Linear Enthalpy Relationships in Co-ordination Reactions of Macrocyclic Ligands with Copper(II)

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The heats of protonation of 12-(3',5'-dibromo-2'-hydroxybenzyl)-1,4,7,10-tetraazacyclotridecane-11,13-dione (hdbtado) have been determined in aqueous solution at 25 ± 0.1 °C and $I = 0.1$ mol dm^{-3} (KNO_3) by means of a model RD-1 automatic conduction calorimeter. The heats of formation of binary complex compounds of this ligand with Cu^{II} and ternary complex compounds of this ligand with Cu^{II}–5-substituted phenanthrolines have also been determined under identical conditions. By utilizing the calorimetric data, the heats of formation of the ternary complex compounds Cu^{II}–α-amino acid–hdbtado have been evaluated. Some linear enthalpy relationships have been found to exist between the heats of protonation of the ligands and the heats of formation of the ternary complex compounds.

The structure and properties of macrocyclic dioxotetraamines are similar to those of tripeptides. They are capable of co-ordinating to divalent 3d cations with simultaneous deprotonation of two amino groups.[1,2] Transition-metal(II) complexes of macrocyclic dioxotetraamines have shown some interesting properties and can be considered as models for metalloproteins and oxygen carriers.[3–6] Their copper(II) complexes can be oxidized at moderately positive potentials to give authentic trivalent copper species which are stable in aqueous solution.[7–9] Such compounds can serve as models for enzymes such as galactose oxidase[10] and may be employed as effective oxidants and redox catalysts.[11] A calorimetric study of the co-ordination reactions in aqueous solution for these macrocyclic dioxotetraamines with metal ions can provide useful information, in particular, the existence of linear enthalpy relationships (l.e.r.s). In this paper, we report the calorimetric measurement of the heats of protonation of 12-(3',5'-dibromo-2'-hydroxybenzyl)-1,4,7,10-tetraazacyclotridecane-11,13-dione (hdbtado) and of the heats of formation of binary (Cu^{II}–hdbtado) and ternary (Cu^{II}–L–hdbtado) systems (L = 5-substituted phenanthroline or α-amino acid).

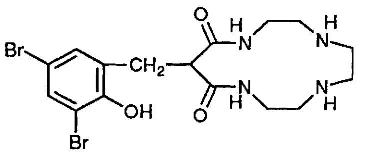
Theoretical.—Since two amino hydrogen ions are extruded upon complexation of these macrocyclic dioxotetraamines with metal(II) ions, equations (1) and (2) must be considered in the total calculation (charges omitted for clarity), where A denotes hdbtado and H denotes hydrogen ion. The overall calculation is the same as reported previously.[12]

$$\mathrm{Cu} + \mathrm{A} \rightleftharpoons \mathrm{Cu(H_{-2}A)} + 2\mathrm{H}$$
$$\beta_{11\text{-}2} = [\mathrm{Cu(H_{-2}A)}][\mathrm{H}]^2/[\mathrm{Cu}][\mathrm{A}] \qquad (1)$$

$$\mathrm{Cu} + \mathrm{A} \rightleftharpoons \mathrm{Cu(H_{-1}A)} + \mathrm{H}$$
$$\beta_{11\text{-}1} = [\mathrm{Cu(H_{-1}A)}][\mathrm{H}]/[\mathrm{Cu}][\mathrm{A}] \qquad (2)$$

Experimental

12-(3',5'-Dibromo-2'-hydroxybenzyl)-1,4,7,10-tetraazacyclotridecane-11,13-dione (hdbtado) was synthesized as reported previously[13] and its structure determined by means of elemental analysis, IR and NMR spectroscopy and by mass spectrometry. Copper(II) nitrate (Tianjin Second Chemical Reagent Factory, A. R.) was recrystallized before use. The concentration of Cu^{II} in the stock solution was analysed by conventional methods. Potassium nitrate (Tianjin Third Chemical Reagent Factory, A. R.) was recrystallized before use. 5-Methyl-1,10-phenanthroline (mphen) and 5-chloro-1,10-phenanthroline (cphen) were obtained from Aldrich. 5-Nitro-1,10-phenanthroline (nphen) and 1,10-phenanthroline (phen) were obtained from Shanghai Chemical Reagent Factory. L-Proline (Pro) was obtained from Sigma Chemical Co. (USA). The amino acids, 2-amino-2-methylpropanoic acid [α-aminoisobutyric acid (Aib)] (BDH, England), glycine (Gly), L-serine (Ser), L-isoleucine (Ile) and L-valine (Val) (Shanghai Chemical Reagent Factory) and 5-substituted phenanthrolines were used without further purification. All solutions were prepared by weighing quantities of the reagents except for the stock solution of Cu^{II}. All the copper(II) binary complexes with 5-substituted phenanthrolines were prepared in warm redistilled water. The ionic strength was adjusted to 0.1 mol dm^{-3} with KNO_3.



hdbtado

A model RD-1 automatic conduction calorimeter with a precision of ±0.5%[14] was used to measure the heat changes. The instrumental constant K was determined as (3.00 ± 0.01) $\times 10^{-3}$ J mm^{-2}, with n (number of tests) = 11, by using electrical power calibration and this was checked by chemical calibration [NaOH (aq) + $HClO_4$ (aq)]. An average value for the heat of neutralization, $\Delta H_N = -56.57 \pm 0.09$ kJ mol^{-1} ($I = 0.1$ mol dm^{-3} $NaClO_4$) ($n = 9$), was obtained.[15] The pH values of solutions were measured with a Beckman Φ 71 pH meter equipped with a type 39 841 combination electrode.

The methods for determining of the heats of protonation of hdbtado and the heats of formation of binary complex compounds of Cu^{II} with hdbtado[16] and of ternary systems, Cu^{II}–Rphen–hdbtado, are the same as reported previously.[17] The method for determination of the heats of formation of ternary systems Cu^{II}–aa–H(aq) + OH(aq) (aa = amino acid) is also the same as reported previously.[12]

All determinations were carried out at 25.0 ± 0.1 °C, $I = 0.1$ mol dm^{-3} (KNO_3). An average value for the heat of neutralization of hdbtado was $\Delta H_N = -59.78 \pm 0.10$ kJ mol^{-1}.[18] The activity coefficient γ_H is 0.8318.[19]

Table 1 Determination of the heats of protonation ($\Delta H_{\mathrm{H}_n\mathrm{A}}$/kJ mol^{-1}) of hdbtado (A) [n = 4; 25 ± 0.1 °C; I = 0.1 mol dm^{-3} (KNO_3)]

$10^3\ c_{\mathrm{H}^+}$	$10^3\ c_\mathrm{A}$									
mol dm^{-3}		pH$_i$	pH$_f$	Q_c/J	pK_{D1}	pK_{D2}	pK_{D3}	ΔH_{HA}	$\Delta H_{\mathrm{H_2A}}$	$\Delta H_{\mathrm{H_3A}}$
3.047	0.9818	9.41	3.34	−0.95 ± 0.01	5.50*			−25.1 ± 0.3		
3.047	1.525	9.61	5.00	−1.48 ± 0.01		7.31			−17.0 ± 0.7	
3.047	2.946	10.15	8.05	−1.69 ± 0.01			9.39			−13.8 ± 1.0

* Ref. 20; K_{D1}, K_{D2} and K_{D3} denote the first, second and third dissociation constants of hdbtado.

Table 2 Determination of the heats of formation ($\Delta H_{\mathrm{Cu-hdbtado}}$/kJ mol^{-1}) of the binary system Cu^{II}–hdbtado [n = 4; 25.0 ± 0.1 °C; I = 0.1 mol dm^{-3} (KNO_3)]

$10^3\ c_\mathrm{A}$	$10^3\ c_\mathrm{Cu}$							
mol dm^{-3}		pH$_i$	pH$_f$	Q_c/J	log $\beta_{\mathrm{Cu(H_{-2}A)}}$	log $\beta_{\mathrm{Cu(H_{-1}A)}}$	$\Delta H_{\mathrm{Cu(H_{-2}A)}}$	$\Delta H_{\mathrm{Cu(H_{-1}A)}}$
3.619	1.807	10.11	7.67	−0.83 ± 0.01	−0.67	4.83	5.40 ± 0.26	
1.809	1.807	9.71	5.29	−0.29 ± 0.01				4.81 ± 0.13

Table 3 Determination of the heats of formation ($\Delta H_{\mathrm{Cu-Rphen-hdbtado/tado}}$/kJ mol^{-1}) of the ternary systems Cu^{II}–Rphen–L [25.0 ± 0.1 °C; I = 0.1 mol dm^{-3} (KNO_3)]

		$10^3\ c_\mathrm{A}$	$10^3\ c_\mathrm{Cu-Rphen}$					
R	n	mol dm^{-3}		pH$_i$	pH$_f$	Q_c/J	log $\beta_{\mathrm{Cu-Rphen}}$	$\Delta H_{\mathrm{Cu-Rphen-L}}$
L = Hdbtado								
CH_3	4	1.805	1.807	10.14	7.06	0.06 ± 0.01	8.08[a]	1.69 ± 0.25
H	4	1.805	1.800	10.14	6.98	−0.02 ± 0.01	8.14	0.30 ± 0.25
Cl	4	1.805	1.807	9.87	6.86	0.06 ± 0.01	8.24	−2.85 ± 0.25
NO_2	4	1.805	1.807	9.81	6.92	−0.00 ± 0.01	8.34	−5.44 ± 0.25
L = tado[b]								
CH_3	6	1.892	1.807	10.76	6.83	−0.97 ± 0.01	6.20	4.90 ± 0.31
H	5	1.892	1.800	10.76	6.75	−1.04 ± 0.01	6.22	3.46 ± 0.31
Cl	5	1.892	1.807	10.43	6.61	−0.72 ± 0.01	6.25	−0.15 ± 0.32
NO_2	6	1.892	1.807	10.43	6.53	−0.83 ± 0.01	6.28	−3.14 ± 0.32

[a] Ref. 21. [b] Ref. 22.

Results and Discussion

The experimental data and the heats of protonation of hdbtado are given in Table 1. Heats of formation for the binary complex system Cu^{II}–hdbtado and of the ternary systems Cu^{II}–Rphen–hdbtado and Cu^{II}–aa–hdbtado are given in Tables 2–4. Heats of formation of ternary systems Cu^{II}–Rphen–1,4,7,10-tetra-azacyclodecane-11,13-dione (tado) are also given in Table 3 for comparison.[22]

The heat of the first protonation of hdbtado, ΔH_{HA}, corresponding to protonation of the oxygen atom of the pendant phenyl group is −25.1 ± 0.3 kJ mol^{-1} close to that of phenol, −25.5 kJ mol^{-1}.[23] The heat of formation (Table 2) of the binary complex compounds Cu(H$_{-2}$A) and Cu(H$_{-1}$A) are 5.40 ± 0.26 and 4.81 ± 0.13 kJ mol^{-1}, respectively. These values are positive, indicating that the overall heat effects for co-ordination of Cu^{II} to hdbtado are endothermic. Since the co-ordination of Cu^{II} with the four nitrogen atoms of hdbtado (Fig. 1) would simultaneously release two hydrogen ions from the amino groups a certain amount of energy must be consumed.[22] Although the co-ordination of oxygen on the phenol group with Cu^{II} or its reaction with the proton released from the amino group [with respect to Cu(H$_{-1}$A)] would release some energy, this is not enough to offset the energy consumed in removal of the two protons from the amino groups of the ligand upon co-ordination to Cu^{II} since the presence of the two bromine atoms on the *ortho* and *para* positions of the phenol group will greatly reduce the electron density of the oxygen atom on the phenol group. Therefore, the net heat effect appears to be endothermic. This may explain why the heats of formation of the binary systems are positive.

It is also seen from Table 3 that the heats of formation of ternary complex compounds Cu^{II}–Rphen–hdbtado are 1.69 ± 0.25(mphen), 0.30 ± 0.25(phen), −2.85 ± 0.25(cphen) and −5.44 ± 0.25 kJ mol^{-1} (nphen), respectively. Since the co-ordination tendency of Cu^{II} toward Rphen is very strong and Cu^{II}–Rphen species do not dissociate in the pH range 2–7, they can be considered to be stable species. Complex ions Cu^{II}–Rphen are unable to complex hdbtado *via* all the available co-ordination sites in a coplanar manner and only two nitrogen atoms of hdbtado can take part in co-ordination. This inability to co-ordinate hdbtado in a macrocyclic manner will lead to a reduction of energy released and furthermore, if the pendant group (2′-hydroxy-3′,5′-dibromobenzyl) is also unco-ordinated to Cu^{II}–Rphen, the heat of reaction of Cu^{II}–Rphen with only the two nitrogen atoms of hdbtado will be small, as found with the ligand tado. For this latter reaction [equation (3)], ΔH is only

$$\mathrm{Cu^{II}\text{–}Rphen} + \mathrm{tado} \rightleftharpoons \mathrm{Cu^{II}\text{–}Rphen\text{–}Tado} \qquad (3)$$

4.90 ± 0.31 (mphen), 3.46 ± 0.31 (phen), −0.15 ± 0.32 (cphen) or −3.14 ± 0.32 kJ mol^{-1} (nphen), respectively.[22] Even if the oxygen atom of the phenol group in hdbtado co-ordinates to Cu^{II}–Rphen the released energy will be small as discussed above. Therefore, the measured heats of formation of the ternary systems Cu^{II}–Rphen–hdbtado [equation (4)] are also low.

$$\mathrm{Cu^{II}\text{–}Rphen} + \mathrm{hdbtado} \rightleftharpoons \mathrm{Cu^{II}\text{–}Rphen\text{–}hdbtado} \qquad (4)$$

If we consider that d–p π-back bonding exists between Cu^{II} and Rphen then it decreases the electron density on Cu^{II} which

Table 4 Determination of the heats of formation ($\Delta H_{Cu^{II}\text{-aa-hdbtado}}$/kJ mol^{-1}) of ternary systems Cu^{II}-aa-hdbtado [25.0 ± 0.1 °C; I = 0.1 mol dm^{-3} (KNO$_3$)] *

α-Amino acid	n	10^3c_A	10^3c_B	10^3c_{Cu}	pH$_i$	pH$_f$	Q_c/J	log $\beta_{CuA(B)}$	$\Delta H_{CuA(B)}$
Proline	5	1.810	1.805	1.807	9.98	5.48	−0.60 ± 0.01	19.13	−42.6 ± 0.4
α-Aminoisobutyric acid	5	1.819	1.803	1.807	9.69	5.43	−0.48 ± 0.01	18.77	−51.3 ± 0.4
Isoleucine	5	1.807	1.805	1.807	9.36	5.44	−0.41 ± 0.01	18.39	−47.8 ± 0.5
Glycine	5	1.803	1.805	1.807	9.78	5.78	−0.96 ± 0.01	18.29	−47.2 ± 0.4
Valine	4	1.813	1.805	1.807	9.35	5.32	−0.55 ± 0.01	18.39	−46.7 ± 0.5
Serine	5	1.811	1.805	1.807	9.48	5.64	−0.98 ± 0.01	18.02	−45.1 ± 0.4

* A = hdbtado, B = amino acid (aa); concentrations, c, in mol dm^{-3}.

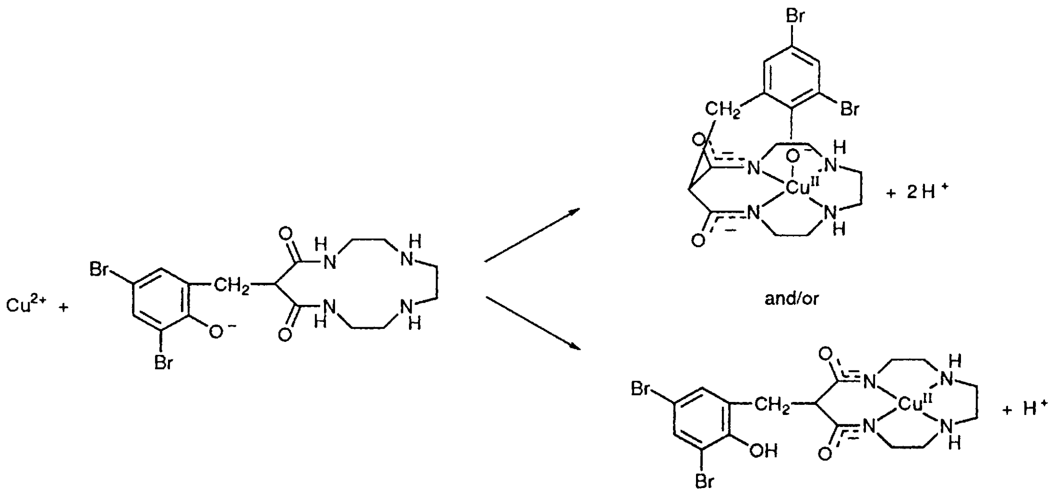


Fig. 1 Proposed binding modes of Cu^{II} to hdbtado

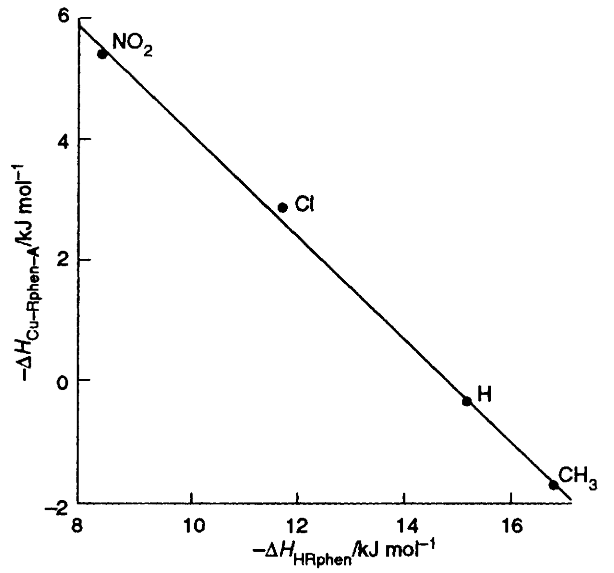


Fig. 2 Linear enthalpy relationship between the heats of formation of ternary systems Cu^{II}-Rphen-hdbtado and the heats of protonation of the ligands Rphen

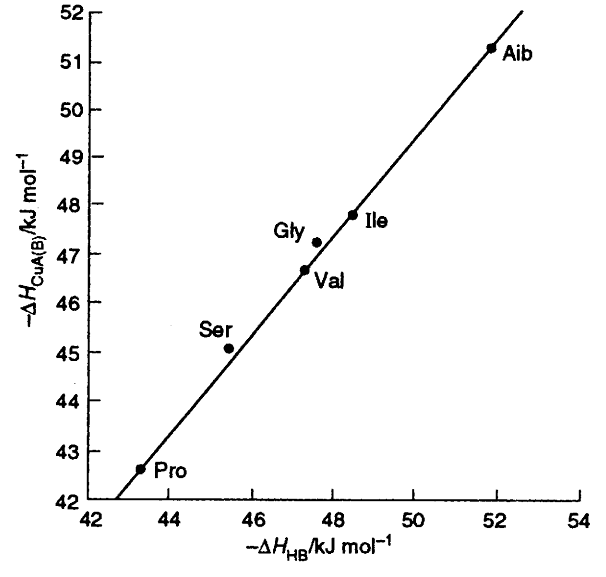
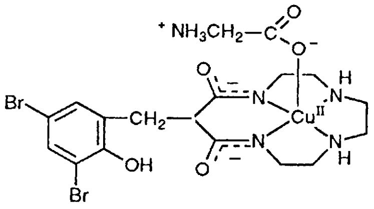


Fig. 3 Linear enthalpy relationship between the heats of formation of ternary systems Cu^{II}-aa-hdbtado and the heats of protonation of the α-amino acids; A = hdbtado, B = amino acid

in turn diminishes the repulsion between the Cu^{II} centre and the co-ordinated electron pair of hdbtado leading to an increase in the strength of the bonding between Cu^{II} and hdbtado. This is reflected in the fact that the heats of formation of the ternary systems Cu^{II}-Rphen-hdbtado increase with increasingly more electron withdrawing groups R and when the heats of formation of ternary systems Cu^{II}-Rphen-hdbtado are plotted against the heats of protonation of ligands Rphen, which also correlate with the electron-withdrawing nature of R, a straight line with negative slope is obtained (Fig. 2). Considering the heat of protonation for ligands Rphen (ΔH_{HRphen}), R = CH$_3$ −16.7, H −15.1, Cl −11.6, NO$_2$ −8.4 kJ mol^{-1} [24] we obtain the correlation given by equation (5) (r = 0.999).

$$\Delta H_{Cu\text{-}Rphen\text{-}hdbtado} = -12.76 - 0.8634\Delta H_{HRphen} \quad (5)$$

It is seen from Table 4 that the heats of formation of ternary



A

complex compounds Cu^{II}A(B) (A = hdbtado, B = α-amino acid) are in the range -42 to -51 kJ mol^{-1}. These values are much larger than the heat of formation of the binary complex Cu^{II}(H$_{-1}$A), 4.81 ± 0.13 kJ mol^{-1}, but are comparable with the heats of the first stepwise protonation of α-amino acids. In order to explain this phenomenon we consider that the ternary complex compounds Cu^{II}A(B) may have structure **A**. When hdbtado co-ordinates to Cu^{II} two protons will be simultaneously released from the amino groups. When the pH of the solutions is 5–6, the oxygen atom of the carboxyl group of the α-amino acids will not be protonated. Therefore, upon co-ordination to Cu^{II}, only the oxygen atom of the carboxyl group can bond to the metal ion. One of the two protons released from an amino group of hdbtado upon co-ordination may add to the nitrogen atom of the amino group of the α-amino acid, while the other may combine with the oxygen atom of the phenol group of hdbtado. When the stability constants of ternary complex compounds Cu^{II}A(B) were calculated by means of the TITFIT program,[25] the calculation converged only when the species CuA(B) was considered. The heat of formation of the binary complex Cu(H$_{-1}$A) is 4.81 ± 0.13 kJ mol^{-1} (see Table 1), the heat of protonation of α-aminoisobutyric acid is $-$ 51.9 ± 0.1 kJ mol^{-1},[12] and the heat of co-ordination of the oxygen atom of the carboxyl group and copper(II) is -4.2 kJ mol^{-1}.[22] Significantly, the sum of the above three heat effects is -51.3 kJ mol^{-1}, which is in agreement with the heat of formation of the ternary complex Cu^{II}–Aib–hdbtado (-51.3 ± 0.4 kJ mol^{-1}, Table 4). Similar phenomena are also found to exist in other ternary systems Cu^{II}–aa–hdbtado and indicate the absence of d-p π-back bonding effects in these ternary systems under which conditions the heat of formation of ternary complexes can be related to additivity effects of the parent binary complex compounds.[12] Furthermore, a linear enthalpy relationship is found to exist between the heats of formation of ternary complex compounds Cu^{II}A(B) and the heats of protonation [ΔH_{HB}; -43.3 ± 0.1 (Pro), -51.9 ± 0.1 (Aib), -48.5 ± 0.1 (Ile), -47.7 ± 0.2 (Gly), -47.3 ± 0.1 (Val), -45.5 ± 0.1 kJ mol^{-1} (Ser)][12] of the amino acid ligands, with a correlation given by equation (6) (r = 0.999) as shown in Fig. 3.

$$\Delta H_{CuA(B)} = 0.5307 + 0.9989\Delta H_{HB} \qquad (6)$$

Acknowledgements

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