Stereoselective Effects in Peptide Complexes

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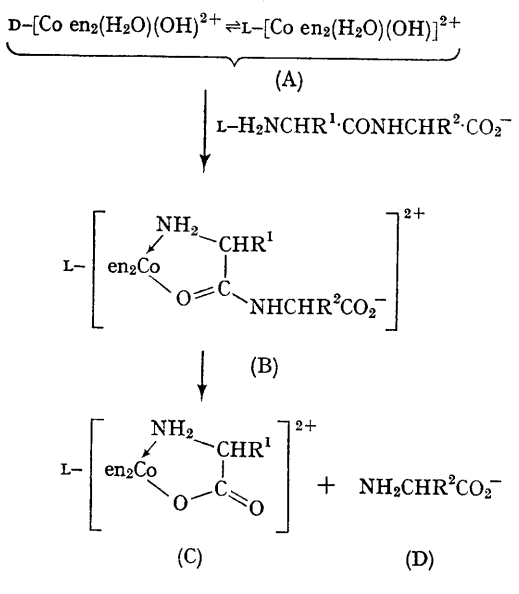
THE diastereoisomers of tris-amino-acid complexes of cobalt(III) have[1] roughly equal stabilities. In general[2] there is not much difference in stability between D- or L-[Co en_2 (L-α)]$^{2+}$, where α is ala, leu, val, or phe. However,[3] a potentially terdentate amino-acid such as L-glutamic acid could discriminate between the D- and L-bisethylenediaminecobalt(III) moieties, to give D-[Co en_2-(L-glu)]$^+$ much more rapidly than its diastereoisomer. Further,[4] complexes of asymmetric dipeptides of the kind [Co($\alpha^1\alpha^2$)$_2$] where α^1 or α^2 is an L-acid (the other being glycine) or where both α^1 and α^2 are L-acids form stereospecifically, giving L-[Co(L- $\alpha^1\alpha^2$)$_2$]$^-$. We now report some of our observations on the complexes [Co en_2($\alpha^1\alpha^2$)]$^{n+}$.

At pH 7, dipeptides combine readily (see Scheme) with the hydroxo-aquobisethylenediaminecobalt(III) ion (A), giving largely (B). (B), at pH 9·0, hydrolyses, giving (C) and (D). Several points are of interest. First, the *N*-terminal residue of the peptide remains co-ordinated in the hydrolysed product (C). [Free (D) was identified by paper chromatography, which also showed the absence of uncomplexed $NH_2CHR^1CO_2^-$]. The conversion of (B) into (C) is readily followed using absorption spectra, since the ratio of the extinction coefficients for the absorption bands at *ca.* 490 mμ and at *ca.* 380 mμ is usually *ca.* 2·0 for the peptide complexes (B), and *ca.* 0·8 for the amino-acid complexes (C). The similar structures suggested here for (B) and (C) are confirmed by this similarity in energy of the ligand-field transitions.

Secondly, the reaction with (A) of peptides containing a *C*-terminal amino-acid α^2 of the L-configuration gives preferentially the L-configuration at cobalt in (B), *whatever the N-terminal amino-acid* (*i.e.*, gly, D- or L-α^1). This stereo-



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selectivity was evaluated as follows. The optical equilibration of (A) is far more rapid than its

combination with peptide. Thus the ratio (L : D) of diastereoisomeric products (B) is a function of the rates of formation of the diastereoisomers (*i.e.*, for D-A + L-$\alpha^1\alpha^2$, and for L-A + L-$\alpha^1\alpha^2$). This ratio L : D is preserved in (C), since the hydrolysis (B) → (C) occurs without breakage of any cobalt–ligand bond. The optical composition (L : D) of (C) is directly determined by comparison of its rotatory dispersion spectrum with that[2] for the optically pure isomers of (C). The absolute configurations given here follow from earlier work.[5]

The optical activity of the products (C), where R^1 = H, is shown in the Table. This stereoselectivity clearly arises from the configuration of the *C*-terminal residue of the dipeptide. It would in any case be expected that the *N*-terminal residue, α^1, will have a less marked effect, since the diastereoisomers D- and L-[Co en_2 (L-α^1)] are of about equal stabilities: indeed L-leu–gly gives no apparent stereoselectivity. Peptides Lα^1–Lα^2 give rather larger degrees of stereoselectivity than do gly–L-α^2. For example, L-leu–L-tyr gives at least 90% D-[Co en_2(L-leu)]$^{2+}$.

The aquations (B → C) of the various complexed peptides proceed at very different rates. We find stereoselective effects similar to those described here with the analogous complexes of triethylenetetramine, in which the model *N*-terminal hydrolysis was first discovered.[6]

The observations recorded here and their extensions emphasise the possibilities inherent in simple metal complex systems as chemical and optical models for the much more complicated and rigorous specificity towards substrates of enzymic systems potentiated by metal ions.

TABLE. *Stereoselectivity in* [Co en_2(H_2NCH_2·CONH·CHR^1CO_2)]$^{2+}$

Peptide		(C)		(D)[d]
α^1[a]	α^2	b	c	
Gly	L-phe	[Coen_2gly]$^{2+}$	70L : 30D	L-phe
Gly	DL-phe	"	50L : 50D	DL-phe
Gly	D-phe	"	26L : 74D	D-phe
Gly	L-tyr	"	62L : 38D	L-tyr

[a] *N*-Terminal.
[b] Complex product [(C) of scheme].
[c] Calculated from values for pure enantiomers (ref. 2).
[d] Identified by R_F values, ultraviolet spectra, and specific tests.

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