# Direct Evidence for an $S_N1CB$ Mechanism III. Observations of Deprotonated Mixed Ligand Chelates of *N*-acetamidoiminodiacetatocopper(II). Evidence for the Intermediate

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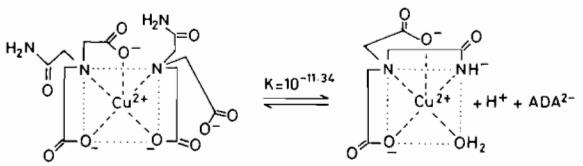
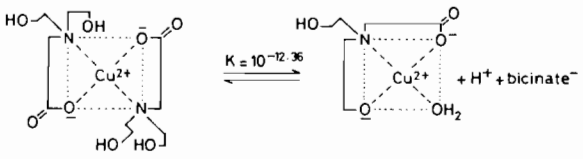
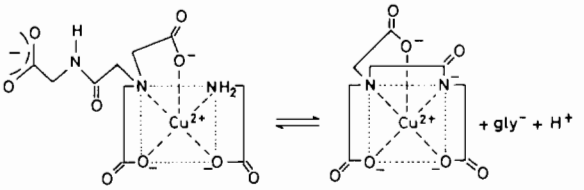
Recently, we have reported aminoacidate dechelation upon amide deprotonation [1] in the bis(*N*-acetamidoiminodiacetato)copper(II) chelate $[Cu(ADA)_2^{2-}]$ (eqn. (1)), upon hydroxy group ionization [2] in the bis(*N*,*N*-bis(2-hydroxyethyl)-glycinatocopper(II) chelate (eqn. (2)) and upon peptide proton ionization [3] in the mixed ligand chelate, (*N*,*N*-bis(carboxymethylglycylglycinato)(glycinato)copper(II) (eqn. (3)). This work was predicated on the belief that the $S_N1CB$ mechanism as developed by Basolo and Pearson [4] for Co(III) substitution reactions in basic solutions (eqn. (4)), could also be operative in those of Cu(II). That hypothesis has come under criticism in that eqns. (1)–(3) 'involve deprotonation and coordination of a pendant arm of a ligand which displaces a coordinated group (albeit a bidentate ligand) and does not necessarily involve an intermediate, such as $[Co(NH_3)_4(NH_2)X^+]$' *i.e.*, one containing a deprotonated ligand. Therefore, we now report evidence for the existence of a deprotonated mixed ligand metal chelate, $[Cu(H_{-1}ADA)(\beta\text{-alanine})^{2-}]$, in the pH region where dechelation of β-alanine was shown to occur and other deprotonated mixed ligand metal chelates where dechelation reactions fail to occur.




(1)




(2)




(3)

$$[Co(NH_3)_5X^{2+}] \underset{-OH^-}{\overset{+OH^-}{\rightleftharpoons}} [Co(NH_3)_4(NH_2)X^+]$$
$$+ H_2O \rightleftharpoons [Co(NH_3)_4(NH_2)^{2+}] + X^- \quad (4)$$
$$[Co(NH_3)_5OH^{2+}] \rightleftharpoons [Co(NH_3)_4(NH_2)(OH_2)^{2+}]$$

Potentiometric formation curves (not shown) of 1:1:1 solutions of Cu(II) to ADA to a non-N-substituted amino acid (AmAc) consist of three buffer zones with inflections at $a = 2.0$ and 3.0, mol of $OH^-$ to mol of Cu(II). In the low pH region, potentiometric, visible, and ESR data* indicate the formation of $[Cu(ADA)(H_2O)]$ (eqn. (5)), while the second buffer zone was found to correspond to

$$Cu^{2+} + H_2ADA \rightleftharpoons [Cu(ADA)(H_2O)] + 2H^+ \quad (5)$$

the formation of mixed ligand metal species, $[Cu(ADA)AmAc^-]$ (eqn. (6))**. In the high pH buffer zone, $[Cu(ADA)(\beta\text{-alanine})^-]$ was found to undergo a dechelation reaction upon amide proton ionization

$$[Cu(ADA)(H_2O] + AmAc^- \overset{K_2}{\rightleftharpoons} [Cu(ADA)(AmAc)^-] \quad (6)$$

$$[Cu(ADA)(\beta\text{-ala}) \overset{K_d}{\rightleftharpoons} [Cu(H_{-1}ADA)(H_2O)^-] + \beta\text{-ala}^- + H^+ \quad (7)$$

(eqn. (7)). On the other hand, the corresponding Cu(ADA) mixed ligand chelates with glycine, alanine, and valine were found to simply undergo deprotonation and coordination of the pendant acetamido moiety with concomitant loss of a coordinated

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*Potentiometric, visible, and ESR data obtained as in refs. 1–3. The $\lambda_{max}$ values at $a = 2.0$ of all Cu(II)–ADA–amino acid systems was 780 ± 2nm and $\epsilon_{max}$ was 50 ± 2 $M^{-1}$ $cm^{-1}$. The ESR spectra at $a = 2.0$ all gave the characteristic five line spectra of $[Cu(ADA)(H_2O)]$ (see ref. 1).

**The $\lambda_{max}$ values for all $[Cu(ADA)(AmAc)]$ species were between 670–710 nm indicating that a donor group stronger than $H_2O$ was added to the coordination sphere of $[Cu(ADA)(H_2O)]$.

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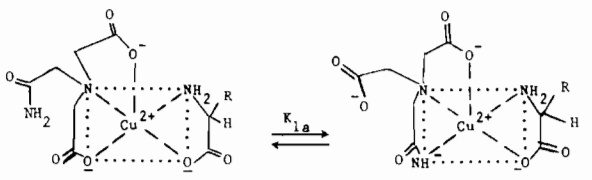

(8)

acetate group to yield $[Cu(H_{-1}ADA)(AmAc)^{2-}]$ species (eqn. (8)). Contrary to the β-alanine system and other previously studied systems [1–3], visible data (Fig. 1) showed that $\lambda_{max}$ shifted to higher, not lower energy in the region $a = 3.0$ to 4.0*. Potentiometric data for the glycine, alanine, and valine systems were solvable assuming only one equilibrium in the region $a = 3.0$ to 4.0 (eqn. (8)).

The $[Cu(ADA)(\beta\text{-alanine})^{-}]$ is remarkable in that $[Cu(H_{-1}ADA)(\beta\text{-alanine})^{2-}]$ must be included in calculations involving the high pH data ($a = 3.0$ to 5.0). Unlike the previously reported reactions involving dechelation (eqns. (1)–(3)) where $K_d$ values were readily obtained without including $[Cu(H_{-1}X)Y^{x+}]$ species, no program excluding $[Cu(H_{-1}ADA)\beta\text{-alanine}^{2-}]$, direct or convergence (Scogs–Cogsnar) [5], would yield a constant. Visible data (Fig. 2) clearly show an initial shift to higher energy above $a = 3.0$ followed by a dramatic shift to lower energy. The initial blue shift which is similar to that observed in the corresponding glycine, alanine, and valine systems represents the formation of $[Cu(H_{-1}ADA)\beta\text{-ala}^{2-}]$, while the latter red shift is the result of the dechelation of β-alanine (eqn. (7)). Therefore, the β-alanine–Cu(ADA) system is the first example of a dechelation reaction in which a large buildup of a deprotonated mixed ligand metal chelate occurs prior to dechelation.

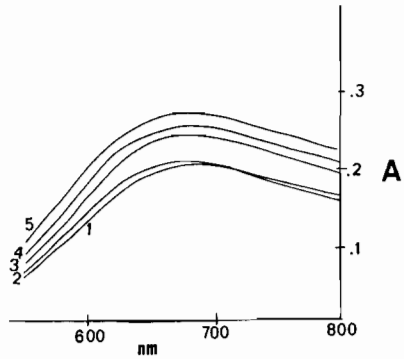


Fig. 1. Spectrophotometric titration of 1:1:1 Cu(II) to $H_2$-ADA to glycine ($5.3 \times 10^{-3}$ M) at various $a$ values, mol of base per mol of Cu(II): (1) $a = 3.0$; (2) $a = 3.1$; (3) $a = 3.3$; (4) $a = 3.6$; and (5) $a = 3.9$.

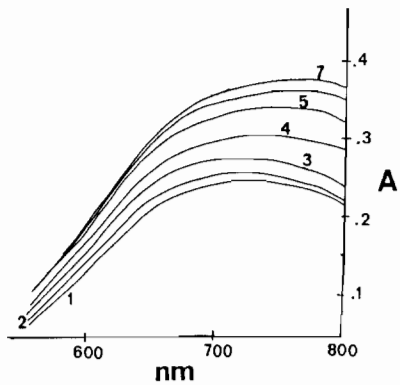


Fig. 2. Spectrophotometric titration of 1:1:1 Cu(II) to $H_2$-ADA to β-alanine ($4.2 \times 10^{-3}$ M) at various $a$ values, mol of base per mol of Cu(II): (1) $a = 3.0$; (2) $a = 3.1$; (3) $a = 3.3$; (4) $a = 3.6$; (5) $a = 3.9$; (6) $a = 4.3$; and (7) $a = 4.9$.

Apparently, glycine, alanine, and valine are too strongly bound to Cu(ADA) and are not sufficiently labilized by the binding of a deprotonated amide

*The $\lambda_{max}$ ($\epsilon_{max}$) values at $a = 5.0$ for the Cu–ADA–β-ala systems was 747 nm (67 $M^{-1}$ $cm^{-1}$) identical to that of $[Cu(H_{-1}ADA)OH^{2-}]$, 745 nm (66 $M^{-1}$ $cm^{-1}$), while those of the corresponding glycine, alanine and valine systems had $\lambda_{max}$ values between 650–665 nm indicating species other than $[Cu(H_{-1}ADA)OH^{2-}]$. ESR spectra of the latter systems at $a = 4.0$ and 5.0 yielded '$g$' values quite different from that of $[Cu(H_{-1}ADAT)OH^{2-}]$.

TABLE I. Formation Constants and Visible Spectra for Various Mixed Ligand Metal Chelates

| Metal chelate | Ancillary ligand | log $K_2$ ($\lambda_{max}$)[a] | log $K_{1a}$ ($\lambda_{max}$)[b] | $K_d$ ($\lambda_{max}$, $\epsilon_{max}$)[c] |
|---|---|---|---|---|
| [Cu(ADA)] | glycine$^-$ | 6.33 ± 0.02 (675) | −9.95 ± 0.02 (665) | |
| [Cu(ADA)] | alanine$^-$ | 6.32 ± 0.02 (670) | −10.12 ± 0.02 (665) | |
| [Cu(ADA)] | valine$^-$ | 6.16 ± 0.01 (670) | −10.09 ± 0.01 (660) | |
| [Cu(ADA)] | β-alanine$^-$ | 5.51 ± 0.01 (710) | −10.04 ± 0.01 (705) | −13.60 ± 0.01 (747,67) |
| [Cu(ADA)][d] | $ADA^{2-}$ | 3.12 (699) | | −11.34 (745,66) |
| $[Cu(bicine)^+]$[e] | bicine$^-$ | 5.40 (610) | | −12.36 (724,65) |
| $[Cu(DGDA)^-]$[f] | glycine$^-$ | 5.95 (665) | | −11.68 (670,120) |

[a] $\lambda_{max}$ in nm of mixed ligand chelates, $[CuLL'^{x+}]$. [b] $\lambda_{max}$ in nm of deprotonated mixed ligand chelates, $[Cu(H_{-1}L)L'^{(x-1)+}]$. [c] $\lambda_{max}$ in nm, $\epsilon_{max}$ in $M^{-1}$ $cm^{-1}$ of $[Cu(H_{-1}L)OH^{(x-2)+}]$ species except $[Cu(H_{-1}DGDA)^{2-}]$. [d] Ref. 1. [e] Ref. 2, bicine = $(HOCH_2CH_2)_2NCH_2COO^-$. [f] Ref. 3, DGDA = $(-OOCCH_2)_2NCH_2C(O)NHCH_2COO^-$.

group (eqn. (8)). β-alanine is a weaker binder to Cu(ADA) (see log $K_2$ values, Table I) by a factor of six. However, the buildup of [Cu(H$_{-1}$ADA)(β-alanine)$^{2-}$] in solution suggests that the deprotonated amide group did not fully labilize β-alanine. Apparently, the added stability of the hydroxo species, [Cu(H$_{-1}$ADA)OH$^{2-}$], is responsible for ultimately pushing the equilibrium toward dechelation (eqn. (9)). Based on the limited number of reported Cu-

$$[Cu(H_{-1}ADA)(\beta\text{-ala})^{2-}] \underset{+\beta\text{-ala}}{\overset{-\beta\text{-ala}}{\rightleftharpoons}}$$

$$[Cu(H_{-1}ADA)(H_2O)^{-}] \underset{+H^+}{\overset{-H^+}{\rightleftharpoons}} [Cu(H_{-1}ADA)(OH)^{2-}] \quad (9)$$

(ADA) systems (Table I), ligands with log $K_2$ values (eqn. (6)) of 3 or below will be labilized by a deprotonated amide group, while those with values of 6 or above will not. Apparently, the log $K_2$ value of 5.5 for β-alanine is near the borderline, and the formation of the hydroxo species is just energetically favorable enough to push the equilibrium toward dechelation (eqn. (9)).

We are presently working on the ADA analog, $HOCH_2CH_2N(CH_2COOH)_2$, which contains a hydroxy group which when deprotonated in the presence of Cu(II) is 18 times more basic than is the $H_2NC(O)CH_2$-moiety of ADA. It is hoped that such a large increase in basicity of the pendant arm of the ligand will lead to dechelation reactions involving ligands with larger log $K_2$ values than those reported in Table I.

## Acknowledgement

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