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Thermodynamic Stereoselectivity and Tridentate Co-ordination in the Formation of the Complexes [Ni(D/L-Methionine)$_2$]

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A small, but reproducible, stereoselective effect has been observed in both the free energy and enthalpy changes associated with the formation of the bis complexes [Ni(D/L-methionine)$_2$], obtained from independent potentiometric and calorimetric measurements. The meso-complex, [Ni(D-Met)(L-Met)], is more stable in ΔH than the optically active bis-complexes by 1.0(±0.1) kJ mol^{-1}. This stereoselectivity is attributed to tridentate binding of the methionine and so supports the existence of weak co-ordination between Ni^{2+} and the thioether sulphur atom.

Introduction

Thermodynamic stereoselectivity in the labile bis-complexes of metal ions with an asymmetric ligand, Y, may be measured quantitatively from the differences in the formation constants, or enthalpies of formation, of the possible bis-species [M(L-Y)$_2$], [M(D-Y)$_2$] and [M(L-Y)(D-Y)]. These quantities may be calculated from potentiometric titrations or calorimetric measurements using the optically active and racemic forms of the ligand.[1–5]

Complexes of α-amino acids and first series transition metal ions which exhibit stereoselectivity have, so far, only involved those amino acids which are potentially tridentate and contain a 'soft' donor centre in the side chain capable of co-ordination. Hence significant stereoselectivity has been found in the free energy and enthalpy changes of formation of the bis(histidinato) complexes of Co^{2+}, Ni^{2+} and Zn^{2+} and in the enthalpy changes of formation of the complex with Cu^{2+}.[2–5] Ternary complexes of Cu(histidine)$^+$ with protonated histidine[5] or with a range of other amino acids[6] have also been shown to exhibit stereoselectivity in formation constants. The histidinate anion is known to co-ordinate as a tridentate ligand using a nitrogen of the imidazole ring as a 'soft' donor atom. Stereoselectivity has been reported in the formation constants of bis(penicillaminato)nickel(II), although there is some uncertainty as to the species actually present in the equilibrium mixture, Penicillamine co-ordinates strongly through the sulphur atom.[7] Another interesting example of stereoselectivity occurs in bis(N-benzylprolinato)copper(II), where the third donor centre appears to be a (soft) phenyl ring.[8,9]

On the other hand, metal complexes of substituted α-amino acids containing a potential third donor centre which is 'hard' appear to show a complete absence of stereoselectivity in either free energy or enthalpy changes of complex formation.[2,3,10] The same conclusion has been reached for complexes of simple glycine-like amino acids.[2,11]

Methionine (Met) is an α-amino acid with a side-chain containing a thioether sulphur atom, *i.e.* $CH_3SCH_2CH_2CH(NH_2)CO_2H$. The donor properties of this 'soft' centre are uncertain, and evidence is somewhat contradictory. An X-ray diffraction study of the bis complex with Cu^{2+} showed that, in the crystals, the sulphur atoms do not co-ordinate[12] and early potentiometric studies have been interpreted as indicating only glycine-like co-ordination in all complexes with 3*d* transition metal ions.[13] Other studies have given less certain conclusions.[14] On the other hand, line widths measured from PMR spectra suggest that, while methionine does not show tridentate behaviour, Mn^{2+} and Cu^{2+} complexes of S-methylcysteine do show weak metal–sulphur interaction.[15] We have studied the nickel bis-complexes of both optically active and racemic methionine, with a particular interest in stereoselectivity in both free energy and enthalpy changes, in order to shed light on the possibility of nickel–sulphur interaction.

Experimental

Materials

Pure L- and D-methionine were obtained from the Sigma Chemical Co. (SIGMA grade). Racemic methionine was made artifically by mixing equal quantities of L and D forms to ensure the averaging of minor differences in purity.

Complex Formation Constants

These were calculated from potentiometric titrations, changes in pH being followed with the help of a glass electrode calibrated in terms of hydrogen ion concentrations.[5] Values for formation constants were calculated with the aid of the MINIQUAD computer program.[16]

Enthalpy changes

These were calculated from calorimetric measurements carried out in the LKB8700 reaction calorimeter, as described previously.[2,5]

All the measurements relate to 25 °C and an ionic strength of 0.10*M* (KNO_3).

Results

Complexes formed between optically active and racemic methionine, and Cd^{2+}, Ni^{2+}, Cu^{2+} and Zn^{2+} were studied potentiometrically. Since only those with Ni^{2+} showed significant stereoselectivity, further study was restricted to this cation. Formation constants for the complexes of Ni^{2+} with optically active and racemic methionine are given in Table I. It must be noted that, with racemic methionine, β_{NiY_2} (rac) is a 'compound' constant relating to the reaction:

Ni + D-Met + L-Met → x[Ni(D-Met)(L-Met)] + y[Ni(D-Met)$_2$] + y[Ni(L-Met)$_2$] and stereoselectivity is reflected is a difference between the formation constants relating to optically pure and racemic ligands.[1] As expected, there is no evidence for stereoselectivity in the mono-complexes or in the bis-complexes of the optically pure ligands, and values for the tris-complexes are too unreliable to be interpreted quantitatively. In the bis-complexes, however, the meso complex formed from the racemic mixture of the ligand is apparently more stable than the optically active complexes by a significant amount, $\log\beta_{NiY_2}$ (rac) being larger by 0.10 ± 0.01 log units. The formation constant for the *meso*-bis-complex can be calculated from the values given in Table I to give a value of $\log\beta_{[Ni(L\text{-}Met)(D\text{-}Met)]} = 10.37$, which incorporates a statistical factor of log2 (*i.e.* 0.30).[1,2]

The reality of this small stereoselective effect has been confirmed by measuring the enthalpy changes accompanying formation of the bis-complexes. The values obtained as a result of carrying out six duplicate calorimetric experiments on the L-, D- and DL-Met under experimental conditions selected to produce over 98% of the bis-complexes are given in Table II. Stepwise enthalpy changes were calculated from a series of 12 calorimetric studies using Met:Ni^{2+} ratios ranging from 0.8 to 2.05 and final pH values of 6.8 to 9.5–pH values being selected to minimise problems from hydrolysis. The stepwise enthalpy changes were then calculated from the formation constants given in Table I and are tabulated in Table II.

TABLE I. Nickel Complex Formation Constants of Optically Active and Racemic Methionine at 25 °C and I = 0.10*M* (KNO_3).

	D-Met	L-Met	DL-Met
$\log K_{NiY}$	5.330(2)	5.318(5)	5.340(2)
$\log K^{NiY}_{NiY_2}$	4.562(4)	4.576(5)	4.650(4)
$\log\beta_{NiY2}$	9.892(3)	9.894(2)	9.990(3)
$\log\beta_{NiY_3}$	11.5(2)	11.7(2)	11.9(2)

Calculated Value for $\log\beta_{[Ni(L\text{-}Met)(D\text{-}Met)]} = 10.37$.

TABLE II. Enthalpy Changes Accompanying the Formation of Ni^{2+}–Methionine Complexes at 25 °C and I = 0.10*M* (KNO_3).

	$-\Delta H$(kJ mol^{-1})		
	D-Met	L-Met	DL-Met
ΔH_{NiY_2}	35.13(6)	35.17(9)	36.09(6)
ΔH_{NiY}	13.2(2)	13.1(2)	13.3(2)
$\Delta H^{NiY}_{NiY_2}$	21.8(2)	22.1(2)	22.8(2)

Calculated Value for $-\Delta H_{[Ni(L\text{-}Met)(D\text{-}Met)]} = 36.76$ kJ mol^{-1}.

TABLE III. Calculated Thermodynamic Functions for [Ni(L-Met)(D-Met)] in kJ mol^{-1}.

	$-\Delta G$	$-\Delta H$	$T\Delta S$
[Ni(L-Met)(D-Met)]	59.17	36.8	22.4
[Ni(L-Met)$_2$]	56.45	35.1	21.3

Direct measurement of ΔH_{NiY_2} gave results with comparatively small standard deviations on the mean and show the *meso*-bis-complex to have a numerically larger heat of formation than the optically active complexes. The quantitative stabilization can be calculated from the relative concentrations in the equilibrium mixture.[2] The enthalpy of formation of the *meso*-complex is calculated to be –36.76 kJ mol^{-1}, giving a stabilization of 1.7 ± 0.1 kJ mol^{-1}. Hence the stabilization in ΔH is of the same type as that found in $\log\beta$ (*i.e.* the *meso*-bis-complex is favoured).

As expected there is no apparent stereoselectivity in ΔH_{NiY}, although the estimated errors here are obviously larger than in the direct formation of the bis-complex. Rather, the difference in the overall heats of formation of the bis-complexes is effectively all included in ΔH^{NiY}_{NiY2}.

Calculated values for the 'true' thermodynamic functions for formation of the optically active and *meso*-complexes of [Ni(Met)$_2$] are given in Table III. The difference in entropy changes is amplified by a

statistical factor of 0.30. If this is neglected the entropy contribution towards the stereoselectivity is comparatively small ($\Delta(T\Delta S) = 0.9$ kJ mol^{-1}) particularly in view of the possible accumulation of errors in this term, making it probable that the stereoselectivity found is almost entirely an enthalpy effect.[5] From the figures given in Table III, the calculated distribution of the isomeric bis-complexes is found to be:

$[Ni(D\text{-}Met)_2]:[Ni(L\text{-}Met)_2]:[Ni(L\text{-}Met)(D\text{-}Met)] = 20.7:20.7:58.6\%$ (assuming $[Ni(L\text{-}Met)_2] = [Ni(D\text{-}Met)_2]$

rather than the distribution expected statistically of 25:25:50%.

Discussion

If the origin of thermodynamic stereoselectivity in labile bis-amino acid complexes involves 3-point facial co-ordination of the ligands to an essentially octahedral metal ion,[17] tridentate co-ordination of methionine to Ni^{2+} is a corollary of the stereoselectivity reported here. Hence the formation of a Ni^{2+}–thioether bond may be assumed. It is difficult to deduce the existence of such a weak bond from a comparison of absolute values for $\log\beta_{NiL_2}$ or ΔH_{NiL_2} for related ligands. For example the bidentate analogue of methionine is nor-leucine but differences in formation constants are obscured by differences in acidity, inductive effects and solvation.[19] However these may be considered, in part, by comparing values for, *e.g.*, $\log\beta_{NiY}$–$\log\beta_{H_2Y}$. Calculated values are methionine, 5.32–11.20 = –5.88 and nor-leucine, 5.40–12.01 = –6.65. These suggest a greater affinity between Ni^{2+} and methionine than would be expected from a knowledge of the affinity for hydrogen ions and are consistent with formation of an extra bond.

Metal ion–thioether interactions have been the subject of a recent review.[14] The thioether sulphur of methionine is known to co-ordinate to 'soft' heavy metals such as Pt(II), Ag(I) and Hg(II), but the PMR evidence of bonding to metals from the first transition series gives ambiguous results.[14]

Weak interactions of amino acid sidechains, are known to have wide biological importance particularly in catalytic exchange at the active sites of metalloenzymes. The sulphur atom of a methionine residue (number 80) is known to co-ordinate to iron in the electron transfer enzyme cytochrome *c*,[20] and other metal–thioether interactions of this type may well be the reason for the positioning of methionine in other protein chains.

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