

Thermodynamic Parameters and Temperature Effects on the Extrastabilisation of Mixed Ligand Complexes containing 2,2'-Bipyridine and Amino Acids

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The formation constants ($\log K_{MAL}^{MA}$) of mixed ligand complexes of the type $[MAL]$ (where $M = Co^{II}, Ni^{II}, Cu^{II}$ or Zn^{II} ; $A = 2,2'$ -bipyridine; $L = \alpha$ -alanine (α -ala), valine (val), leucine (leu), iso-leucine (iso-leu) or nor-valine (nor-val) have been determined by SCOGS computer programme at 25, 35 and 45° and at $I = 0.2$ mol dm^{-3} (KNO_3).

The thermodynamic parameters (ΔH and ΔS) of binary ML and ternary MAL complexes have been found to be favourable. The stability quantifying parameter $\Delta \log K$ becomes usually less negative at higher temperatures and the actual values of $\log K_{MAL}^{MA}$ increase with temperature. The ternary complexes are extrastabilised in solution. The extrastabilisation increases (i) in the order $val < nor-val < leu \sim iso-leu$, which is significantly the sequence of increasing length of non-coordinating hydrocarbon side-chain of the amino acids and (ii) also, in general, with temperature. Its extent depends on the nature of the metal ion and the geometry of the complex.

Mixed ligand complexes of the type $M(II).bipy/phen.$ amino acid, where $M(II)$ = bivalent metal ions, bipy = 2,2'-bipyridine, phen = 1,10-phenanthroline, have been considered as simple models for ternary systems like (metal ion.enzyme.ATP/inhibitor) and hence they are biochemically important^{1,2}. Such ternary complexes containing amino acids with sufficiently long non-coordinating side-chains may be extrastabilised in solution due to intramolecular inter-ligand interaction²⁻⁵ or enhanced hydrophobicity in the vicinity of metal ion⁶. Simultaneous structural modifications occurring due to folding of amino acid molecules are also biochemically important².

The present work was undertaken with a view to determine thermodynamic parameters ΔH and ΔS and to investigate the influence of temperature on the stability quantifying parameter $\Delta \log K$ and the extrastabilisation parameter $\Delta \Delta \log K$ for the mixed ligand complexes of the type $[M(II).bipy.L]$, where $M(II) = Co^{II}, Ni^{II}, Cu^{II}$ or Zn^{II} and $L = \alpha$ -alanine (α -ala), valine (val), leucine (leu), iso-leucine (iso-leu) or nor-valine (nor-val).

Results and Discussion

The SCOGS refined values of formation constants

JICS-3

for binary ($\log K_{ML}^M$) and ternary ($\log K_{MAL}^{MA}$) complexes are recorded in Table 1. The $\log K_{ML}^M$ values follow the expected sequence of ligand basicity, in general with respect to the amino acids and the Irving-Williams order with respect to the metal ions. Both $\log K_{ML}^M$ as well as $\log K_{MAL}^{MA}$ values increase, in general, with the rise in temperature indicating the endothermic nature of the complexation reactions, $M + L \rightarrow ML$ and $MA + L \rightarrow MAL$ (charges omitted). The temperature range chosen for the present study lies in the vicinity of body temperature (37.5°). Our results are suggestive of the fact that the biosystems like (metal ion.enzyme.inhibitor) may be stabilised to a greater extent at a higher temperature in this range.

Evaluation of thermodynamic parameters of MAL complexes may be done keeping in view that in these heterosystems two different sets of metal-ligand bonds M-A and M-L are involved and one would succeed in knowing the resultant effect only. The values of enthalpy (ΔH) and entropy (ΔS) factors for ML and MAL complexes are recorded in Table 2. The validity of the temperature coefficient method used in the present work has been ascertained by means of linear plots

TABLE 1—FORMATION CONSTANT VALUES FOR [M(II).AMINO ACID] ($\log K_{ML}^M$) AND [M(II).BIPY. AMINO ACID] ($\log K_{MAL}^{MA}$) COMPLEXES AT DIFFERENT TEMPERATURES

$I = 0.2 \text{ mol dm}^{-3} (\text{KNO}_3)$					
Parameter	Temp. °C	Co ^{II}	Ni ^{II}	Cu ^{II}	Zn ^{II}
α -ala					
$\log K_{ML}^M$	25	4.69	5.38	8.10	5.19
$\log K_{MAL}^{MA}$		4.31	5.00	7.70	4.85
$\log K_{ML}^M$	35	4.71	5.40	8.15	5.22
$\log K_{MAL}^{MA}$		4.35	4.95	7.75	4.95
$\log K_{ML}^M$	45	4.82	5.51	8.22	5.31
$\log K_{MAL}^{MA}$		4.36	5.05	7.85	5.05
val					
$\log K_{ML}^M$	25	4.24	4.74	7.50	5.33
$\log K_{MAL}^{MA}$		3.54	3.24	6.95	5.06
$\log K_{ML}^M$	35	4.74	4.86	7.50	5.54
$\log K_{MAL}^{MA}$		4.00	3.50	6.98	4.80
$\log K_{ML}^M$	45	4.82	4.93	7.30	5.69
$\log K_{MAL}^{MA}$		4.15	3.81	7.20	4.89
leu					
$\log K_{ML}^M$	25	5.11	5.36	7.22	5.09
$\log K_{MAL}^{MA}$		4.60	4.81	6.42	4.52
$\log K_{ML}^M$	35	5.28	5.41	7.32	5.17
$\log K_{MAL}^{MA}$		4.98	5.01	6.50	4.69
$\log K_{ML}^M$	45	5.21	5.55	7.41	5.23
$\log K_{MAL}^{MA}$		4.83	5.12	6.69	4.70
iso-leu					
$\log K_{ML}^M$	25	4.51	5.31	7.90	5.20
$\log K_{MAL}^{MA}$		4.16	4.70	7.58	5.12
$\log K_{ML}^M$	35	4.63	5.40	7.86	5.31
$\log K_{MAL}^{MA}$		4.28	4.79	7.63	5.16
$\log K_{ML}^M$	45	4.72	4.72	7.98	5.45
$\log K_{MAL}^{MA}$		4.31	4.32	7.72	5.36
nor-val					
$\log K_{ML}^M$	25	4.44	5.45	8.10	4.50
$\log K_{MAL}^{MA}$		4.11	5.15	7.80	4.25
$\log K_{ML}^M$	35	5.05	5.55	8.05	4.59
$\log K_{MAL}^{MA}$		4.75	5.25	7.75	4.34
$\log K_{ML}^M$	45	5.14	5.54	8.17	5.22
$\log K_{MAL}^{MA}$		4.74	5.25	7.82	4.95

TABLE 2—THERMODYNAMIC PARAMETERS ΔH (kcal mol⁻¹) AND ΔS (cal K⁻¹ mol⁻¹) FOR BINARY (ML) AND MIXED LIGAND (MAL) COMPLEXES

System	Parameter	Temp. °C	Co ^{II}	Ni ^{II}	Cu ^{II}	Zn ^{II}
[M(II). α -ala]	ΔH	25–35	-2.5	-0.8	-2.1	-1.3
	ΔS		0.8	0.8	2.1	1.3
[M(II).bipy. α -ala]	ΔH	25–35	-1.7	-2.1	-2.1	-4.2
	ΔS		14.4	29.4	28.2	9.0
[M(II).val]	ΔH	25–35	-21.0	-5.0	-8.8	-5.8
	ΔS		51.1	4.8	34.3	5.2
[M(II).bipy.val]	ΔH	25–35	-19.3	-10.9	-1.3	11.0
	ΔS		48.6	21.8	27.9	13.5
[M(II).leu]	ΔH	25–35	-7.1	-2.1	-4.2	3.4
	ΔS		0.6	18.0	18.9	12.8
[M(II).bipy.leu]	ΔH	25–35	-16.0	-8.4	-3.4	-7.1
	ΔS		32.1	6.2	19.0	3.2
[M(II).iso-leu]	ΔH	25–35	-5.0	-3.8	-1.7	-4.6
	ΔS		3.7	11.6	41.8	8.3
[M(II).bipy.iso-leu]	ΔH	25–35	-2.1	-8.8	-2.1	-1.7
	ΔS		2.1	8.8	27.7	17.8
[M(II).nor-val]	ΔH	25–35	-25.6	-4.2	-2.1	-4.2
	ΔS		65.7	10.8	44.1	7.9
[M(II).bipy.nor-val]	ΔH	25–35	-26.9	-4.2	-2.1	-3.8
	ΔS		71.5	5.1	42.8	6.8

between $\log K$ vs T^{-1} , where K is the formation constant of ML or MAL complex and T the temperature (K). Also the values of the correlation coefficient have been found to lie around 0.99 indicating excellent linearity. The uncertainty in $\log K$ values is very small (standard deviation, ± 0.01 to 0.03) in view of their refinement by SCOGS software, which further minimises uncertainties in the enthalpy factor. For both ML and MAL complexes the enthalpy and entropy factors are found to be favourable. The enthalpy changes are generally large in binary complexation than in the formation of the ternary complexes, but the entropy factors are numerically higher and more favourable for the ternary complexes perhaps because 2,2'-bipyridine is a neutral ligand and considerable desolvation occurs in the combination $MA + L$ due to the charged nature of combining species.

The numerical values of the stability quantifying

parameter $\Delta \log K (= \log K_{\text{MAL}}^{\text{MA}} - \log K_{\text{ML}}^{\text{M}})$ are, in general, found to be somewhat greater at higher temperatures due to nominal differences in the rate of change of $\log K_{\text{MAL}}^{\text{MA}}$ and $\log K_{\text{ML}}^{\text{M}}$ with temperature (plots of $\log K$ vs T not shown). Further analysis of the formation constant data has been done to examine the extrastabilisation of the mixed ligand complexes in solution and also to study the influence of temperature on their extrastabilisation. The basic approach followed is the same as published earlier^{4,5}. In the present work, α -ala possesses a negligibly small side-chain ($-\text{CH}_3$) attached to its aminocarboxylate end which is invariably involved in complexation in each case. The non-coordinating side-chains in the rest of the amino acids are : val, $(\text{CH}_3)_2\text{CH}-$; leu, $(\text{CH}_3)_2\text{CHCH}_2-$; nor-val, $\text{CH}_3\text{CH}_2\text{CH}_2-$; iso-leu, $\text{CH}_3\text{CH}_2\text{CH}(\text{CH}_3)-$.

Increase in the length or bulk of non-coordinating side-chain is expected to lower the stability of the resulting mixed ligand complex, but preliminary examination shows that the $\Delta \log K$ values generally become less negative in these cases indicating greater stabilisation of the ternary complexes. The extent of this extrastabilisation may be assessed quantitatively in terms of a parameter $\Delta \Delta \log K$ defined as

$$\Delta \Delta \log K = \Delta \log K_1 - \Delta \log K_s \quad (1)$$

where $\Delta \log K_1$ stands for the observed value of $\Delta \log K$ with a 'large-sized' ligand (*viz.* val, leu, iso-leu, nor-val) and $\Delta \log K_s$ for the experimental value of $\Delta \log K$ with the 'small-sized' ligand (here, α -ala) which may be used as a reference² for comparison. The calculated values of $\Delta \Delta \log K$ are presented in Table 3. Positive and significant values of $\Delta \Delta \log K$ obtained in several cases indicate extrastabilisation. The non-coordinating hydrophobic ends cause folding of the amphiphile amino acid molecule, the extent of which depends on the hydrophobicity⁷ (α -ala, -500 ; val, -1500 , leu, $-1800 \text{ cal mol}^{-1}$) of the side-chain. The folded end of the amino acid may undergo intramolecular inter-ligand interaction with the bonded primary ligand (bipy) due to its proximity with the latter. The interaction becomes more probable and significant if the side-chain is sufficiently long and ca-

TABLE 3—CALCULATED VALUES OF EXTRASTABILISATION PARAMETER ($\Delta \Delta \log K$), EQUILIBRIUM CONSTANT (K_1), PERCENTAGE OF EXTRASTABILISED FORM (%) MAL_{es} AT DIFFERENT TEMPERATURES FOR [M(II) BIPY AMINO ACID] MIXED LIGAND COMPLEXES

Parameter	Temp. °C	Co ^{II}	Ni ^{II}	Cu ^{II}	Zn ^{II}
[M(II).bipy.val] :					
$\Delta \Delta \log K$	25	-0.32	-1.12	-0.15	+0.08
K_1		-	-	-	0.202
(%) MAL_{es}		-	-	-	16.80
$\Delta \Delta \log K$	35	-0.38	-0.91	-0.12	-0.47
K_1		-	-	-	-
(%) MAL_{es}		-	-	-	-
$\Delta \Delta \log K$	45	-0.21	-0.66	+0.04	-0.54
K_1		-	-	0.07	-
(%) MAL_{es}		-	-	8.75	-
[M(II).bipy.leu] :					
$\Delta \Delta \log K$	25	-0.13	-0.17	-0.40	-0.23
K_1		-	-	-	-
(%) MAL_{es}		-	-	-	-
$\Delta \Delta \log K$	35	+0.06	+0.05	-0.42	-0.25
K_1		0.14	0.12	-	-
(%) MAL_{es}		12.89	10.87	-	-
$\Delta \Delta \log K$	45	+0.08	+0.03	-0.35	-0.27
K_1		0.20	0.07	-	-
(%) MAL_{es}		16.81	6.62	-	-
[M(II).bipy.iso-leu] :					
$\Delta \Delta \log K$	25	+0.03	-0.23	+0.08	+0.26
K_1		0.07	-	-0.20	0.81
(%) MAL_{es}		6.62	-	16.80	45.01
$\Delta \Delta \log K$	35	+0.01	-0.16	+0.17	+0.12
K_1		0.02	-	0.47	0.31
(%) MAL_{es}		2.24	-	32.38	24.13
$\Delta \Delta \log K$	45	+0.06	-0.19	+0.11	+0.17
K_1		0.14	-	0.28	0.47
(%) MAL_{es}		12.89	-	22.36	32.38
[M(II).bipy.nor-val] :					
$\Delta \Delta \log K$	25	+0.05	+0.08	+0.08	+0.09
K_1		0.12	0.20	0.202	0.23
(%) MAL_{es}		10.87	16.80	16.80	18.71
$\Delta \Delta \log K$	35	+0.06	+0.15	+0.10	+0.02
K_1		0.14	0.41	0.25	0.04
(%) MAL_{es}		12.90	29.16	20.00	4.50
$\Delta \Delta \log K$	45	+0.06	+0.17	+0.04	+0.01
K_1		0.14	0.47	0.07	0.02
(%) MAL_{es}		12.90	32.38	8.75	2.24

pable of extending itself beyond the axial region of metal ion. Details of mechanistic and structural aspects have been discussed earlier^{2,5,6}.

In view of the tetrahedral network of water molecules all the molecules of the ternary complex may not be folded. The hydrophobic ends are believed⁸ to be housed in the polyhedral cavities in the network of water molecules. There may thus exist an equilibrium between the 'extrastabilised' (interacted) form MAL_{es} and the 'open' or uninteracted form MAL_{op} of the ternary complex as shown below.



The equilibrium constant, K_1 of this equilibrium involving two isomeric forms of the ternary complex is a dimensionless quantity given by the expression,

$$K_1 = \frac{[MAL_{es}]}{[MAL_{op}]} \quad (3)$$

K_1 may be expressed in terms of $\Delta\Delta \log K$ as^{2,4}

$$K_1 = [10^{\Delta\Delta \log K} - 1] \quad (4)$$

The percentage of extrastabilised form, (%) MAL_{es} may be expressed in terms of K_1 as

$$(\%) MAL_{es} = \left[\frac{K_1}{1 + K_1} \right] \times 100 \quad (5)$$

The calculated values (only in those cases where $\Delta\Delta \log K$ has been found to be significant and positive) of K_1 and (%) MAL_{es} have been recorded in Table 3. The data indicate that extrastabilisation of the mixed ligand complexes occurs in the general sequence, val < leu < iso-leu < nor-val. It appears that the length of side-chain rather than its bulk (volume) is more important, because in comparable cases straight side-chain amino acids are associated with greater extrastabilisation than their branched chain isomers. Variations observed with the metal ions also indicate that the geometry and stereochemistry of the complexes also matter. The data further reveal that extrastabilisation is generally more at higher temperature in the

temperature range under study.

Experimental

Chemicals of standard purity (AnalaR; Merck, G.R.; Loba, A.R.; Sigma) were used. The solutions were prepared in double-distilled water. The metal ion solutions were standardised by complexometric titrations⁹. The formation constants of the binary and ternary complexes were determined initially by potentiometric pH-titrations using the Irving-Rossotti approach^{10,11} at 25, 35 and 45° and at $I = 0.2 \text{ mol dm}^{-3}$ (KNO_3). The final metal and ligand concentration was maintained at $[M] = [A] = [L] = 2.0 \times 10^{-3} \text{ mol dm}^{-3}$. The titrations were performed on an Elico LI-120 pH meter. A 2.0 mol dm^{-3} carbonate-free NaOH solution was used for the titrations. Refined values of formation constants considering protonated species were evaluated by using the SCOGS computer programme¹²⁻¹⁴.

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