Stabilities of the Copper(II) Complexes with Quadridentate Derivatives of L-Prolinamide and L-Proline Methylamide

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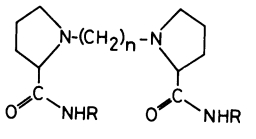
Synopsis. The stability constants of the copper(II) complexes with potentially quadridentate derivatives of L-prolinamide and L-proline methylamide (see text) have been determined by potentiometric titrations. The amide-proton dissociations from the complexes have also been estimated. These were then discussed in terms of the ligand structure and the complex geometry.

Chelating ligands with amide groups have been of considerable interest in connection with the biological signification that the amide group has a character essentially identical with those of peptide bonds in proteins.[1] This work is concerned with the stability of the copper(II) complexes with the potentially quadridentate ligands (shown in Chart 1) which have two L-prolinamide and L-proline methylamide moieties linked by ethylene and trimethylene. Some of the complexes with neutral or anionic amide ligands have exhibited unique absorption, circular dichroism (CD), and ESR spectra very different from those usually observed for ordinary square-planar copper(II) complexes; hence, unusual complex geometries have been postulated for such complexes.[2,3] Therefore, it seemed that it would be worthwhile to estimate the stability of these complexes, to study the ease of the proton dissociation of the amide groups, and to connect them with the ligand structure.



$n=2$	R=H	H_2epa
$n=2$	R=CH_3	H_2epma
$n=3$	R=H	H_2tpa
$n=3$	R=CH_3	H_2tpma

Chart 1. Structure and abbreviations of quadridentate derivatives of L-prolinamide and L-proline methylamide.

Experimental

Reagents. The synthesis and nomenclature of the diamides in Chart 1 have been described in previous papers.[4,5] The stock solutions of the diamides were prepared by the addition of twice equimolar amounts of HCl prior to titration. The $Cu(NO_3)_2$ solution was standardized by chelatometry with edta. The ionic strengths of the sample solutions were adjusted to 0.1 M (1 M=1 mol dm^{-3}) with KNO_3.

pH Titrations. The potentiometric titrations were carried out with a TOA HM-50AT auto pH meter, equipped with a TOA GC-125C multiple electrode and a temperture probe, and a TOA ADT-1 automatic dispenser synchronized with the pH meter. The apparent ion product of water was 0.719×10^{-14} M^2 at I=0.1 M. Solutions (1×10^{-3} M) of ligands only and of copper(II) and each ligand (molar ratio 1:1) were titrated with 0.1 M of NaOH at 25±0.1 °C under moistened N_2. Each titration was run at least three times. Some typical titration curves are shown in Fig. 1.

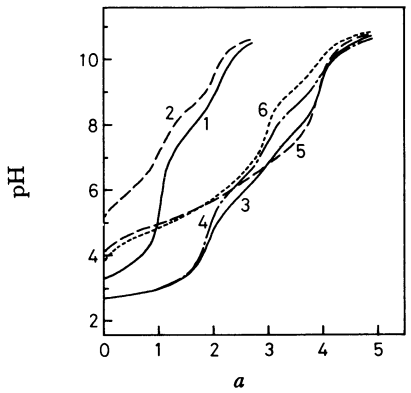


Fig. 1. Typical titration curves for proton-ligand and 1 : 1 Cu(II)-ligand systems. Curves: 1: H_4epa^{2+}, 2: H_4tpa^{2+}, 3: Cu(II)–H_4epa^{2+}, 4: Cu(II)–H_4epma^{2+}, 5: Cu(II)–H_4tpa^{2+}, 6: Cu(II)–H_4tpma^{2+}. a represents moles of NaOH added per mole of ligand.

Calculations. The proton-dissociation process of the protonated ligands occurs in two steps (the charges are omitted for the sake of clarity):

$$H_4L \rightleftharpoons H_3L + H \qquad K_{a_1} = \frac{[H_3L][H]}{[H_4L]}$$

$$H_3L \rightleftharpoons H_2L + H \qquad K_{a_2} = \frac{[H_2L][H]}{[H_3L]}$$

where H_2L represents neutral ligands. The copper(II) ion reacts with the neutral ligands to form Cu (H_2L):

$$Cu + H_2L \rightleftharpoons Cu(H_2L) \qquad K = \frac{[Cu(H_2L)]}{[Cu][H_2L]}$$

Since these ligands possess two amide groups, two protons can be released step-by-step from Cu (H_2L):

$$Cu(H_2L) \rightleftharpoons Cu(HL) + H \qquad K_{a_3'} = \frac{[Cu(HL)][H]}{[Cu(H_2L)]}$$

$$Cu(HL) \rightleftharpoons Cu(L) + H \qquad K_{a_4'} = \frac{[Cu(L)][H]}{[Cu(HL)]}$$

All these constants were calculated by the method of linear least-squares by means of a micro computer.[6]

Results and Discussion

Table 1 lists the obtained data, and also those for 3,7-diazanonanedioic acid diamide (H_2DANA) and its bis-(diethylamide) (H_2 DANEA),[7] which are open-

R-NHCOCH$_2$NHCH$_2$CH$_2$CH$_2$NHCH$_2$CONH-R

R=H: H_2DANA R=C_2H_5: H_2DANEA

chain analogues of H_2tpa and H_2tpma, and for *N,N'*-dimethylethylenediamine(dmen)[8] and *N,N'*-dimethyl-1,3-propanediamine(dmtn).[7]

Table 1. Proton-Dissociation Constants and Stability Constants at 25 °C and I=0.1 M(KNO_3)[a]

Ligand	pK_{a_1}	pK_{a_2}	log K	$pK_{a_3'}$	$pK_{a_4'}$
H_2epa	3.46(1)	7.75(1)	8.03(3)	6.06(1)	7.77(1)
H_2epma	3.31(2)	7.57(1)	7.75(1)	6.50(1)	7.84(2)
H_2tpa	5.31(1)	7.68(2)	6.49(2)	6.44(1)	7.59(2)
H_2tpma	5.70(1)	8.02(1)	7.41(1)	6.74(3)	8.42(3)
H_2DANA[b]	6.55	8.40	10.23	7.14	8.38
H_2DANEA[b]	6.54	8.38	10.73	7.75	11.72
dmen[c]	7.30	10.17	10.09		
dmtn[b]	9.10	10.80	8.38		

a) Values in parentheses denote errors in the last figures, calculated from three different titrations. b) From Ref. 7 (I=0.5 M KCl). c) From Ref. 8 (I=0.5 M KNO_3).

Table 2. Stabilizing Effect in the Linear Relationship between Ligand Basicities and Complex Stabilities

Ligand	ΔpK[a]	Δ_R[b]
H_2epa	3.18	0.05
H_2epma	3.13	
H_2tpa	6.50	0.19
H_2tpma	6.31	
H_2DANA	4.72	0.53
H_2DANEA	4.19	
dmen	7.38	
dmtn	11.52	

a) $\Delta pK = pK_{a_1} + pK_{a_2} - \log K$. b) Δ_R represents the stabilizing effect by the inductive effect of alkyl substituents on the amide group.

Proton Dissociation of Ligand. The K_{a_1} and K_{a_2} values of H_2tpa and H_2tpma are larger than those of H_2DANA and H_2DANEA. This indicates that the steric effect of the methylene groups hindering the proton association on the tertiary amino group is superior to their electron-donating inductive effect, as is commonly observed in going from a secondary to a tertiary amine.

Formation of Cu(H_2L). The inspection of the linear relationship between the proton-dissociation and complex-formation constants of structurally similar ligands[9] often reveals the factor favoring complex formation.[7] Table 2 gives the values of $\Delta pK = pK_{a_1} + pK_{a_2} - \log K$ for the systems studied. A small ΔpK value implies that the stabilizing effect for the complex is more than would be expected from the ligand basicity. For example, the ΔpK values of $Cu(H_2DANA)^{2+}$ and $Cu(H_2DANEA)^{2+}$ are smaller than that of $Cu(dmtn)^{2+}$ by about 7 log units, which indicates a strong stabilizing effect attributable to the noticeable carbonyl coordination forming a 5,6,5-membered trifused chelate.[7] In addition, the inductive effect of the ethyl substituent which increases the electron density on the carbonyl group properly makes $Cu(H_2DANEA)^{2+}$ more stable than $Cu(H_2DANA)^{2+}$ (see Table 2).

Table 2 also shows that $Cu(H_2tpa)^{2+}$ and $Cu(H_2tpma)^{2+}$ have an instability factor of 2 log units compared with $Cu(H_2DANA)^{2+}$ and $Cu(H_2DANEA)^{2+}$. This may be a result of the steric restriction of the pyrrolidine rings, which makes the planar geometry unfavorable[10,11] and, consequently, the carbonyl coordination weaker. The small difference in ΔpK between $Cu(H_2tpa)^{2+}$ and $Cu(H_2tpma)^{2+}$ is other evidence that the carbonyl coordination is weak. The view that these ligands containing pyrrolidine rings act essentially as bidentate in aqueous solutions is supported also by the fact that the stabilizing effect in H_2epa-type complexes is larger than that in H_2tpa-type complexes, just as in the case of the dmen and dmtn complexes. In methanol, however, these neutral ligands seem to act as quadridentate rather than as bidentate[2,3] as a result of the change in the coordination ability of the solvent.

Proton Dissociation from Cu(H_2L). The $pK_{a_3'}$ value corresponding to the first amide-proton dissociation is smaller for the complexes with alkyl-substituted amide groups (Table 1). The electron-donating property of alkyl groups suppresses the proton dissociation.

The second proton dissociation from $Cu(Htpa)^+$ is easier than that from $Cu(Htpma)^+$ because of the ability of dianionic tpa to form a stable planar chelate. For dianionic tpma, the large repulsion between the *N*-methyl groups, in addition to the steric effect of the pyrrolidine rings, forces it to take a non-planar geometry, an unsymmetric cis form.[2,3] Thus, the second amide-proton dissociation takes place in a rather high pH region, corresponding to the inflection at a=3.5 in the titration curve. The tpma complex exhibits the spectral features typical for the tetragonal ligand-field, with a strong apical coordination.[2,3]

Although, in DANEA, the steric repulsion between the amide groups would be almost the same as in tpma, there is no reason why this linear ligand should favor any cis form containing an apical coordination of the ionic amide group.[12,13] Therefore, it is much harder for the second proton dissociation corresponding to $K_{a_4'}$ to occur, and this dissociation has been assigned to a coordinated water.[7]

The complexes with dianionic epa and epma, on the other hand, have been considered, on the basis of their visible and ESR spectra,[2,3] to have a similar

geometry, one highly distorted, probably to a tetrahedral form, from a squre-planar geometry. Whether or not the amide group is methyl-substituted seems to be insignificant for the proton release leading to such a distorted geometry.

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