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Steric Effects and the Stability of Complex Compounds. III. The Chelating Tendencies of N-Alkylglycines and N-Dialkylglycines with Copper(II) and Nickel(II) Ions[1]

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The effect of steric hindrance on the chelating tendencies of some amino acids with copper(II) and nickel(II) ions has been investigated using N-alkylglycines and N-dialkylglycines. The stepwise formation constants of these two ions with $RNHCH_2COOH$ (R = H, CH_3, C_2H_5, n-C_3H_7, n-C_4H_9 and i-C_3H_7) and R_2NCH_2COOH (R = CH_3 and C_2H_5) were determined at 25°. The complex stability of the straight chained N-alkylglycines is less than that of glycine. There is a rapid decrease to N-ethylglycine followed by practically no further change with increasing chain length of the alkyl group. The chelating ability of N-dimethylglycine is comparable to N-ethylglycine but that of N-diethylglycine is smaller. The least stable complexes were formed with the branched chain alkyl derivative, N-isopropylglycine.

The effect of steric hindrance on the chelating tendencies of N-substituted ethylenediamines toward copper(II) and nickel(II) was reported earlier.[2] This paper deals with chelating molecules of a different kind, namely, the N-substituted glycines which in solution exist as zwitterions. All the metal complexes derived from these zwitterions were sufficiently soluble to be studied in water solutions.

Stepwise formation constants for complexes of copper(II) and nickel(II) ions with N-alkylglycines and N-dialkylglycines were determined by the method of Bjerrum.[3] Both the effect of increasing chain length of a straight chain alkyl group and that of introducing a branched chain on the chelating tendency of substituted glycines were investigated.[4]

Experimental

Reagents.—Copper(II) perchlorate, nickel(II) perchlorate, perchloric acid and sodium perchlorate used in this study were of reagent grade. Glycine and sarcosine obtained commercially were of C.P. grade and were recrystallized twice from 50% ethyl alcohol.

EG and n-PG were prepared by the method of Crocker.[5] The products were converted to the corresponding hydrochloride salts in view of their highly hygroscopic property.

i-PG, n-BG and E_2G were prepared by the method of Kuebler and Bailar.[6] The hydrochloride salts were recrystallized several times from absolute alcohol and absolute ether (i-PG from 95% alcohol).

M_2G was prepared by the method of Pearson and Bruton.[7] The product was recrystallized from absolute alcohol and twice from glacial acetic acid.

The melting points (with decomposition), analyses and yields of the hydrochloride salts of these amino acids are summarized in Table I.

Standard Solutions.—Standard solutions of copper(II) perchlorate and nickel(II) perchlorate were prepared which contained approximately 0.005 M metal ion and 0.05 M perchloric acid. The exact concentration of the metal ions was determined by the methods described previously.[2a]

Standard solutions of the amino acids were prepared directly from the vacuum-dried compound and dissolved in water in a volumetric flask to which was added a calculated amount of sodium perchlorate. These standard solutions contained approximately 0.02 M amino acid and 0.20 M $NaClO_4$.

Dissociation Constants of the Amino Acids.—The dissociation constants of these amino acids were determined by titrating 25.00 ml. of the standard solution (diluted with an equal volume of water) with standard acid and with standard base. Separate samples were used for each titration. Measurements were made with a Beckman pH meter, Model G, equipped with extension electrodes. The pK values were calculated by the following formulas[8]

$$pK_{\mathrm{COOH}} = p\mathrm{H} - \log\left(\frac{C}{A - [\mathrm{H}^+]} - 1\right) \qquad (1)$$

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[1] This investigation was supported by a grant-in-aid from the National Institutes of Health, Grant No. G-3239.

[2] (a) F. Basolo and R. K. Murmann, THIS JOURNAL, **74**, 5243 (1952); (b) **75**, 211 (1953).

[3] J. Bjerrum, "Metal Ammine Formation in Aqueous Solutions," P. Haase and Son, Copenhagen, 1941.

[4] The amino acids studied are designated as follows: G = glycine, MG = N-methylglycine (sarcosine), EG = N-ethylglycine, n-PG = N-n-propylglycine, i-PG = N-isopropylglycine, n-BG = N-n-butylglycine, M_2G = N-dimethylglycine and E_2G = N-diethylglycine.

[5] W. Crocker, *J. Chem. Soc.*, 1693 (1937).

[6] J. R. Kuebler and J. C. Bailar, Jr., THIS JOURNAL, **74**, 3525 (1952).

[7] D. E. Pearson and J. D. Bruton, *ibid.*, **73**, 864 (1951).

[8] C. L. A. Schmidt, "Chemistry of the Amino Acids and Proteins," C. C. Thomas, 1938, p. 604.

TABLE I

N-ALKYLGLYCINE AND N-DIALKYLGLYCINE HYDROCHLORIDES

Amino acids	M.p., °C.	Yield, %	Analyses, % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found	Nitrogen Calcd.	Nitrogen Found	Chlorine Calcd.	Chlorine Found
EG	176–178	20	34.41	34.33	7.17	7.16	10.04	10.71	25.45	25.46
n-PG	199–200	35	39.09	39.18	7.82	8.10	9.12	9.53	23.13	23.56
n-BG	204–205	70	43.03	43.23	8.40	8.45	8.40	8.96	21.15	21.40
i-PG	205–207	78	39.09	39.50	7.82	7.91	9.12	8.97	23.13	23.25
M_2G	187–189	75	34.41	34.84	7.17	7.27	10.04	10.12	25.45	25.51
E_2G	125–126	57	43.03	43.12	8.40	8.41	8.40	8.40	21.15	21.25

and

$$pK_{R_2NH^+} = pH + \log\left(\frac{C}{B - [OH^-]} - 1\right) \qquad (2)$$

where

C = concn. of the amino acid
A = concn. of standard acid added to the soln.
B = concn. of standard base added to the soln.

Formation Constants.—In the determination of formation constants, equal volumes (25.00 ml.) of standard metal ion solution and standard amino acid solution were mixed and titrated with standard KOH solution from a microburet. The pH values were measured with a Beckman pH meter as previously described.[2a] The data thus obtained were calculated by the method of Maley and Mellor.[9] It should be mentioned that when the hydrochloride salt of the amino acid was used, it was necessary to correct for the volume of standard base required to neutralize the HCl.

Results.—The acid dissociation constants of the N-alkylglycines and N-dialkylglycines at 25° are listed in Table II.

TABLE II

DISSOCIATION CONSTANTS FOR N-SUBSTITUTED GLYCINES (25°)

	pK_{COOH}	$pK_{R_2NH^+}$		pK_{COOH}	$pK_{R_2NH^+}$
G[a]	2.43	9.62	*n*-BG	2.29	10.07
MG[a]	2.24	10.01	*i*-PG	2.36	10.06
EG	2.30	10.10	M_2G[a]	2.08	9.80
n-PG	2.28	10.03	E_2G	2.04	10.47

[a] G, pK_{COOH} = 2.34, $pK_{R_2NH^+}$ = 9.60 (E. J. Czarnetsky and C. L. A. Schmidt, *Z. physik. Chem.*, **204**, 129 (1932); MG, pK_{COOH} = 2.23, $pK_{R_2NH^+}$ = 10.01 (P. A. Levene, H. S. Simms and M. H. Pfaltz, *J. Biol. Chem.*, 61, 445 (1924); M_2G, pK_{COOH} = 1.94, $pK_{R_2NH^+}$ = 9.86 (J. Johnston, *Proc. Roy. Soc.* (*London*), **A78**, 101 (1906).

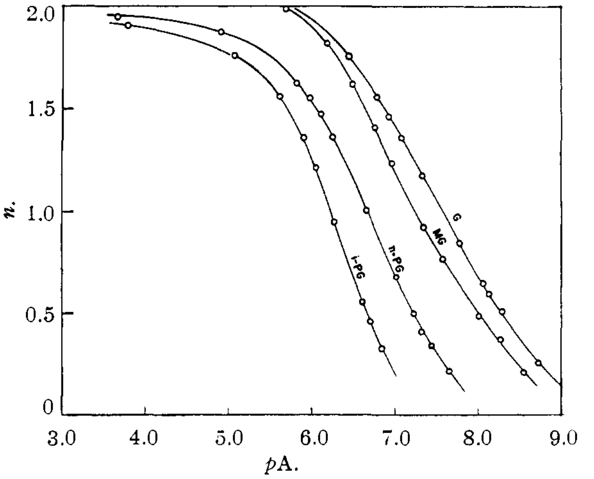

Fig. 1.—Formation curves of copper(II) with N-alkylglycines (25°).

Examples of formation curves for some of the copper(II) and nickel(II) complexes are illustrated in Figs. 1 and 2, respectively. The formation (concentration) constants obtained are listed in Table III.

Discussion

The concentration dissociation constants of glycine and the N-substituted glycines as determined in 0.1 M $NaClO_4$ at 25° are summarized in Table II. The values of pK_{COOH} for all N-alkylglycines are approximately the same as is to be expected. Similarly N-dimethylglycine and N-diethylglycine have essentially the same acid strengths. It is however somewhat surprising that the acid strength of the carboxylic acid group increases slightly with progressive replacement of the hydrogen atoms attached to the nitrogen of glycine with alkyl groups. One would expect the normal inductive effect of the alkyls to slightly increase the electron density on the oxygen and give rise to a weaker acid. Since the experimental facts are that the acid strength actually increases with increasing alkyl substitution, it would appear that changes in solvation energies are more important than the inductive effects.[10]

The values of $pK_{R_2NH^+}$ are approximately the same for all of the N-alkylglycines investigated and it is to be expected that these amine groups should have similar base strengths. That they are slightly stronger bases than glycine is in accord with the greater base strength of dialkylamines as compared to alkylamines. The decrease in base strength in going from N-methylglycine to N-dimethylglycine is also consistent with the base

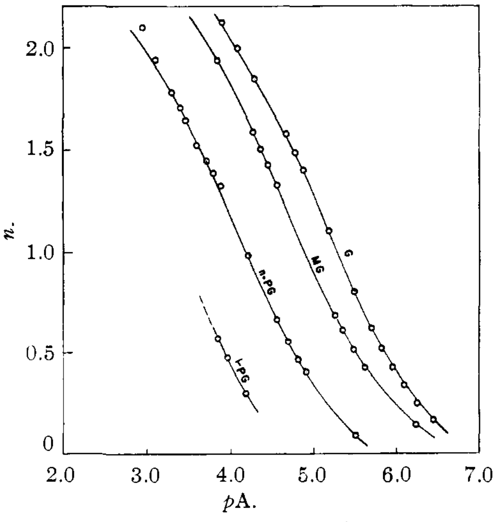

Fig. 2.—Formation curves for nickel(II) with N-alkylglycines (25°).

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[9] L. E. Maley and D. P. Mellor, *Aust. J. Sci. Res.*, **A2**, 579 (1949).

[10] G. Branch and M. Calvin, "Theories of Organic Chemistry," Prentice-Hall, Inc., New York, N. Y., 1941, p. 229.

TABLE III

FORMATION CONSTANTS OF COPPER(II) AND NICKEL(II) WITH N-SUBSTITUTED GLYCINES (25°)

	Copper(II)					Nickel(II)				
Amino acid	log K_1	log K_2	log K_T	$\log \frac{K_1G}{K_1XG}$	$\log \frac{K_2G}{K_2XG}$	log K_1	log K_2	log K_T	$\log \frac{K_1G}{K_1XG}$	$\log \frac{K_2G}{K_2XG}$
G[a]	8.38	6.87	15.17	..	..	5.86	4.78	10.64	..	..
MG	7.94	6.65	14.59	0.44	0.22	5.50	4.38	9.88	0.36	0.40
EG	7.34	6.21	13.55	1.04	.66	4.81	3.73	8.54	1.05	1.05
n-PG	7.25	6.06	13.31	1.13	.81	4.79	3.67	8.46	1.07	1.11
n-BG	7.32	6.20	13.52	1.06	.67	4.76	3.62	8.38	1.10	1.16
M_2G	7.30	6.35	13.65	1.08	.52	4.82	3.78	8.60	1.04	1.00
E_2G	6.88	5.98	12.86	1.50	.89	4.21	..	...	1.65	..
i-PG	6.70	5.75	12.45	1.68	1.12	3.94	..	...	1.92	..

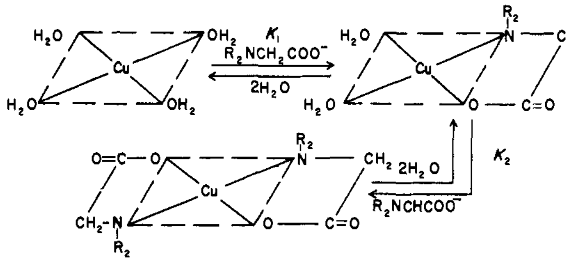
[a] Previous references to measurements on glycine complexes under different conditions are tabulated in A. E. Martell and M. Calvin, "Chemistry of Metal Chelate Compounds," Prentice–Hall, Inc., New York, N. Y., 1952, p. 528.

strength of trimethylamine being lower than that of dimethylamine.[11]

The data in Table III show clearly that the chelating tendency of the N-alkylglycines is less than that of glycine. This decreasing tendency drops through the methyl to the ethyl derivative after which it virtually levels off through the N-*n*-butylglycine. It is also apparent from these data that the branched chain alkyl group, isopropyl, gives rise to the maximum steric effects of all the compounds studied. Thus the least stable complexes of copper(II) and nickel(II) are formed with N-isopropylglycine. The chelating tendency of N-dimethylglycine is comparable to that of N-ethyl, N-*n*-propyl and N-*n*-butylglycines. However complexes of N-diethylglycines are less stable than those of N-dimethylglycines. That this difference is in some measure caused by an increase in steric hindrance is supported by the abnormally large base strength of the amine group in N-diethylglycine which would be expected to enhance its chelating ability.

A comparison of log K_1 and log K_2 for glycine with those for each of the substituted glycines is afforded in columns log K_1G/K_1XG and log K_2G/K_2XG of Table III. The values for log K_1G/K_1XG are a measure of the effect that substitution on glycine has upon the chelating tendencies of these amino acids with copper(II) and nickel(II) ions. It is apparent that the effect of one methyl group is only approximately one-third that of the next three straight chain alkyls or of two methyl groups. The steric effect is larger with the diethyl derivative and reaches a maximum in N-isopropylglycine. It is also of interest that the results with $[Cu(H_2O)_4]^{+2}$ and $[Ni(H_2O)_6]^{+2}$ are very similar.

The values observed for log K_2G/K_2XG should furnish some indication as to the effect of increasing steric hindrance upon the entrance of the second substituted glycine into the coördination sphere as compared to glycine itself. Earlier work on N-alkylethylenediamines[2a] and N,N′-dialkylethylenediamines[2b] showed that the presence of one molecule of the diamine in the complex offered greater steric hindrance toward entry of the second molecule of diamine than did the molecules of water to the entry of the first substituted ethylenediamine. However the data in Table III show that the presence of one molecule of a substituted glycine in the complex offers no greater resistance to the entrance of a second molecule than the presence of water did to the addition of the amino acid group. A consideration of the molecular models shows that these results indicate the formation of *trans* complexes



In such a case it is apparent that any steric resistance due to the alkyl groups on the nitrogen is kept at a minimum. In fact the results show that with nickel(II) the respective differences in chelating tendencies of glycine and substituted glycines are the same whether the ion be $[Ni(H_2O)_6]^{+2}$ or $[Ni\text{-}R_2NCH_2COO(H_2O)_4]^{+}$. It is not known why the values of log K_2G/K_2XG for copper(II) are consistently lower than log K_1G/K_1XG.

A consideration of molecular models indicates that alkyl substitution on the nitrogen atom of glycine offers greater steric resistance to chelate formation than does substitution on the methylene carbon. That this is correct is borne out by a comparison of our results on the N-alkylglycines with the data of Maley and Mellor[9] on corresponding C-alkylglycines. For example the values of log K_T for copper(II) complexes are: (1) N-methylglycine, 14.59; α-alanine, 14.83; (2) N-isopropylglycine, 12.45; valine, 14.45.

Finally it should be stated that preliminary measurements were also made at 0° but the differences in formation constants were too slight to allow reliable estimates of enthalpy and entropy changes. In the case of nickel(II) the titration curves with some amino acids did indicate that at higher *p*H's a third molecule of amino acid entered the complex. However the data in this region were not very accurate and no attempt was made to calculate a formation constant for this step. The separation of nickel(II) hydroxide during titrations of solutions containing N-isopropylglycine and N-diethylglycine accounts for the absence of values for log K_2 in Table III.

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[11] D. H. Everett and W. F. K. Wynne-Jones, *Proc. Roy. Soc.* (*London*), **177A**, 449 (1941).