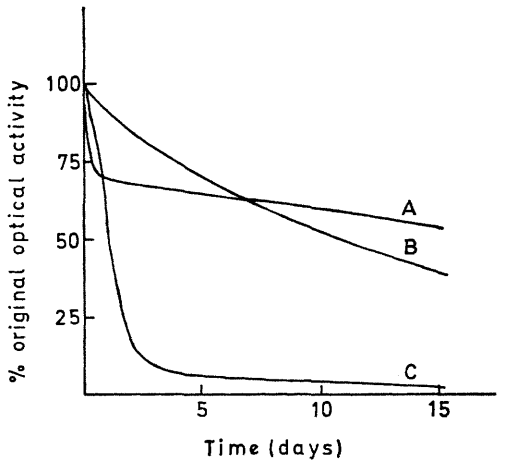

FIGURE. *Racemisation of bis-dipeptidecobalt*(III) *complexes*, $[Co^{III}(\alpha_1\alpha_2)_2]^-$ *in* 0·5M-NaOH. A: $\alpha_1\alpha_2$ = L-*alanyl*-L-*alanine*; B: $\alpha_1\alpha_2$ = L-*alanyl-glycine*; C: $\alpha_1\alpha_2$ = *glycyl*-L-*alanine*.

We have also prepared the new complexes $[Co^{III}(NH_3)_3$(edma)$]^{2+}$ and two of the isomers of $[Co^{III}(edma)_2]^+$ (edma = ethylenediaminemonoacetic acid) which, judging from their electronic spectra, are *cis* and *trans*, and have shown that the methylene group of the glycinate ring is activated to exchange in alkaline D_2O. A similar result has been obtained for [Co(edda)(en)] by Sudmeier and Occupati,[8] who showed that the exchange was stereoselective as had already been demonstrated for $[Co^{III}(edta)]^-$ by Williams and Busch.[1] A comparison of the results gives the approximate order for rate of exchange as $[(Co\ dipep)_2]^- \simeq [Co^{III}(edta)]^- < [Co^{III}(edda)(en)]^+ \simeq [Co^{III}(edma)_2]^+ < [Co^{III}(L)_3\alpha_1\alpha_2]^+ < [Co^{III}(edma)(NH_3)_3]^{2+} \simeq [Co(en)_2gly]^{2+}$ which is a reflection of the fact that the rate is governed by the electron-withdrawing power of the metal.

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