Selective Activation of Methylene Groups in Co-ordinated Peptides

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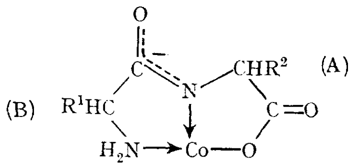
RECENTLY we found[1] that dipeptides ($H\alpha_1 \cdot H\alpha_2$) reacted with cobalt(II) or cobalt(III) to give, finally, $[Co(\alpha_1\alpha_2)_2]^-$. The mode of attachment[2] of each peptide unit, in neutral solution, is as shown in (I).

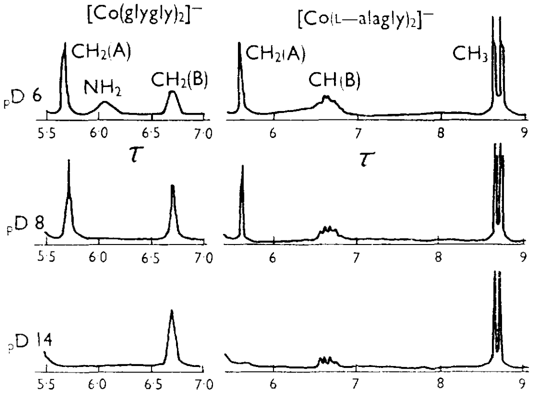


(I)

We now find for the glycylglycinate complex that the protons of the methylene group A (R^2 = H) exchange readily in alkaline solution with the deuterons of heavy water, whereas the protons of the methylene group B (R^1 = H) do not exchange under the same conditions, nor when kept in alkali for four weeks.

The ^1H n.m.r. spectra (in neutral heavy water) of (Ia; $R^1 = R^2 = H$) and (Ib; R^1 = Me; R^2 = H) are shown in the Figure. The assignments given rest on: (*a*) the very rapid disappearance at pD 7 of the broad signal† at τ 6, due to exchange of the NH_2 protons; (*b*) the slight splitting of the *N*-terminal methylene signal, B, by the NH_2 group—this splitting collapses rapidly at pD 7 as the NH_2 exchanges; (*c*) the change of the signal at τ 6·7 in passing from (Ia) to (Ib), the resonance at τ 5·6 being essentially unchanged.

At pD $\gg$ 11, exchange of the protons A in (Ia) occurs at a measurable rate. For example, at pD 14, the half-time for the exchange is *ca.* 15 min. at 35°; the resonance signal at τ 5·6 has entirely disappeared after 2 hr. At pD 11, exchange is complete in *ca.* 14 days. We find similar exchange with other complexed peptides such as L-alanylglycine (see Figure) and glycyl-L-alanine. We have also measured the ^1H n.m.r. spectra of these three dipeptides uncomplexed, as a function of pD, extending the measurements of Sheinblatt,[3] and find shifts of the resonances at pD$\sim$ $pK_{NH_3^+}$ and at pD$\sim$$pK_{CO_2^-}$, but no evidence of exchange of any of the methylene protons, even in alkaline solution.



FIGURE

The present cases constitute a further example of the selective reactions possible in metal complexes of organic substrates. The protons of the *C*-terminal residue, bonded in an amino-acid chelate ring, are activated to exchange; those of the *N*-

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† ^1H resonances are referenced from internal t-butyl alcohol τ 8·73.

terminal residue (bonded in an N–N chelate ring) are not.

When taken in conjunction with the stereoselectivity of formation[4] of these dipeptide metal complexes, a number of useful extensions are possible. For example, during the time required for complete exchange of the protons A in (Ib) and (Ic) (R^1 = H, R^1 = Me), the circular dichroism of the complexes is quite unaffected. In the case of (Ic), this observation strongly suggests that the exchange at the asymmetric carbon of the *C*-terminal L-alanine residue is stereospecific. It therefore seems likely that the conformation of the terdentate bipeptide unit in (I) is fixed.

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[3] M. Sheinblatt, *J. Amer. Chem. Soc.*, 1965, **87**, 572.

[4] N. C. Payne, Ph.D. Thesis, University of Sheffield, 1967.