

292. *The Stabilities of Metal Complexes of Some C-Substituted Derivatives of Glycine.*

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The acid dissociation constants of α -alanine, α -aminoisobutyric acid, and of 1-amino-cyclopentane-, -cyclohexane-, and -cycloheptane-carboxylic acid, and the stabilities of their complexes with bivalent cobalt, nickel, copper, and zinc ions are reported for 20° and $\mu = 0.1M$ -potassium chloride. Correlations between the stability constants are discussed in relation to theoretical predictions and the conformations of the ligands and their metal chelates.

RELATIONSHIPS, based on thermodynamic reasoning, between the stability constants of metal complexes of a closely related series of ligands were first proposed by one of us and Rossotti in 1956.¹ If the complex ML formed by the ligand acid HL has a stability constant defined by $K_{ML} = [ML]/[M][L]$ it was shown, *inter alia*, that, under certain conditions, (a) a plot of $\log K_{ML}$ against $\log K_{ML'}$ for complexes of two ligand acids HL and HL' would be a straight line of unit slope, independent of the nature of the metal M, and (b) a plot of $\log K_{ML}$ against pK_{HL} would also be a line of unit slope for a closely related series of ligands. Examples of these relations were given.¹ Jones, Poole, Tomkinson, and Williams subsequently suggested that such correlations can be fortuitous,² but extensive measurements by Perrin,³ and by Datta, Leberman, and Rabin,^{4,5} have fully established their validity under the conditions originally postulated,¹ and the basic thermodynamic treatment has since been extended.⁶

Most measurements on metal complexes of amino-acids have been made with analogues of glycine in which one or more of the amino-hydrogen atoms or one of the methylene

¹ Irving and Rossotti, *Acta Chem. Scand.*, 1956, **10**, 72.

² Jones, Poole, Tomkinson, and Williams, *J.*, 1958, 2001.

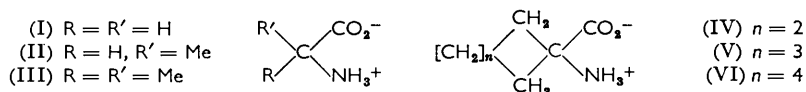
³ Perrin, *J.*, 1958, 3125.

⁴ Datta and Rabin, *Trans. Faraday Soc.*, 1956, **52**, 1117, 1123.

⁵ Datta, Leberman, and Rabin, *Trans. Faraday Soc.*, 1959, **55**, 1982, 2141.

⁶ Leberman and Rabin, *Trans. Faraday Soc.*, 1961, **57**, 785.

hydrogen atoms has been replaced by alkyl groups. We now report measurements on analogues of glycine in which both the methylene-hydrogen atoms have been replaced by alkyl groups (as III) or by an alkylene group (giving a carboxylic ring) (as IV, V, and VI). The compounds studied (I—VI) were prepared by standard methods and their acid



dissociation constants and the stabilities of their complexes with nickel, copper, and zinc were determined by potentiometric titrations at 20.0° in a medium maintained at constant ionic strength 0.1M by additions of "AnalaR" potassium chloride.

EXPERIMENTAL

Materials.— α -Aminoisobutyric acid (α -amino- α -methylpropionic acid) (III). The nitrile prepared ⁷ from sodium cyanide (25 g.), ammonium chloride (30 g.), ammonia (13 ml.; d 0.880), and acetone (36 ml.) in aqueous methanol was hydrolysed with hydrogen chloride, and inorganic salts were removed by evaporation to dryness and leaching of the amino-acid hydrochloride with dry alcohol containing a little ether. An aqueous solution of the hydrochloride was treated with an excess of freshly prepared, hydrated silver oxide to remove chloride ions; the excess of silver was then removed as the sulphide by introducing hydrogen sulphide. The amino-acid was finally recrystallised twice from 95% aqueous ethanol (yield, 28%) and had m. p. 200° (decomp.) (Found: C, 46.8; H, 8.7. Calc. for C₄H₉NO₂: C, 46.6; H, 8.85%).

1-Aminocyclohexanecarboxylic acid (V). The nitrile prepared ⁸ from potassium cyanide (6.5 g.), ammonium chloride (5.4 g.), and cyclohexanone (9.8 g.) was hydrolysed and the resulting amino-acid (20%), when purified as described above, had m. p. 209° (decomp.) (Found: C, 58.8; H, 9.2. Calc. for C₇H₁₃NO₂: C, 58.6; H, 9.1%).

1-Aminocycloheptanecarboxylic acid (VI). This acid, prepared similarly, formed a *monohydrate* (yield 25%), m. p. 215° (decomp.), which was dehydrated at 125° (Found: C, 54.9; H, 9.6. C₈H₁₅NO₂·H₂O requires C, 54.8; H, 9.8%).

1-Aminocyclopentanecarboxylic acid (IV) was a gift from Professor W. C. Fernelius, of Pennsylvania State University, U.S.A.

α -Alanine (II) (B.D.H. analytical grade) was recrystallised from water and dried to constant weight.

Titration Procedures.—Preliminary titrations were carried out with the automatic titrimeter previously described,⁹ in conjunction with a direct reading pH-meter (Electronic Instruments Ltd., model 23). Definitive proton and metal stability constants were calculated from data obtained by titrating solutions (20—30 ml.) of the appropriate amino-acid, in the presence and in the absence of metal ions, with carbonate-free ~5M-potassium hydroxide in a double-walled glass vessel maintained at 20.0° ± 0.05° by the circulation of water from a thermostat-bath. The ionic strength was adjusted to 0.10M with "AnalaR" potassium chloride. The pH of the solution was measured by means of a Radiometer pH-meter, model PHM 4b, with a saturated calomel reference electrode and a glass electrode whose linearity was checked at intervals with standard buffers. The pH-meter was calibrated at pH 4.00 with 0.05M-potassium hydrogen phthalate. Alkali was added from a calibrated 0.50-ml. "Agla" micrometer syringe, and to prevent the ingress of carbon dioxide during the titration a slight positive pressure of nitrogen was maintained by introducing the pre-saturated gas through a tube which terminated just above the surface of the liquid in the titration cell. The ionic strengths of solutions of both amino-acids (usually 0.02M) and metal ions (usually 0.01M) were adjusted to 0.10M with potassium chloride. End-points of titrations were located by Gran's method.¹⁰

Determination of Acid Dissociation Constants.—Hydrochloric acid (20 ml.) of known concentration, C_H, was titrated in the absence and in the presence of a known concentration, C_L, of amino-acid. The results of a typical titration are given in Table 1.

⁷ *Org. Synth.*, 1942, **22**, 13.

⁸ Zelinsky and Stadnikoff, *Ber.*, 1906, **39**, 1728.

⁹ Irving and Pettit, *Analyst*, 1959, **84**, 641.

¹⁰ Gran, *Acta Chem. Scand.*, 1950, **1**, 559.

TABLE 1.

Titration of α -aminoisobutyric acid (III) (20 ml.).

$C_A = 0.0506M$. $C_L = 0.0500M$. Strength of alkali 4.169N.

Vol. alkali added, $V_{alk.}$ (ml.)	0.00	0.02	0.04	0.06	0.08	0.10	0.12	0.14	0.16	0.18				
pH: (a) HCl only	1.33	—	—	—	1.45	—	1.58	—	1.77	1.91				
(b) HCl + ligand	1.85	1.94	2.03	2.13	2.23	2.33	2.44	2.57	2.71	2.87				
$V_{alk.}$	0.20	0.22	0.24	0.26	0.28	0.30	0.32	0.34	0.36	0.38	0.40	0.42	0.44	0.46
pH (a)	2.07	2.34	3.10	11.57	11.90	—	—	—	—	—	—	—	—	—
(b)	3.07	3.38	4.24	9.11	9.50	9.75	9.93	10.10	10.24	10.39	10.54	10.70	10.89	11.12

The degrees of formation of the ligand-proton complexes, \bar{n}_H , and the dissociation constants of the corresponding acids were calculated by Irving and Rossotti's method¹¹ with the results given in Table 2, where the pH values have been interpolated from a large-scale graph.

TABLE 2.

pH	1.90	2.00	2.10	2.20	2.30	2.40	2.50	2.60	2.70	2.80	2.90
\bar{n}	1.726	1.679	1.629	1.578	1.532	1.468	1.414	1.363	1.317	1.270	1.228
pK_1	2.33	2.33	2.33	2.34	2.35	2.34	2.35	2.35	2.36	2.36	2.37
pH	9.30	9.40	9.50	9.60	9.70	9.80	9.90	10.00	10.10	10.20	10.30
\bar{n}	0.897	0.873	0.844	0.810	0.776	0.734	0.692	0.641	0.591	0.541	0.491
pK_2	10.24	10.24	10.23	10.24	10.24	10.25	10.25	10.25	10.25	10.25	10.25
pH	10.20	10.30	10.40	10.50	10.60	10.70	10.80	10.90	11.00	11.10	11.20
\bar{n}	0.536	0.477	0.418	0.363	0.312	0.266	0.223	0.185	0.147	0.110	0.073
pK_2	10.26	10.26	10.26	10.26	10.26	10.26	10.26	10.26	10.26	10.26	10.26

Average values are $K_1 = [H^+][HL^\pm]/[H_2L^+] = 10^{-2.35}$, and $K_2 = [H^+][L^-]/[HL^\pm] = 10^{-10.25}$. Calculated values for other ligands are summarised in Table 3. The apparatus and procedure were checked by determining the acid dissociation constants of glycine. The values found, $pK_1 = 2.27$, $pK_2 = 9.86$, agree well with those previously reported¹² ($pK_1 = 2.24$, $pK_2 = 9.85$).

TABLE 3.

Stability constants of metal complexes of α -amino-acids at 20.0° and $\mu = 0.1M$ -KCl.

Ligand	(I)	(II)	(III)	(IV)	(V)	(VI)
pK_1 (H_2L^+)	2.24 *	2.30	2.35	2.40 (2.54) §	2.41 (2.27)	2.59 (2.67)
pK_2 (HL^\pm)	9.85	9.93	10.25	10.31 (10.33)	10.13 (9.83)	10.46 (9.78)
<i>Copper complexes</i>						
$\log \beta_1$	8.12 *	8.15	8.26	8.63	8.59	8.62
$\log K_{ML_2}$	6.91	6.78	6.84	7.29	7.26	7.37
$\log \beta_2$	15.03	14.93	15.10	15.92	15.85	15.99
<i>Nickel complexes</i>						
$\log \beta_1$	5.73 *	5.40	5.16	5.60	5.50	5.33
$\log K_{ML_2}$	4.76	4.50	4.23	4.63	4.55	4.5
$\log \beta_2$	10.49	9.90	9.39	10.23	10.05	9.8
<i>Zinc complexes</i>						
$\log \beta_1$	5.16 *	4.55	4.55	4.76	4.78	4.61
$\log K_{ML_2}$	4.34	4.1	4.0	4.4	4.4	4.6
$\log \beta_2$	9.50	8.7	8.6	9.2	9.2	9.2
<i>Cobalt complexes</i>						
$\log \beta_1$	5.1 †	4.32	4.11	4.46	4.47	4.17
$\log K_{ML_2}$	3.8	3.6	3.4	3.7	3.7	3.7
$\log \beta_2$	8.9	7.9	7.5	8.2	8.15	7.9
<i>Calcium complexes</i>						
$\log \beta_1$	1.43	1.24 ‡	—	—	1.2	—

* Irving, Williams, Ferrett, and Williams, *J.*, 1954, 3494. † Albert, *Biochem. J.*, 1950, 47, 531; valid for $\mu = 0.01M$. ‡ Davies and Waind, *J.*, 1950, 301; valid for 25° and $\mu \rightarrow 0$. § The values in parentheses were calculated from the pH of solutions of ligand (at 20° and $\mu = 0.1$) half-neutralised with hydrochloric acid or sodium hydroxide (Munday, *J.*, 1961, 4372).

¹¹ Irving and Rossotti, *J.*, 1954, 2904.¹² Irving, Williams, Ferrett, and Williams, *J.*, 1954, 3494.

Determination of Metal-Ligand Stability Constants.—A known concentration, C_L , of the appropriate amino-acid was titrated in the absence, and in the presence, of a known concentration, C_M , of metal ions. The ratio $C_L : C_M$ was usually 2 : 1 to favour the formation of complexes of the formula ML_2 . The degrees of formation of the metal complexes, \bar{n} , were calculated from the titration curves by Irving and Rossotti's difference method,¹¹ and values for the free ligand exponent were obtained from the equation

$$pL = \log_{10} \frac{\{1 + ([H^+]/K_2) + ([H^+]^2/K_1K_2)\}}{(C_L - \bar{n} \cdot C_M)}$$

Stability constants for metal complexes were then calculated from pairs of values of \bar{n} and pL by Irving and Rossotti's correction-term method¹³ provided that the formation curve extended beyond $\bar{n} = 1.5$ before precipitation had occurred. Otherwise they were calculated from the equation to the straight line

$$\bar{n}/(2 - \bar{n})[L^-]^2 = (1 - \bar{n})\beta_1/(2 - \bar{n})[L^-] + \beta_2, \quad (1)$$

the best values of the gradient, β_1 , and intercept, β_2 , being calculated by the method of least squares. The results of a typical experiment are given in Table 4.

TABLE 4.

Titration of α -aminoisobutyric acid in the presence of copper ions.
Initial volume = 20.0 ml.; $C_H = 0.0125M$; $C_L = 0.0200M$; $C_M = 0.0100M$;
Strength of alkali = 1.726N.

pH	3.0	3.2	3.4	3.6	3.8	4.0	4.2	4.4	4.6	4.8
\bar{n}	0.147	0.208	0.295	0.384	0.498	0.607	0.714	0.830	0.938	1.035
pL	9.120	8.892	8.688	8.493	8.314	8.138	7.969	7.806	7.646	7.488
pH	5.0	5.2	5.4	5.6	5.8	6.0	6.2	6.6	7.0	7.4
\bar{n}	1.138	1.241	1.336	1.431	1.500	1.587	1.635	1.759	1.828	1.879
pL	7.335	7.190	7.048	6.914	6.772	6.654	6.532	6.287	6.034	5.787

TABLE 5.

Metal complexes of 1-aminocyclohexanecarboxylic acid.

	Copper		Nickel		Zinc	
C_L (M)	0.0500	0.0196	0.0500	0.0196	0.0500	0.0196
$\log K_{ML}$	8.60	8.59	5.53	5.50	4.82	4.78
$\log K_{ML_2}$	7.26	7.26	4.55	4.55	4.50	4.45

Calculated values of metal stability constants are summarised in Table 3. In many cases the titrations were repeated with fresh solutions of acid, ligand, metal, and alkali, and excellent agreement was obtained as illustrated by the results in Table 5 for the metal complexes of 1-aminocyclohexanecarboxylic acid (V).

RESULTS AND DISCUSSION

The formation curves (cf. Fig. 1) showed that values of $\log K_{ML}$ and $\log K_{ML_2}$ were not widely separated. The presence of 1 : 1 and 1 : 2 complexes was established with all three metals and there was evidence for 1 : 3 complexes with nickel. Equilibrium was always established very slowly in the presence of nickel, possibly owing to the slow dissociation of NiL_3 which would tend to be formed at the point where alkali is introduced into solution. Oxidation of cobalt(II) to cobalt(III) at high pH values was detected by the appearance of a violet colour and by deviations from the straight line predicted by eqn. (1); values which deviated from this relationship were therefore rejected. Deep-blue solutions were obtained in all titrations with copper, but a precipitate containing carbon was formed with 1-aminocycloheptanecarboxylic acid at pH 4.5; since this did not occur until \bar{n} had exceeded the value 1.4 quite accurate values for both stability

¹³ Irving and Rossotti, *J.*, 1953, 3397.

constants could be calculated. When the titration was repeated with a different metal: ligand ratio (1:2.5), the derived formation curve was identical, thus establishing the absence of polynuclear complexes. Precipitation took place at approximately the same pH.

Replacement of the methylene-hydrogen atoms in glycine is seen to produce a small but regular increase in pK_1 , the increase being larger as the substituent in the glycine skeleton becomes larger. This is the expected consequence of electron repulsion by the alkyl groups. There is a similar trend in values of pK_2 , save with the cyclohexane derivative (V) where the ammonium-hydrogen atom is more acidic than expected to the extent

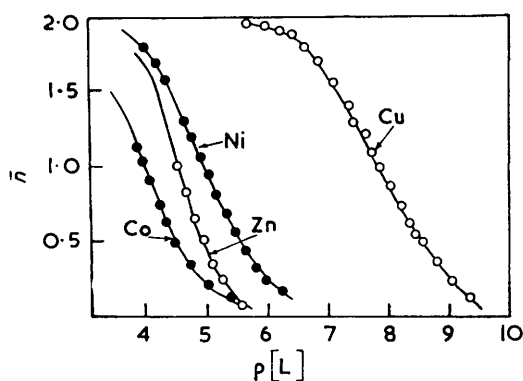


FIG. 1. Formation curves for complexes of 1-aminocyclohexanecarboxylic acid. The solid lines are drawn from the stability constants listed in Table 3.

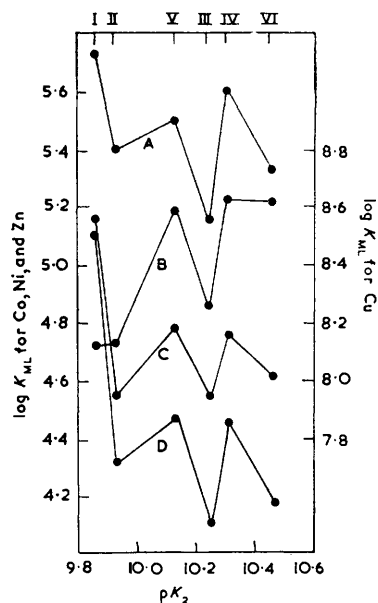
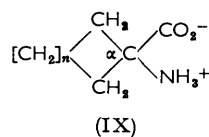
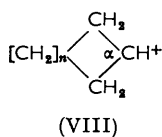
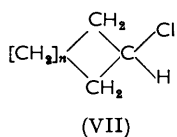


FIG. 2. Variations in the value of $\log K_{ML}$ for 1:1 complexes of the ligands (I)–(VI) with the basicity of the amino-nitrogen atoms as measured by pK_2 .

(A) Ni^{2+} . (B) Cu^{2+} . (C) Zn^{2+} . (D) Co^{2+} .

of about 0.2 log unit. That this effect was real was confirmed by redetermining the dissociation constants with different concentrations of acid, whereupon the calculated pK values did not vary by more than 0.01 log unit. Work on the stabilities of aliphatic rings may provide an explanation for this increased acidity, as Brown and Borkowski¹⁴ observed



that hydrolysis of compounds of the type (VII) proceed at comparable rates with cyclopentane and cycloheptane derivatives ($n = 2$ or 4) whilst that of chlorocyclohexane was about 100 times slower. This difference was attributed to distortion of bond angles, for if the hydrolysis is a first-order reaction the intermediate ion (VIII) will have a bond

¹⁴ Brown and Borkowski, *J. Amer. Chem. Soc.*, 1952, **74**, 1894.

angle of $\alpha = 120^\circ$. This will stabilise the cyclopentane and cycloheptane rings but decrease the stability of the previously strainless cyclohexane ring. Hence reactions involving such intermediates will be less favourable in the case of cyclohexane derivatives. Many other similar examples of this effect have been cited.¹⁵ With the ion ${}^+\text{HL}^-$ derived from (V) (as IX; $n = 3$) the mutual attraction of the oppositely charged groups will decrease the angle β , so increasing α and decreasing the stability of the cyclohexane ring. When ionisation of the second proton takes place, to give the ion L^- , the mutual attraction will cease, thus allowing the energy of the cyclohexane ring to return to its normal value. Hence the reaction



will be favoured and the value of $\text{p}K_2$ will be depressed. No similar effect would be predicted for the cyclopentane or cycloheptane derivatives. A further factor which could promote the observed higher acidity is the energy difference between the "boat" and the "chair" conformation of the cyclohexane ring. Scale models show that with the ion ${}^+\text{HL}^-$ the boat conformation has only one axial hydrogen atom which could interfere with the NH_3^+ or CO_2^- group, while the chair conformation has two. This will tend to stabilise the boat conformation and so encourage the ionisation shown in eqn. (2).

For the metal chelates the stability order is $\text{Co} < \text{Zn} < \text{Ni} < \text{Cu}$ for both K_{ML} and K_{ML_2} . A plot of $\log K_{\text{ML}}$ against corresponding values of $\log K_{\text{ML}'}$, where HL and HL' represent the ligands (III) and (IV) and $\text{M} = \text{Ni}^{2+}$, Co^{3+} , Cu^{2+} , and Zn^{2+} approximates to a straight line of unit slope which also includes values for $\text{M} = \text{H}^+$. Plots (not reproduced) for the pairs of ligands (III) and (V), and (III) and (VI) are similar. On the other hand, there is no simple linear relation between $\log K_{\text{ML}}$ and $\text{p}K_{\text{HL}}$ (Fig. 2), and indeed increase in the basicity of the nitrogen atom in L does not always produce an increase in the value of K_{ML} .

In an extensive series of papers^{4,5} Datta, Leberman, and Rabin report measurements of the stabilities of metal complexes derived from three series of ligands based on the parent compound $\text{R}\cdot\text{NH}\cdot\text{CHR}'\cdot\text{CO}\cdot\text{X}$ where X had a wide variety of structures, e.g., O^- (amino-acid), NH_2 (amino-amide), $\text{NH}\cdot\text{CH}_2\cdot\text{CO}_2^-$ (dipeptide), etc. The three series were glycyl ($\text{R} = \text{R}' = \text{H}$), sarcosyl ($\text{R}' = \text{H}$, $\text{R} = \text{Me}$), and leucyl ($\text{R} = \text{H}$, $\text{R}' = \text{Me}_2\text{CH}\cdot\text{CH}_2$). Excellent linear relations between $\text{p}K_2$ (amino) and $\log_{10} K_{\text{ML}}$ were demonstrated for each of these series with any single metal ion, e.g., Co^{2+} , Mn^{2+} , or Cu^{2+} , doubtless because modifications in X influenced only $\text{p}K$ values of the ligand without seriously modifying the structure of the chelated complex. Perrin³ has found a reasonably good linear relation for complexes of ferric iron with α -amino-acids, $\text{NH}_2\cdot\text{CHR}\cdot\text{CO}_2\text{H}$. The relation, $\log K_{\text{ML}} = 1.8\text{p}K_2 - 7.5$, fits data for complexes of Fe^{3+} with α -amino-acids of this type. Aspartic and glutamic acid give complexes of much higher stability than predicted, probably because they are terdentate. Ligands in which an amino-nitrogen atom is substituted (sarcosine, proline, and hydroxyproline) form less stable complexes and lead to a separate correlation line.³ Leberman and Rabin have also commented on the effect of replacing a hydrogen atom by a methyl group in their comparison of glycyl and sarcosyl complexes.⁶ Although the basicity of the α -amino-group is increased and hence its donor properties, the tendency to form more stable metal complexes is outweighed by other factors.

In the present series of compounds we note that despite the increased basicity of the nitrogen in acids (II) and (III) compared with glycine (I) there is little apparent change, or even a decrease, in the stability of the metal chelates. To take into account these changes in basicity we compare equilibrium constants K' and K'' for the reactions



¹⁵ Brown, Brewster, and Shechter, *J. Amer. Chem. Soc.*, 1954, **76**, 467

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which are given, respectively, by $pK' = pK_2 - \log K_{ML}$, and $pK'' = pK_2 - \log K_{ML_2}$. Values of pK' and pK'' are shown in Table 6.

TABLE 6.

Values of pK' and pK'' for the equilibrium constants of reactions 3 and 4.

Ligand	(I)	(II)	(III)	(IV)	(V)	(VI)	
pK'	Cu	1.7	1.8	2.0	1.7	1.5	1.8
	Ni	4.1	4.5	5.1	4.7	4.6	5.1
	Zn	4.7	5.4	5.7	5.6	5.4	5.9
	Co	4.8	5.6	6.1	5.9	5.7	6.3
pK''	Cu	3.0	3.2	3.4	3.0	2.9	3.1
	Ni	5.1	5.4	6.0	5.7	5.6	6.0
	Zn	5.5	5.8	6.3	5.9	5.7	5.8
	Co	6.0	6.3	6.9	6.6	6.4	6.8

The increase in the values of pK' or pK'' compared with values for glycine (I) indicate a decrease in metal-ligand stability relative to that of the proton-ligand complex. Since the amino-acids are so similar in structure and contain the same five-atom chelate rings it is probable that the differences are primarily steric in origin, arising because the substituents on the carbon atom distort bond angles or lengths and force the chelate ring into a less favourable conformation. Since the ratio K_{ML}/K_{ML_2} is approximately constant for all the chelates of each metal studied it appears that, in this series, the conformational factors involved in the formation of the first chelate ring do not significantly influence the attachment of the second.

Complexes of the amino-acids (II) and (III) are less stable than those of glycine (I). This would arise if the substituents on the α -carbon atom [particularly in the *gem*-dimethyl group of (III)] distort the bond angle between the remaining two bonds which participate in the chelate ring. Corey and Bailar¹⁶ have shown that the chelate ring formed by an amino-acid, in contrast to that formed by ethylenediamine, is essentially planar. Further ring-flattening cannot therefore occur and any decrease in the angle subtended by the α -carbon atom in the chelate ring must lower the stability of the metal complex. The same explanation is clearly applicable to *NN'*-ethylenedi-(α -aminopropionic acid) $HO_2C \cdot CHMe \cdot NH \cdot C_2H_4 \cdot NH \cdot CHMe \cdot CO_2H$ which forms weaker complexes with a number of metals than does *NN'*-ethylenediglycine $HO_2C \cdot CH_2 \cdot NH \cdot C_2H_4 \cdot NH \cdot CH_2 \cdot CO_2H$.¹⁷

The metal chelates formed by the cyclic amino-acids (IV)—(VI) do not vary much in stability from ligand to ligand and tend to be more stable (relative to glycine) than are complexes with the ligand (III) which contains the *gem*-dimethyl group. This is not unexpected since, while free rotation about the C-Me bonds in the methyl-substituted glycines is possible, the methylene groups of the cyclic acids will be locked in one of two possible conformations. A freely rotating methyl group would naturally sweep out a larger volume than does a fixed methylene group and the latter would adopt the most favourable conformation. Although the proton affinity of the ligand (V) containing the cyclohexane ring ($pK_{+HL^-} = 10.13$) is less than those of the ligands (IV) and (VI) ($pK_{+HL^-} = 10.31$ and 10.46 , respectively) all three ligands form metal complexes of much the same stability. Reasons have been given why the value of pK_2 for (V) is lower than that for the other cyclic amino-acids, and if a value greater by 0.2 log unit had been used in the calculation of pK' and pK'' the anomaly would have disappeared.

Since the zwitterion $^+HL^-$ has a large range of existence (pH \sim 2—10) there is also the possibility that the 1:1 complex ML^+ would take up a proton to form MHL^{2+} at high acidities. Such a species would be most likely with copper where the reaction $Cu^{2+} + ^+HL^- \rightarrow CuL^+$ is detectable at pH as low as 2.8. The species $CuHL^{2+}$ would not be expected to be very stable since the nitrogen atom will no longer be able to form a bond

¹⁶ Corey and Bailar, *J. Amer. Chem. Soc.*, 1959, **81**, 2620.

¹⁷ Irving, Shelton, and Evans, *J.*, 1958, 3540.

to copper and the ligand $^+NH_3 \cdot CH_2 \cdot CO_2^-$ will be effectively monodentate. Curchod¹⁸ has measured the stability of the complex $CuHL^{2+}$, where L is α -alanine, by using successive approximations. Similar calculations programmed with the electronic computer "Mercury" led to the values of $K_{CuHL}^{Cu} = [CuHL^{2+}]/[CuL^+][H^+]$ listed in Table 7.

TABLE 7.

Stability constants of protonate complexes of α -amino-acids.

Ligand	(II) *	(II) †	(III) ‡	(IV) ‡	(VI) ‡
$\log K_{CuHL}^{Cu}$	0.57	0.72	1.2	1.9	1.1
$\log K_{CuL}^{Cu}$	7.51	8.07	8.29	8.72	8.74
$\log K_{CuL_2}^{Cu}$	6.52	6.72	6.81	7.35	7.26

*† Data for 25° and $\mu = 3.0M$ - and $0.375M$ - K_2SO_4 , respectively (ref. 16). ‡ Present paper; data valid for 20° and $\mu = 0.1M$ -KCl.

Our values for K_{CuHL}^{Cu} show how weak the complexes are between cupric ions and the monodentate zwitterions. Since $\log K_{CuHL}^H = \log K_{CuHL}^{Cu} + pK_2 - \log K_{CuL}$ it can be shown that the protonated species $CuHL^{2+}$ formed by the ligands (III), (IV), and (VI) are moderately strong acids with $pK = 3.2, 3.6,$ and $2.9,$ respectively. Since we have established the existence of protonated complexes in solutions of low pH we can calculate values of the three constants $K_{MHL}, K_{ML},$ and K_{ML_2} that best represent the whole course of the titration curve. The recalculated values for K_{ML} and K_{ML_2} , shown in Table 7 did not differ significantly from those of Table 3, but they actually showed a larger standard deviation since the values computed electronically oscillated by up to 0.1 log unit between successive cycles of approximation.

We have commented elsewhere on the solubilities of the various copper bis-chelates in water.¹⁹

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¹⁸ Irving and Pettit, *Chem. and Ind.*, 1960, 1268.

¹⁹ Curchod, Doctoral Thesis, Paris, 1956.