reasonably constant over the narrow range of ring size studied (five to seven), and the very large differences in the rate constants comes mainly from changes in ΔH^*. The major changes in ΔS^* are observed on going from the intermolecular reaction [$\Delta S^* = -34$ cal K^{-1} mol^{-1} for the reaction between *trans*-$[Pt(NH_3)_2Cl_2]$ and NH_3[13]] to the intramolecular process [$\Delta S^* = -15$ to -16 cal K^{-1} mol^{-1}]. It has previously been suggested that, in the closing of the five-membered ring, the ground state of the reagents already corresponds to a position well along the reaction coordinate of the intermolecular process to the point where the adjustment of the solvation of the interacting species is well advanced;[1] to what extent does the longer chain length between the functional groups in the tn and bn complexes reduce this "prearrangement"? Some years ago Cotton and Harris[22] calculated the probability of finding the second amino group of a monocoordinated diamine within the region 1.6–2.0 Å of the metal ion and showed that it did not vary greatly on going along the series 1,2-diaminoethane to 1,5-diaminopropane. They concluded that this consideration would therefore make only a small and fairly constant contribution to the entropy change associated with cyclization and calculated that the different losses of entropy associated with closing rings of different sizes arose from the differing conformational restrictions on closing the rings. The four-coordinate planar d^8 complexes are, in principle, coordinately unsaturated, and the possibility of loose coordination in the axial position will greatly increase the probability of finding the free end of the diamine in the vicinity of the Pt(II). The Monte Carlo or random walk treatment will greatly underestimate this probability. The weak coordination will also serve to close the ring loosely so that the changes of entropy due to conformational restrictions will have occurred in the ground state and therefore will not appear in the entropy of activation. Such incipient chelation is an alternative way of viewing the suggestion made above that the ring-closing process starts from a position some way along the reaction coordinate that is appropriate for the intermolecular process. Once the ring size becomes large enough for only a small fraction of the substrate to be incipiently chelated at any time, it is likely that the entropies of activation will decrease with increasing ring size in the way observed elsewhere. The tightening of the ring as the NH_2 group becomes more tightly bound to the Pt will lead to ring strain and interatomic repulsions, and these will result in an increase in the enthalpy of activation as ring size increases. In the range of ring size covered by this work it is suggested that this is the main cause of the decrease in the rate of ring closing. The organic ring closing reactions do not have the benefit of incipient chelation in the noncyclic substrate since the carbon is coordinately saturated.

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Registry No. *trans*-$[Pt(NH_3)(NH_2(CH_2)_2NH_2)Cl_2]$, 80243-17-0; *trans*-$[Pt(NH_3)(NH_2(CH_2)_3NH_2)Cl_2]$, 80243-18-1; *trans*-$[Pt(NH_3)(NH_2(CH_2)_4NH_2)Cl_2]$, 80243-19-2; *trans*-$[Pt(NH_3)(NH_2(CH_2)_2NH_3)Cl_2]^+$, 80243-20-5; *trans*-$[Pt(NH_3)(NH_2(CH_2)_3NH_3)Cl_2]^+$, 80243-21-6; *trans*-$[Pt(NH_3)(NH_2(CH_2)_4NH_3)Cl_2]^+$, 80243-22-7; Pt(pe)$Cl_2$, 80243-50-1.

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Apical Interactions in Copper(II) Complexes. Stability and Structure of the Binary and Ternary Copper(II) Complexes Formed with L-Alaninamide and Diethylenetriamine in Aqueous Solution[1]

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By potentiometric pH titrations the stability constants were determined in aqueous solutions of the binary parent and mixed-ligand complexes formed in systems containing L-alaninamide (AlaA), diethylenetriamine (dien), and Cu^{2+}. In contrast to an earlier claim, where for the species Cu(dien)(AlaA-H)$^+$ an apical coordination of the ionized amide nitrogen was suggested, in the present work this deprotonated ternary complex could not even be detected. All experimental data could be perfectly fitted by assuming the species Cu(AlaA)$^{2+}$, Cu(AlaA)$_2^{2+}$, Cu(AlaA-H)$^+$, Cu(AlaA)(AlaA-H)$^+$, Cu(AlaA-H)$_2$, Cu(dien)$^{2+}$, Cu(dien)(OH)$^+$, Cu(dien)(H·dien)$^{3+}$, Cu(dien)$_2^{2+}$, and Cu(dien)(AlaA)$^{2+}$. These results were confirmed by spectrophotometric measurements, and the spectral characteristics (λ_{max} and extinction coefficient) were determined. By comparisons with literature data it becomes evident, in agreement with earlier conclusions, that in Cu(dien)(H·dien)$^{3+}$ four amino nitrogens are equatorially coordinated while one N interacts apically; in Cu(dien)$_2^{2+}$ clearly all six nitrogens participate in complex formation; i.e., two nitrogens interact apically. For Cu(dien)(AlaA)$^{2+}$ there is evidence that four nitrogens are equatorially coordinated and that the carbonyl oxygen of AlaA interacts to a significant extent with an apical position of Cu^{2+}. Regarding biological systems two important conclusions may be drawn from this and related work: (i) An apical coordination of amino nitrogens or of oxygen donors to Cu^{2+} is easily achieved in the physiological pH range, while there is *no* such evidence for the coordination of an ionized amide nitrogen. (ii) In a mixed-ligand complex an ionized amide group may be formed and coordinated only if *two equatorial* coordination positions of Cu^{2+} are accessible, namely, for the terminal amino nitrogen and the neighboring ionized amide nitrogen of the "peptide" ligand.

The ionized amide residue is an important ligating group in low molecular weight Cu^{2+} peptide complexes.[4] The same type of coordination is also known to occur in nature, e.g., in human serum albumin;[5,6] similarly, the antibiotic bleomycin is most probably active via metal ion complexes and the one

(1) Part 7 of the series "Transition Metal Ions and Amides" (published by A.D.Z.) and part 39 of the series "Ternary Complexes in Solution" (published by H.S.); for parts 6 and 38 see ref 2 and 3, respectively.
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with Cu^{2+} contains also a coordinated ionized amide nitrogen.[7-9] Hence, it is not surprising that the binding properties of the amide group have received much attention[4] in studies concerning binary[2,10,11] and ternary complexes.[12-15]

In general, coordination compounds of Cu^{2+} have four nearby donor atoms arranged equatorially around the metal ion with the possibility of one or two more distant axial donors.[16] There is also a progressive reduction in the sum of the bond orders of the two axial metal–ligand bonds as the number of ionized N peptide donors attached to Cu^{2+} increases.[4a] The maximum number of ionized amide groups coordinating to Cu^{2+} in solutions or in the solid state is three for peptides; i.e., in linear oligopeptide complexes Cu^{2+} coordinates to its four equatorial positions the terminal amino group and three nitrogens of the next neighboring amide groups. The simplest examples of such complexes are those with triglycylglycinate[17,18] and tetraglycylglycinate:[19] in Cu(triglycylglycinate-H_3)$^{2-}$ and Cu(tetraglycylglycinate-H_3)$^{2-}$ no axial interaction is observed in the solid state and Cu^{2+} has coordination number 4. This means in detail, e.g., for Cu(tetraglycylglycinate-H_3)$^{2-}$, that the fourth peptide group is *not* deprotonated; neither this nor the terminal carboxylate group plays any part in metal ion binding.

The weak apical coordination of amino[20-22] and other[14,23] groups is well-known. The question about an apical coordination of an *ionized* amide group under certain conditions has been raised,[24] and for the Cu^{2+}/diethylenetriamine/L-alaninamide system the occurrence of such an interaction was claimed[25] on the basis of absorption and circular dichroism spectral data. This conclusion has been challenged,[18] and indeed, we have now shown by carefully determining all the species present in aqueous solutions of the binary parent and the mixed-ligand Cu^{2+} systems of diethylenetriamine (dien) and L-alaninamide (AlaA) that no apically coordinated ionized amide species is formed. However, the apical coordination of amino and to some extent also of O-donor groups, including the oxygen of the neutral amide group, does play a role in these and related systems.

Experimental Section

Materials. NaOH (Titrisol), KCl, and $CuSO_4 \cdot 5H_2O$ (all of p.A. grade) were from Merck AG, Darmstadt, FRG. The hydrochloride of L-alaninamide was purchased from ICN Pharmaceuticals Inc., Plainview, N.Y.

The tris(hydrochloride) of diethylenetriamine [=bis(2-aminoethyl)amine = 1,4,7-triazaheptane] was a gift from Dr. M. Zehnder. The dien·3HCl had been prepared by distilling the free base ("for synthesis", from Merck AG) three times through a column, checking the purity of the base by thin-layer chromatography, adding an excess of concentrated HCl, and precipitating the trihydrochloride by adding ethanol. This product was then in addition recrystallized three times from a HCl/ethanol mixture.

The titer of the NaOH used for the titrations was determined with potassium hydrogen phthalate (Merck AG); the exact concentrations of the stock solutions of the ligands were measured by titrations with NaOH.

The buffers (pH 4.00 and 7.00) used for calibrating the potentiometers were from Metrohm AG, Herisau, Switzerland. The direct pH-meter readings were used in the calculations.

Apparatus. The potentiometric pH titrations were carried out in a microprocessor-controlled way with a Metrohm E 600 digital pH meter equipped with a Metrohm EA 121 glass electrode and a Metrohm E 412 microdosimat as described recently in detail.[26]

The spectrophotometric measurements were done with the described automatic titration system using a Cary 118C spectrophotometer,[27] but the whole procedure (stepwise addition of reagent, reading pH and absorption, recording the data on a floppy disk) was now controlled by an Apple II desk computer.

Measurements. The acidity constant of $H(AlaA)^+$ was measured by *potentiometric pH titrations*: 25 mL of aqueous 0.0064 M AlaA·HCl (I = 0.5, KCl; 25 °C) was titrated under N_2 with 1 mL of 0.4 M NaOH. The equilibrium constants of the corresponding binary Cu^{2+} systems were determined from solutions that were in addition 0.0016 or 0.00305 M in $CuSO_4$. Further titrations were carried out with solutions being 0.0016 M in AlaA·HCl and 0.000 40 or 0.000 77 M in $CuSO_4$.

The acidity constants of $H_3(dien)^{3+}$ were measured by titrating 25 mL of aqueous 0.0030 M dien·3HCl under N_2 with 0.4 M NaOH (I = 0.5, KCl; 25 °C). The equilibrium constants of the Cu^{2+} 1:1

Table I. Logarithms of Single-Step Equilibrium Constants, log K, for the H^+ and Cu^{2+} Complexes of L-Alaninamide (AlaA) and Diethylenetriamine (dien) and the Corresponding Mixed-Ligand System, together with Some Related Data (25 °C)[a]

no.	equilibrium	log K
1	$H^+ + AlaA \rightleftharpoons H(AlaA)^+$	8.18
2	$Cu^{2+} + AlaA \rightleftharpoons Cu(AlaA)^{2+}$	5.07
3	$Cu(AlaA)^{2+} + AlaA \rightleftharpoons Cu(AlaA)_2^{2+}$	3.92
4	$Cu(AlaA)^{2+} \rightleftharpoons Cu(AlaA\text{-}H)^+ + H^+$	−7.22
5	$Cu(AlaA)_2^{2+} \rightleftharpoons Cu(AlaA)(AlaA\text{-}H)^+ + H^+$	−6.97
6	$Cu(AlaA)(AlaA\text{-}H)^+ \rightleftharpoons Cu(AlaA\text{-}H)_2 + H^+$	−8.16
7	$H^+ + dien \rightleftharpoons H(dien)^+$	10.18
8	$H^+ + H(dien)^+ \rightleftharpoons H_2(dien)^{2+}$	9.41
9	$H^+ + H_2(dien)^{2+} \rightleftharpoons H_3(dien)^{3+}$	4.83
10	$Cu^{2+} + dien \rightleftharpoons Cu(dien)^{2+}$	16.55
11	$Cu(dien)^{2+} + dien \rightleftharpoons Cu(dien)_2^{2+}$	4.60
12	$Cu(dien)^{2+} + H(dien)^+ \rightleftharpoons Cu(dien)(H\cdot dien)^{3+}$	2.94
13	$Cu(dien)(H_2O)^{2+} \rightleftharpoons Cu(dien)(OH)^+ + H^+$	−9.49
14	$Cu(dien)^{2+} + AlaA \rightleftharpoons Cu(dien)(AlaA)^{2+}$	2.03
15	$Cu(dien)(AlaA)^{2+} \rightleftharpoons Cu(dien)(AlaA\text{-}H)^+ + H^+$	ne[b]
16[c]	$Cu(dien)^{2+} + NH_3 \rightleftharpoons Cu(dien)(NH_3)^{2+}$	3.15
17[d,e]	$Cu(dien)^{2+} + Ggg^- \rightleftharpoons Cu(dien)(Ggg)^+$	2.90
18[d,e]	$Cu(en)^{2+} + Ggg^- \rightleftharpoons Cu(en)(Ggg)^+$	4.48
19[d,e]	$Cu(en)(Ggg)^+ \rightleftharpoons Cu(en)(Ggg\text{-}H) + H^+$	6.83
20[d,f]	$Cu^{2+} + GlyA \rightleftharpoons Cu(GlyA)^{2+}$	5.40
21[d,f]	$Cu(GlyA)^{2+} \rightleftharpoons Cu(GlyA\text{-}H)^+ + H^+$	−7.01
22[d,f]	$Cu(bpy)^{2+} + GlyA \rightleftharpoons Cu(bpy)(GlyA)^{2+}$	5.01
23[d,f]	$Cu(bpy)(GlyA)^{2+} \rightleftharpoons Cu(bpy)(GlyA\text{-}H)^+ + H^+$	−7.71

[a] The data of the present work refer to I = 0.5 M, KCl.[30] The range of error resulting from two independent sets of experiments is ≤±0.02 log unit. The only exception is no. 4; due to the relatively low concentration of $Cu(AlaA\text{-}H)^+$ the error is somewhat larger: ±0.04 log unit. [b] No evidence was observed for this equilibrium; see text. [c] From ref 35: I = 1, NH_4NO_3; log $K^{H}_{H(NH_3)}$ = 9.43; log $K^{Cu}_{Cu(NH_3)}$ = 4.14. [d] Abbreviations: bpy, 2,2'-bipyridyl; en, ethylenediamine; Ggg, glycylglycylglycinate; Gly, glycinate; GlyA, glycinamide. [e] From ref 36: I = 0.1, $NaClO_4$; log $K^{H}_{H(Ggg)}$ = 7.88; log $K^{Cu}_{Cu(Ggg)}$ = 5.12. [f] From ref 37: I = 0.1, $NaClO_4$; log $K^{H}_{H(GlyA)}$ = 8.04.

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complexes were determined under the same conditions with the additional presence of 0.00294 M $CuSO_4$; hence, 1:2 complexes are not important under these conditions but they were considered in the calculations by using the corresponding constants published earlier.[22]

The titration solutions (25 mL) of the mixed-ligand systems were 0.00294 M in $CuSO_4$, 0.0030 M in dien·3HCl, and 0.0030, 0.0060, or 0.0090 M in AlaA·HCl. All experiments were done twice, and the final result is the average of the calculations based on two independent sets of experiments.

The evaluation of the potentiometric pH titrations was carried out on a Hewlett-Packard HP 9835 desk-top computer using a new program with analytical derivatives for parameter optimization.[28] In all computations overall formation constants were calculated, with the ionic product of water in 0.5 M KCl at 25 °C as $K_w = 1.40 \times 10^{-14}$ M^2 taken into account. The agreement between the two independent sets of experiments was good; e.g., for the mixed-ligand system we obtained for $\log \beta^{Cu}_{Cu(dien)(AlaA)}$ the values 18.59 and 18.57. All the experimental data could be excellently satisfied without the assumption of the species Cu(dien)(AlaA-H)$^+$.

The experimental conditions for the *spectrophotometric titrations* of the binary Cu^{2+}/dien system, including the concentrations of the reactants, were very similar to those described recently.[29]

In the other binary system, AlaA·HCl was 0.012 M and $CuSO_4$ 0.003 or 0.0055 M. For the ternary system we used [dien·3HCl] = [AlaA·HCl] = 0.005 M and [$CuSO_4$] = 0.0049 M (I = 0.5, KCl; 25 °C).[30] The latter two systems were titrated with 0.2 M NaOH (in 0.3 M KCl) between pH 4 and pH 11.5. In addition, mixtures of 0.005 M dien and 0.0049 M $CuSO_4$ were adjusted to pH 8.75 or 11.00 and titrated with 0.2 M AlaA of the same pH until the final concentration of AlaA in the titration mixture was 0.025 M. All these experiments were done twice and the absorption data stored between 460 and 780 nm at 20-nm intervals. Such a digitization at every 20 nm leads to an agreement of the calculated absorption maxima between different experiments of 1–4 nm for those complexes that are formed to at least 20%.

The data, stored on floppy disks, were evaluated in two steps with the aid of an Apple II desk computer. First the number of absorbing species in a set of spectra was determined by means of an eigenvector analysis.[29] Representation of the measured spectra in the eigenvector basis leads to a significant data reduction[29] and allows in a second step the calculation of the equilibrium constants on the Apple II. A fitting program was used that demands only initial estimates of the equilibrium constants while the molar absorption coefficients are eliminated from the iterative refinement.[34]

Results and Discussion

The stability constants determined by potentiometric pH titrations for the binary parent and the mixed-ligand Cu^{2+} complexes of L-alaninamide (AlaA) and diethylenetriamine (dien) are given in Table I together with some related data from the literature.[35–37]

Stability of Binary Complexes. The constants determined now for the binary Cu^{2+}/dien system agree well with earlier results.[22,29] The low stability of $Cu(dien)_2^{2+}$ (no. 11 of Table I) compared with that of $Cu(dien)^{2+}$ (no. 10) reflects the fact that for the coordination of the second dien only one of the four equatorial coordination positions at Cu^{2+} remains available and that the expected coordination tendency of the apical positions is low. The even smaller stability of Cu(dien)(H·dien)$^{3+}$ (no. 12) is expected, as both reactants, $Cu(dien)^{2+}$ and $H(dien)^+$, are positively charged. The formation of the hydroxo complex Cu(dien)(OH)$^+$ in the pH range around 9.5 (no. 13) agrees well with the stability of hydroxo species of other Cu^{2+} complexes with tridentate ligands.[38]

The stability of Cu(AlaA)$^{2+}$ (no. 2) is similar to that of Cu(GlyA)$^{2+}$ (no. 20),[37] but the slightly larger stability of Cu(GlyA)$^{2+}$[39] corresponds to the observations made with those of the complexes of glycinate and alaninate: despite the lower basicity of glycinate, its complexes are somewhat more stable.[24] There appear to be differences in solvation and/or some steric hindrance by the methyl group; this conclusion agrees also with the results obtained for the Cu^{2+} complexes of (α-alkylglycyl)glycinates.[12] That in Cu(AlaA)$^{2+}$ and Cu(GlyA)$^{2+}$ chelate formation occurs under coordination of the amino nitrogen and the carbonyl oxygen to Cu^{2+} is evident from a comparison[18] with the stability, e.g., of $Cu(NH_3)^{2+}$.

The formation of the amide ionized Cu(AlaA-H)$^+$ and Cu(GlyA-H)$^+$ complexes (nos. 4 and 21) occurs, as one would expect, in a similar pH range. The 1:2 complex $Cu(AlaA)_2^{2+}$ (no. 5) may also be deprotonated at its amide groups; in fact, its slightly enhanced acidity (0.25 log unit), compared with that of Cu(AlaA)$^{2+}$ (no. 4), corresponds well with the statistical expectation for the possibility of two deprotonation sites (0.3 log unit) in the 1:2 complex. That the ionization of the second amide nitrogen (no. 6) occurs only at higher pH reflects the lower positive charge of Cu(AlaA)(AlaA-H)$^+$, compared with that of Cu(AlaA)$^{2+}$.

Stability of Mixed-Ligand Complexes. The stability of ternary complexes is best quantified in relation to the corresponding binary parent complexes,[40–42] i.e., by considering equilibrium 1. The logarithm of the corresponding equilib-

$$Cu(dien)^{2+} + Cu(L)^{2+} \rightleftharpoons Cu(dien)(L)^{2+} + Cu^{2+}$$

$$10^{\Delta \log K_{Cu/dien/L}} = [Cu(dien)(L)^{2+}][Cu^{2+}]/([Cu(dien)^{2+}][Cu(L)^{2+}]) \quad (1)$$

rium constant is calculated with eq 2. For the Cu^{2+}/dien/

$$\Delta \log K_{Cu/dien/L} = \log K^{Cu(dien)}_{Cu(dien)(L)} - \log K^{Cu}_{Cu(L)} \quad (2)$$

AlaA system (no. 14 of Table I) equilibrium 1 is far on its left side and one obtains $\Delta \log K_{Cu/dien/AlaA} = -3.04$. A comparison of this value with the one due to the Cu^{2+}/dien/NH_3 system (no. 16), $\Delta \log K_{Cu/dien/NH_3} = \log K^{Cu(dien)}_{Cu(dien)(NH_3)} - \log K^{Cu}_{Cu(NH_3)} = 3.15 - 4.14^{35} = -0.99$, reveals that the coordination tendency of AlaA toward $Cu(dien)^{2+}$ is lower by about 3 log units than toward Cu^{2+}(aq), while the same difference for the NH_3 system is only in the order of 1 log unit.

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(42) Sigel, H. "Coordination Chemistry—20"; Banerjea, D., Ed.; published by IUPAC through Pergamon Press: Oxford and New York, 1980; p 27.

These different qualities originate in the bidentate coordination of AlaA toward the equatorial positions of $Cu^{2+}(aq)$; in $Cu(dien)^{2+}$ only one such position remains and this is enough for full coordination of the monodentate NH_3 but not of the bidentate AlaA.

For the further evaluation of the coordinating properties of AlaA and NH_3 toward $Cu(dien)^{2+}$, the different basicities of the two ligands must be taken into account. This may be done by considering equilibrium 3. The corresponding equilibrium

$$Cu(dien)^{2+} + H(L)^{+} \rightleftharpoons Cu(dien)(L)^{2+} + H^{+}$$

$$K^{H}_{Cu(dien)/H(L)} = [Cu(dien)(L)^{2+}][H^{+}]/([Cu(dien)^{2+}][H(L)^{+}]) \quad (3)$$

constant follows from eq 4. For the $Cu(dien)^{2+}/NH_3$ system

$$pK^{H}_{Cu(dien)/H(L)} = pK^{H}_{H(L)} - \log K^{Cu(dien)}_{Cu(dien)(L)} \quad (4)$$

one obtains $pK^{H}_{Cu(dien)/H(NH_3)} = 6.28$ and for the $Cu(dien)^{2+}$/AlaA system $pK^{H}_{Cu(dien)/H(AlaA)} = 6.15$. Hence, roughly speaking, the coordinating properties of AlaA and NH_3 toward $Cu(dien)^{2+}$ are similar, although those of AlaA appear to be slightly more pronounced ($pK^{H}_{Cu(dien)/H(AlaA)} < pK^{H}_{Cu(dien)/H(NH_3)}$), thus giving a first hint for a weak additional apical interaction of AlaA in $Cu(dien)(AlaA)^{2+}$.

Of additional interest is a comparison of the stabilities of $Cu(dien)(Ggg)^{+}$ (no. 17) and $Cu(en)(Ggg)^{+}$ (no. 18). It is evident that the coordination tendency of diglycylglycinate (Ggg) toward $Cu(en)^{2+}$ is by a factor of about 40 larger than that toward $Cu(dien)^{2+}$; this is a reflection of the fact that Ggg^{-} is able to coordinate in a bidentate fashion toward two equatorial Cu^{2+} positions in $Cu(en)^{2+}$ but not in $Cu(dien)^{2+}$.

This possibility for a bidentate equatorial coordination is crucial for the formation of ionized amide-*N*-coordinated species. Only if this condition is fulfilled are amide-deprotonated mixed-ligand complexes formed: examples are Cu(en)(Ggg-H) (no. 19 of Table I), Cu(bpy)(GlyA-H)$^{+}$ (no. 23), Cu(bpy)(Ggg-H),[18] or Cu(glycinate)(Ggg-H)$^{-}$.[43] In agreement herewith is the fact that in the Cu^{2+}/dien/Ggg^{-} system no amide-deprotonated ternary complex was observed;[36] the same is true for the Cu^{2+}/dien/AlaA system. In contrast to an earlier claim[25] the species Cu(dien)(AlaA-H)$^{+}$ could *not* be detected: all experimental data of the potentiometric pH titrations could be perfectly fitted by the computer calculations without the assumption of such a complex. Moreover, in the spectrophotometric experiments also only the species Cu(dien)$(AlaA)^{2+}$ could be detected and the corresponding stability constant was within experimental error identical with the one given in Table I (no. 14); there was again *no* evidence for the formation of Cu(dien)(AlaA-H)$^{+}$.

The distribution of the several complex species in the mixed-ligand system is shown in dependence on pH in the upper part of Figure 1 for 1:1:1 conditions ($[Cu^{2+}]_{tot} = [dien]_{tot} = [AlaA]_{tot} = 0.005$ M). The ternary complex Cu(dien)$(AlaA)^{2+}$ reaches its maximum concentration of 22% only at pH 8.8, but its formation extends well into the physiological pH range. Under conditions where a 20-fold excess of AlaA is present, i.e., $[Cu^{2+}]_{tot} = [dien]_{tot} = 0.005$ M and $[AlaA]_{tot} = 0.1$ M, the mixed-ligand species becomes prominent as is seen in the lower part of Figure 1. There is one further aspect evident: under these conditions at higher pH the species $Cu(AlaA\text{-}H)_2$ becomes also important and as a consequence $Cu(dien)_2^{2+}$ is also formed. This is obviously due to the "disproportionation" reaction (5). Displacement of equilibrium 5 to the right side is clearly possible only at high pH. As emphasized above, we could not detect by the two methods used in this study any hint for the formation of Cu(dien)-(AlaA-H)$^{+}$. Indeed, the absorption spectral data given earlier[25] for Cu(dien)(AlaA-H)$^{+}$ are identical with those of Cu(dien)$(OH)^{+}$ (cf. next section and Table II) and must in our opinion be attributed to this latter species. Correspondingly, the amide deprotonation, also observed earlier,[25] must be assigned to $Cu(AlaA\text{-}H)_2$ rather than to any ternary complex. To conclude, Cu(dien)(AlaA-H)$^{+}$ is clearly not formed in any appreciable amounts; at best it might occur in traces during the structural reorganization of the species in connection with equilibrium 5.

$$2Cu(dien)(AlaA)^{2+} \rightleftharpoons Cu(dien)_2^{2+} + Cu(AlaA\text{-}H)_2 + 2H^{+} \quad (5)$$

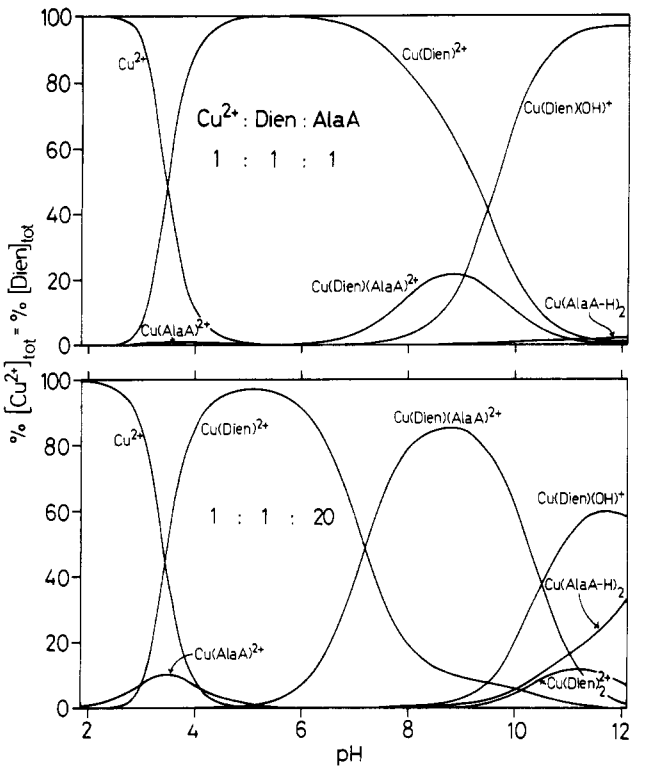

Figure 1. Effect of pH on the concentration of the species present in an aqueous solution (I = 0.5, KCl; 25 °C) of Cu^{2+}, diethylenetriamine (dien), and L-alaninamide (AlaA). The results are given as the percentage of the total Cu^{2+} (=total dien) present and were computed with the potentiometrically determined constants of Table I. Upper part: $[Cu^{2+}]_{tot} = [dien]_{tot} = [AlaA]_{tot} = 0.005$ M; $[Cu(AlaA)_2^{2+}] < 0.03\%$, $[Cu(AlaA\text{-}H)^{+}] < 0.01\%$, $[Cu(AlaA)(AlaA\text{-}H)^{+}] \leq 0.06\%$, $[Cu(dien)(H\cdot dien)^{3+}] \leq 0.05\%$, $[Cu(dien)_2^{2+}] < 1.2\%$. Lower part: $[Cu^{2+}]_{tot} = [dien]_{tot} = 0.005$ M and $[AlaA]_{tot} = 0.1$ M; $[Cu(AlaA)_2^{2+}] < 0.9\%$, $[Cu(AlaA\text{-}H)^{+}] < 0.01\%$, $[Cu(AlaA)(AlaA\text{-}H)^{+}] < 0.8\%$, $[Cu(dien)(H\cdot dien)^{3+}] < 0.2\%$.

Further Structural Considerations. Additional information on the structure of the binary and ternary complexes may be gained from their absorption spectral data; these are summarized in Table II,[44-47] together with some results from the

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(44) It is assumed in Table II that Cu^{2+} has six coordination positions and that those not occupied by the donor atoms of the ligand(s) are occupied by water. In certain cases, e.g., in $Cu(AlaA\text{-}H)_2$, it may well be that the apical interactions become extremely weak and that five- or even only four-coordinated complexes result (for such examples see the references cited in the introduction). It may be added in this connection that in a recent crystal structure study of $K[Cu(NH_3)_5](PF_6)_3$ it was shown[45] that the $Cu(NH_3)_5^{2+}$ unit is square pyramidal, in accordance with earlier conclusions,[46] while from X-ray scattering measurements on aqueous Cu^{2+}/NH_3 solutions[47] it follows that both apical positions of Cu^{2+} are occupied. This means the structures of the Cu^{2+} complexes with four or more ammonia groups in aqueous solution are different from those in the solid state.

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Table II. Absorption Maxima, λ_{max}, and Extinction Coefficients, ϵ, for the Cu^{2+} Complexes of L-Alaninamide (AlaA) and Diethylenetriamine (dien) and the Corresponding Mixed-Ligand Complex, together with Some Related Data[a]

no.	complex	λ_{max},[b] nm	ϵ, M^{-1} cm^{-1}	equatorial donor atoms[44]	apical donor atoms[44]
1	$Cu(AlaA)^{2+}$	748	40	N, 3 O	2 O
2	$Cu(AlaA)_2^{2+}$	651	56	2 N, 2 O	2 O
3	$Cu(AlaA\text{-}H)^{+}$	648	56	N, N^-, 2 O	2 O
4	$Cu(AlaA)(AlaA\text{-}H)^{+}$	584	59	2 N, N^-, O	2 O
5	$Cu(AlaA\text{-}H)_2$	516	52	2 N, 2 N^-	2 O
6[c]	$Cu(Gly)_2$	633		2 N, 2 O	2 O
7[c]	$Cu(Gly)_3^-$	662		2 N, 2 O	N, O
8	$Cu(dien)^{2+}$	615	82	3 N, O	2 O
9	$Cu(dien)(OH)^{+}$	605	73	3 N, O	2 O
10[d]	$Cu(dien)(NH_3)^{2+}$	576	84	4 N	2 O
11	$Cu(dien)(H\cdot dien)^{3+}$	610	102	4 N	N, O
12	$Cu(dien)_2^{2+}$	631	110	4 N	2 N
13	$Cu(dien)(AlaA)^{2+}$	592	88	4 N	2 O
14[e]	$Cu(en)_2^{2+}$	550	63	4 N	2 O
15[e]	$Cu(en)_3^{2+}$	~610	~110	4 N	N, O
16[f]	$Cu(NH_3)_4^{2+}$	590	53	4 N	2 O
17[f]	$Cu(NH_3)_5^{2+}$	640	83	4 N	N, O

[a] For abbreviations, see footnote *d* of Table I. The data of this work were obtained at $I = 0.5$ M (KCl) and 25 °C. [b] The range of error resulting from two independent sets of experiments is $\leq \pm 2$ nm. [c] Reference 48. [d] Reference 49. [e] References 48–50. [f] References 20 and 51.

literature.[20,48-51] The present data for the binary dien complexes agree well with those of earlier studies.[22,29]

It is instructive to compare first the absorption maxima of some Cu^{2+} complexes that have four N donors equatorially coordinated with only a solvent interaction in the two apical positions;[44] within the following series the maxima are shifted toward shorter wavelengths: $Cu(NH_3)_4^{2+}$ (Table II, no. 16) > $Cu(dien)(NH_3)^{2+}$ (no. 10) > $Cu(en)_2^{2+}$ (no. 14) > $Cu(AlaA\text{-}H)_2$ (no. 5). This demonstrates that the extent of the shift to lower wavelengths depends on the presence and kind of linkages between the amino donors, i.e., if and how they are linked in chelates; moreover, an ionized amide nitrogen shifts more effectively than an amino nitrogen as is evident from the last two examples (nos. 5 and 14). That replacement of O donors by an increasing number of N donors in the equatorial positions shifts the absorption maxima systematically toward shorter wavelengths is well-known[20] and confirmed by the complexes of nos. 1–5 in Table II. The difference of about 18 nm in the maxima of $Cu(AlaA)_2^{2+}$ (no. 2) and $Cu(Gly)_2$ (no. 6) indicates, as one might expect, that the ligand field strength of a carbonyl oxygen is not quite as pronounced as that of the negatively charged carboxylate oxygen.

The production of a red shift upon an apical N coordination to a complex with four equatorially coordinated nitrogens is also well-known;[20,51] by going from $Cu(NH_3)_4^{2+}$ to $Cu(NH_3)_5^{2+}$ the red shift amounts to 50 nm (nos. 16 and 17 in Table II). The additional coordination of ethylenediamine to the "square-planar" $Cu(en)_2^{2+}$ complex produces also a red shift of about 60 nm; from this and the differences between the stability constants ($\log K^{Cu}_{Cu(en)} = 10.72$, $\log K^{Cu(en)}_{Cu(en)_2} = 9.31$, $\log K^{Cu(en)_2}_{Cu(en)_3} = -1.0$)[52] it was concluded that the third ethylenediamine is only unidentately coordinated to an apical position.[21,52-54] Indeed, the log (stability constant) for the apically coordinated NH_3 to $Cu(NH_3)_4^{2+}$ ($\log K^{Cu(NH_3)_4}_{Cu(NH_3)_5} = -0.5$)[55] is comparable to $\log K^{Cu(en)_2}_{Cu(en)_3} = -1.0$,[52] while the stabilities of the corresponding 1:1 complexes are very different, i.e., $\log K^{Cu}_{Cu(NH_3)} = 4.31$[55] vs. $\log K^{Cu}_{Cu(en)} = 10.72$.[52]

Similarly, the coordination of a further glycinate to $Cu(Gly)_2$, i.e., to a 2 N, 2 O equatorial donor combination, produces also a red shift of about 30 nm (nos. 6 and 7). This together with the stability constants of the Cu^{2+}–glycinate complexes ($\log K^{Cu}_{Cu(Gly)} = 8.12$,[56] $\log K^{Cu(Gly)}_{Cu(Gly)_2} = 6.75$,[56] $\log K^{Cu(Gly)_2}_{Cu(Gly)_3} = 0.4$[56] to 1.3[57]) and the absolute size of the last constant indicates also a unidentate apical coordination predominantly via the amino group of the third glycinate.[58] If all three amino groups of the glycinates would mainly coordinate equatorially, rather, a shift toward lower wavelengths should have been observed.

These observations and conclusions are meaningful with regard to the structure of the ternary $Cu(dien)(AlaA)^{2+}$ complex. From the stability of this complex (Table I) it is clear that the equatorial positions are occupied by four N donors, and from stability comparisons we have obtained already in the previous section a first hint for an additional apical interaction of the carbonyl oxygen of AlaA. That a significant percentage of $Cu(dien)(AlaA)^{2+}$ exists with such an interaction is in line with the red shift of about 16 nm if the absorption maximum of $Cu(dien)(AlaA)^{2+}$ (no. 13 of Table II) is compared with that of $Cu(dien)(NH_3)^{2+}$ (no. 10). This conclusion agrees with a similar suggestion for the structure of ternary complexes formed by $Cu(dien)^{2+}$ and the anion of amino acids;[59] there is also evidence of an apical carboxylate coordination in the Cu^{2+} complexes of 2,3-diaminopropionate[60] and histidinate,[60,61] as well as for carboxylate groups of peptide side chains in Cu^{2+}–peptide complexes.[23]

That in $Cu(dien)(H\cdot dien)^{3+}$ (no. 11) one N is clearly apically coordinated[22] follows also from a comparison of the absorption maximum with that of $Cu(dien)(NH_3)^{2+}$ (no. 10). The red shift is now about 35 nm and hence more pronounced than with $Cu(dien)(AlaA)^{2+}$ (no. 13); indeed, the effect of an apical N coordination is expected to be more pronounced than that of an O coordination. Moreover, the absorption maxima of $Cu(dien)(H\cdot dien)^{3+}$ and $Cu(en)_3^{2+}$ (no. 15) are practically identical. If these results are compared with the absorption maximum of $Cu(dien)_2^{2+}$ (no. 12), it is evident that an additional red shift of about 20 nm has occurred, indicating that all six N donors coordinate. The most plausible arrangement of the two dien ligands seems to be a meridional one.[22] This would also allow, by assuming a dynamic Jahn–Teller distortion,[62] that in an alternating way the three nitrogens of one

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dien are in the favored equatorial positions followed then by those of the other dien.

General Conclusions

On the basis of the apical coordination of pyridine to square-planar Cu^{2+} complexes in benzene it was suggested[63] that such interactions might be relevant for the catalytic properties of Cu^{2+} complexes in biological systems. This possibility cannot be excluded, but it contrasts with the observations made with Cu^{2+} and its complexes in the catalyzed coupling of phenols: free sites at the cupric catalyst are necessary; as soon as four sites are occupied, e.g., in $Cu(en)_2^{2+}$, the complex is no longer a catalyst.[64,65] Correspondingly, in the metal-ion-promoted disproportionation[66] of H_2O_2 or in the superoxide dismutase reaction[67] Cu^{2+} is only catalytically effective as long as the substrate has the possibility to coordinate to the equatorial position(s) of Cu^{2+}. However, it must also be mentioned in this connection that in Cu^{2+}/Zn^{2+} superoxide dismutase one of the axial directions of Cu^{2+} is quite wide open to solvent access;[68-70] one could imagine here also the possibility of some fluxional motion of the coordination sphere.

It is clear from the present results that, in contrast to the earlier claim,[25] there is no indication for an apical coordination of an ionized amide nitrogen in any of the studied binary or mixed-ligand complexes.[4] Thus, in tetragonal Cu^{2+} complexes ionization of amide groups is restricted to equatorial positions. In this connection tetraaza macrocyclic Cu^{2+} complexes with an amide function in a side chain[71,72] should also be mentioned. These complexes do *not*, however, possess the spectral characteristics of tetragonal Cu^{2+} complexes with strong equatorial and weak apical coordination sites. In addition, the amide function is ionized only at pH about 9.9,[71] which is clearly outside of the physiological pH range.

To summarize, there is no indication for the possibility that an apically coordinated ionized amide nitrogen could play any role in biological systems. However, that an apical coordination of amino nitrogens or of oxygen donor sites (including the oxygen of a neutral amide group) is possible in binary and mixed-ligand complexes is clear, and this must also be envisaged for natural systems. Indeed, there are indications that in Cu/Zn superoxide dismutase[70] a water molecule is apically coordinated to Cu^{2+}, while in the Cu^{2+} complex of bleomycin[7-9] an apical position is occupied by an amino group, and in human serum albumin[6] a carboxylate group seems to be coordinated apically to Cu^{2+}.

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Registry No. AlaA, 7324-05-2; dien, 111-40-0; Cu, 7440-50-8.

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