# A Contrast in Stereoselectivity in the Formation of Copper and Nickel Bis-complexes of Histidine

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*Summary* While the racemic bis-complex formed between nickel and histidine (His), Ni[(+)-His][(−)-His], has a more favourable heat of formation than its optically pure analogue, Ni[(−)-His]$_2$, the opposite is found in the copper complexes.

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THERMODYNAMIC stereoselectivity has been shown to be absent in the formation of bis-complexes between metals and 1,2-diamines[1] and bidentate α-amino-acids.[2] There is evidence, however, for its existence in the formation of some bis-histidine (His) complexes. For instance, the formation of the racemic species Co[(+)-His][(−)-His] has been shown by both n.m.r. studies[3] and potentiometric titrations[4] to be preferred to that of the optically pure complex, Co[(−)-His]$_2$, with a difference in $\Delta G$ of 1·3 kJ mole$^{-1}$. The racemic complex of nickel[4] is similarly favoured ($\Delta G$ difference = 2·1 kJ mole$^{-1}$). We report the enthalpy changes accompanying the formation of optically pure and racemic bis-complexes of a number of potentially terdentate amino-acids with nickel, copper, and, in the case of histidine, zinc.

Enthalpy changes were measured with the aid of the LKB precision reaction calorimeter, concentrated solutions of metal ions being added to solution of the (+)-form of the ligand, the (−)-form, and a racemic mixture prepared from equal quantities of the (+)- and (−)-solutions. The heats of protonation were measured and corrections applied for changes in protonation of the ligands, the formation of water due to changes in pH, and heat of dilution. In all cases it was found that $\Delta H$ values for the formation of complexes of pure (+)- and (−)-isomers of the ligands were identical. Significant stereoselectivity was found to be absent in the formation of complexes of glutamic (Glu) acid, absent or very small with asparagine (Asp), but clearly present in the histidine complexes of all metals studied. Experimental results are shown in the Table, where the numbers in parentheses are standard deviations over 4—8 separate determinations. Stereoselectivity in the formation of nickel complexes was confirmed by measuring the differences in the heat of mixing of Ni[(−)-His]$_2$ with Ni[(−)-His]$_2$ and Ni[(−)-His]$_2$ with Ni[(+)-His]$_2$. The difference corresponded to a value of $\Delta(\Delta H) = -1{\cdot}50(8)$ kJ mole$^{-1}$, in good agreement with that shown in the Table.

*Enthalpy changes accompanying the formation of bis-complexes of some amino-acids at* 25°, $I = 0{\cdot}1$M

| | | $\Delta H_{\beta 2}$(kJ mole$^{-1}$) | |
|---|---|---|---|
| Ligand | Cu$^{2+}$ | Ni$^{2+}$ | Zn$^{2+}$ |
| (+)-Glu | 47·65(27) | 30·92(13) | |
| (−)-Glu | 47·33(21) | 30·55(11) | |
| (+) + (−)-Glu | 47·86(26) | 30·71(20) | |
| (−)-Asp | 47.50(14) | | |
| (±)-Asp | 47·16(10) | | |
| (+)-His | 83·64(22) | 69·11(30) | 47·86(19) |
| (−)-His | 83·64(23) | 68·91(18) | 47·72(18) |
| (+) + (−)-His | 82·58(11) | 70·92(22) | 49·22(16) |

The stereoselectivity previously reported in $\Delta G$ is very close to that found here in $\Delta H$, showing it to be an enthalpy rather than an entropy effect. Of more interest is the fact that while the racemic bis-complexes of nickel and zinc with histidine are preferred over the optically pure species, $\Delta H_{(+-)} - \Delta H_{(++)}$ being $-1{\cdot}9$ and $-1{\cdot}4$ kJ mole$^{-1}$, respectively, the opposite stereoselectivity is found with copper [$\Delta(\Delta H) = +1{\cdot}1$ kJ mole$^{-1}$]. Such a difference must have biological significance and has been indirectly anticipated by Gillard.[5] Nickel is known to co-ordinate octahedrally in the bis-histidine complexes[6] while, in the crystalline state, copper co-ordinates with the amino- and carboxyl groups only, giving a square-planar complex.[7] However in solution there will, presumably, be some interaction between an imidazole nitrogen atom (or other free co-ordinating centre) and the copper ion along the $z$-axis as suggested by the numerically large values for $\Delta H$, but this will only be possible for both imidazole groups in the bis-complex if either both ligands are of the same optical hand and are orientated *cis* on the copper, or are of opposite optical hand *trans* on the copper. In the nickel complexes, however, histidine could co-ordinate as a bidentate ligand either *cis* or *trans* on the Ni$^{2+}$ octahedron so allowing the third co-ordinating centre a greater variety of co-ordination sites. Dynamic fluctuations in copper–histidine co-ordination in solution have been postulated,[8] and these would complicate any interpretation, but would not markedly affect the supposition that co-ordination of histidine molecules around octahedral ions may be markedly different from co-ordination around tetragonal (*e.g.* Cu$^{2+}$) ions.

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