of the sample was determined as follows: Water in the thermos flask was completely removed through the suction tube extending to the bottom of the thermos, and replaced with a wash solution of 200 ml. of the sample previously adjusted to 0.0 ± 0.2°. This was stirred, and the liquid was again removed and replaced with another 200 ml. of the sample. The thermometer readings were taken every three to five minutes (occasionally stirring) until a steady temperature had been reached. The degree of polymerization of the silicic acid in the sample was then calculated, after obtaining an analysis for silica in the solution by evaporating a sample of the solution to dryness, igniting, weighing and fuming off the silica with HF, igniting and reweighing. A correction was made for the freezing point depression due to the sulfuric acid, by measuring a blank solution containing an amount of sulfuric acid equivalent to that present in the silicic acid solution.

The accuracy of the method was considered adequate, since check readings over a 24-hour period with 0.100 M solution of mannite were all 0.186 ± 0.003°, corresponding to the known freezing point constant for water.

The Preparation of Monosilicic Acid from Crystalline Sodium Silicate.[3]—In a typical preparation of 0.1 M solution of monosilicic acid (0.6% SiO_2), 200 g. of air-dried resin was slurried in 1 liter of 0.0050 M H_2SO_4 in a Pyrex beaker, cooled to 2°, and vigorously agitated with a high speed, air-driven stirrer, and 30.6 g. of pulverized crystalline $Na_2SiO_3 \cdot 9H_2O$ was added over about 15 minutes at a uniform rate. The pH of the mixture (as determined by a Beckman Model G pH meter) was never allowed to exceed 3.5. Filtration gave a clear solution having a pH of 2.6. The degree of polymerization of the silicic acid so obtained was about 1.1.

The pH of the solution could be adjusted, when desired, by the addition of solid sodium metasilicate, or sulfuric acid, in either case with vigorous agitation.

The Preparation of Silicic Acid from an Aqueous Solution of Sodium Silicate.[3]—Several attempts were made to prepare monosilicic acid from aqueous solutions of sodium metasilicate, but in no case was a degree of polymerization lower than 1.5 obtained. Since the solid hydrated sodium metasilicate gave essentially monomer, it is evident that some polymerization of metasilicate ions to disilicate must occur in aqueous solution.

The details for the preparation of silicic acid from aqueous sodium metasilicate solutions are: 400 ml. of 0.20 M Na_2SiO_3 solution was added through a capillary tube to a slurry of 400 ml. of 0.01 M H_2SO_4 and 150 g. of exchange resin. During the reaction, the temperature was maintained at 2°, and the pH below 2.5. After addition of silicate solution, the slurry was filtered and the degree of polymerization of the silicic acid found to be 1.5.

Preparation of Monosilicic Acid from Sodium Orthosilicate.[3]—Monosilicic acid, having a degree of polymerization of about 1.1, has been prepared from sodium orthosilicate either by dissolving crystalline sodium orthosilicate in a slurry of ion-exchange resin in dilute H_2SO_4, or by adding sodium orthosilicate solution through a capillary tube.

Acknowledgment.—The author wishes to acknowledge the helpful suggestions of R. K. Iler, both in the experimental studies and in preparing the manuscript.

WILMINGTON, DELAWARE

[CONTRIBUTION OF THE DEPARTMENT OF CHEMISTRY AT CLARK UNIVERSITY]

Stability of Metal Chelates. VI. Nitrilotricarboxylic Acids

BY S. CHABEREK, JR.,[1] AND A. E. MARTELL

RECEIVED NOVEMBER 19, 1952

The acid dissociation constants of nitrilodiaceticpropionic acid, nitrilodipropionicacetic acid, nitrilotripropionic acid, and the stabilities of the corresponding chelates formed with Cu^{+2}, Ni^{+2}, Co^{+2}, Zn^{+2}, Cd^{+2} and Mg^{+2} ions were studied at 30° in 0.1 M aqueous potassium chloride solution. Relationships are given for calculation of the chelate stability constants by the Bjerrum method. Acid dissociation constants and equilibrium constants for the 1:1 chelates are reported, and the results are interpreted in the light of certain factors recognized as having a bearing on the stability of chelate compounds.

Although the metal chelating tendencies of nitrilotriacetic acid (NTA) have been extensively investigated,[2] little attention has been paid to the corresponding behavior of nitrilotripropionic and the mixed propionicacetic acids. The only propionic acid derivative previously studied is nitrilodiaceticpropionic acid, for which Schwarzenbach, *et al.*,[2a] have reported interactions with alkaline earth ions. An investigation of metal ion equilibria of all the possible combinations resulting from the substitution of acetate and propionate groups on a basic nitrogen atom would make possible a systematic study of the relative stabilities of 5- and 6-rings derived from aliphatic amino acids. In the present paper, the chelating tendencies of nitrilotripropionic acid (NTP), nitrilodipropionicacetic acid (NDPA), and of nitrilodiaceticpropionic acid (NDAP) toward a representative group of metal ions is described. Taken with the work of Schwarzenbach, *et al.*,[2] on nitrilotriacetic acid, the investigation completes the series involving all combinations from the tripropionic to the triacetic acid.

Experimental

Apparatus and Procedure.—The experimental method and conditions employed in this investigation are similar to those described in a previous publication.[3] The amino acids were titrated at 30° with standard 0.1 M KOH solution both in the absence of and in the presence of metal ions. Potentiometric measurements of pH were made with a "calibrated" cell consisting of a shielded glass electrode *vs.* a calomel electrode measured by means of a Beckman Model G pH meter. The calibration was carried out with a cell consisting of a number of platinum (hydrogen) electrodes measured against a number of Ag–AgCl electrodes with a Leeds and Northrup type K potentiometer. This calibration was repeated a number of times with actual experimental runs and a correction curve of pH *vs.* pH meter reading was set up for the normal runs made with the glass–calomel cell only. This procedure had the advantage of allowing rapid determinations equivalent to the hydrogen Ag–AgCl measurements within the limits of reading of the pH meter scale. The experimental solution was regulated at an ionic strength of 0.100 by maintaining a large excess of potassium chloride over all other ionic species present. An inert, CO_2-free atmosphere was employed throughout the titrations. The pH values were converted to hydrogen ion concentration by the assumption that the value of $\gamma_{\pm} = 0.78$ for 0.1 M KCl obtained by Shedlovsky and MacInnes[4] to hold for the experimental solutions. The concentration of amino

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[2] (a) G. Schwarzenbach, H. Ackermann and P. Ruckstuhl, *Helv. Chim. Acta*, **32**, 1175 (1949); (b) G. Schwarzenbach and E. Freitag, *ibid.*, **34**, 1492 (1951).

[3] S. Chaberek, Jr., and A. E. Martell, THIS JOURNAL, **74**, 5052 (1952).

[4] T. Shedlovsky and D. A. MacInnes, *ibid.*, **59**, 503 (1937).

acid employed never exceeded 0.002 *M* and the metal chelate titrations were carried out with 1:1 and 2:1 ratios of moles of amino acid to moles of metal ion. The metal salt solutions were A.C.S. reagent grade standardized by the method of Jones and Martell.[5] The amino acids investigated, nitrilotripropionic acid, nitrilodipropionicacetic acid and nitrilopropionicdiacetic acid, were prepared and purified by a method to be described later.[6]

Experimental Data.—The titration data obtained are presented in graphical form in Figs. 1–4. In Fig. 1 the *p*H values, corrected as described above, are shown plotted *vs.* the moles of base added per mole of amino acid present, for the pure amino acids in 0.1 *M* KCl, and for each of the amino acids in the presence of an equimolar ratio of magnesium ion. Although not shown on the figures, each curve involved between thirty and forty separate measurements of *p*H. In Figs. 2, 3 and 4 are presented similar data for each of the amino acids investigated with the exception that the ratio of metal ion to amino acid was 1:2 and that the abscissa used is *M*, moles of base added per mole of metal ion.

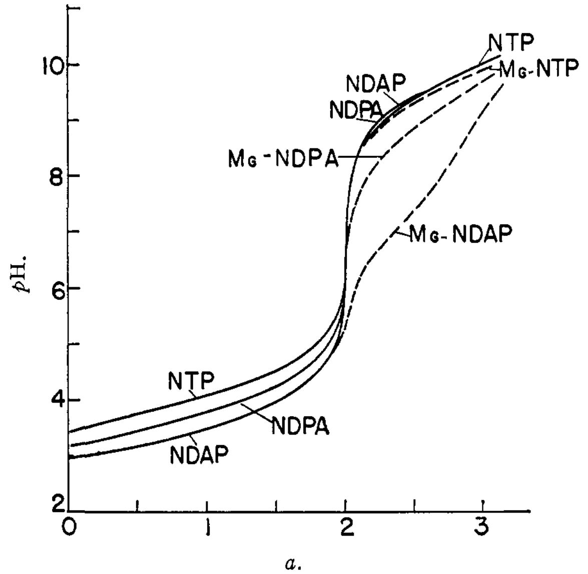

Fig. 1.—Potentiometric titration of nitrilodiaceticpropionic, nitrilodipropionicacetic and nitrilotripropionic acids: —, free amino acid, —, amino acid in presence of equimolar Mg^{+2} ion; *a* = moles of KOH added per mole of amino acid.

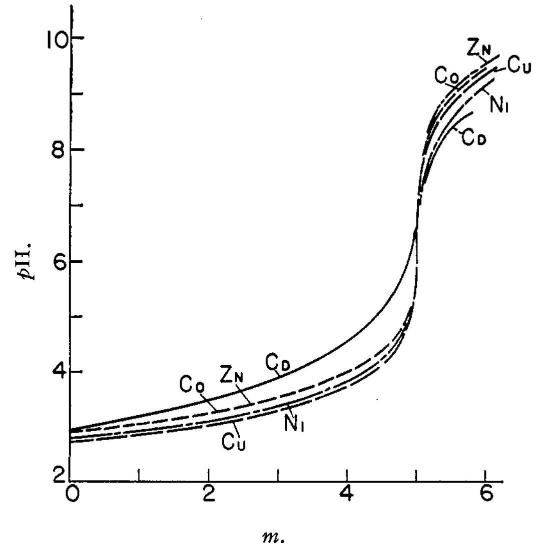

Fig. 2.—Potentiometric titration of nitrilodiaceticpropionic acid in the presence of a 2:1 molar ratio of amino acid to metal ion; *m* = moles of KOH added per mole of metal ion.

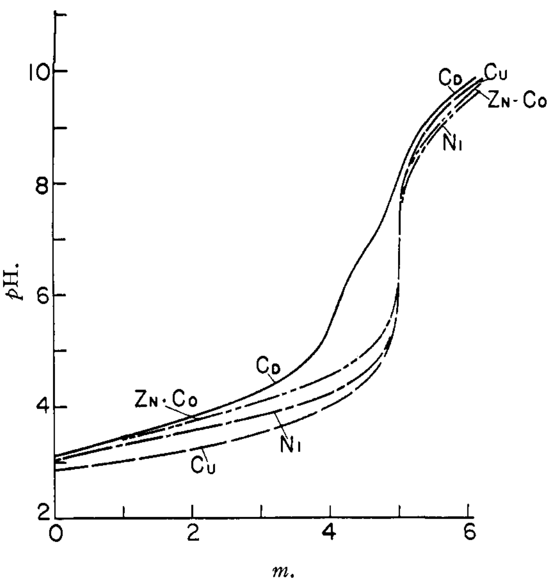

Fig. 3.—Potentiometric titration of nitrilodipropionicacetic acid in the presence of a 2:1 molar ratio of amino acid to metal ion; *m* = moles of KOH added per mole of metal ion.

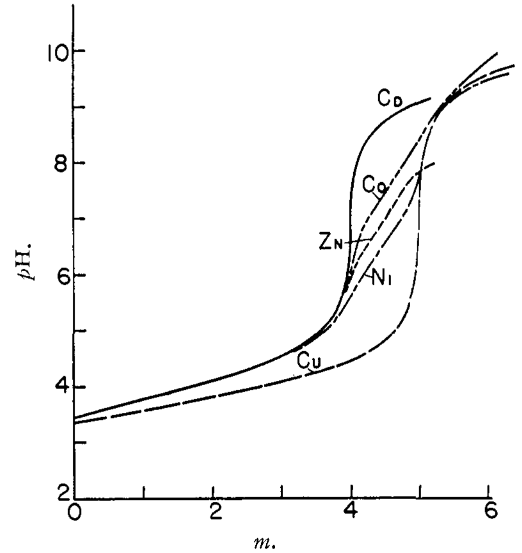

Fig. 4.—Potentiometric titration of nitrilotripropionic acid in the presence of a 2:1 molar ratio of amino acid to metal ion; *m* = moles of KOH added per mole of metal ion.

Calculations.—For the purposes of describing the equilibria measured in this research, the amino acids may be represented by the formula H_3A, and the chelates by MA^{-1} and MA_2^{-4}. There are three dissociation constants k_1, k_2 and k_3 corresponding to the species H_3A, H_2A^- and HA^{-2}, respectively. The two chelate stability constants are

$$M^{+2} + A^{-3} \longrightarrow MA^{-1} \quad K_1 = (MA^{-1})/(M^{+2})(A^{-3})$$

$$MA^{-1} + A^{-3} \longrightarrow MA_2^{-4} \quad K_2 = (MA_2^{-4})/(MA^{-1})(A^{-3})$$

where ( ) represent molar concentration, and the other terms have their usual meaning.

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(5) L. Jones and A. E. Martell, unpublished work.

(6) S. Chaberek, Jr., A. E. Martell and F. C. Bersworth, unpublished work.

The acid dissociation constants of the nitrilocarboxylic acids were determined by the method described by Schwarzenbach and co-workers.[7] The first chelate stability constant, K_1, was obtained in most cases by the modified Bjerrum method previously described.[3] The equations developed for this research differed somewhat because of the difference in the amino acid species present in the solution. In this case the formation function $\bar{n}$, the number of moles of ligand bound per mole of metal ion, and the concentration of ligand, (A^{-3}), are expressed by the relationships

$$\bar{n} = [C_A - \beta(A^{-3})]/C_M$$

$$(A^{-3}) = [(3-a)C_A - (H^+) + (OH^-)]/X$$

where

C_A = total molar concentration of amino acid species

C_M = total molar concentration of metal ion species

$$X = \frac{3(H^+)^3}{k_1k_2k_3} + \frac{2(H^+)^2}{k_2k_3} + \frac{(H^+)}{k_3}$$

$$\beta = \frac{(H^+)^3}{k_1k_2k_3} + \frac{(H^+)^2}{k_2k_3} + \frac{(H^+)}{k_3} + 1$$

a = moles of base added in the titration per mole of amino acid present

In the case of the cupric and nickelous complexes of nitrilodiaceticpropionic acid, and of the cupric complex of nitrilodipropionicacetic acid, the Bjerrum method could not be used since the degree of dissociation was considerably less than 50% even in the most acid solutions. However, if the reasonable assumption is made that (MA_2^{-4}) is negligible in the strongly acid region, then it follows that

$$K_1 = \frac{C_A - \beta(A^{-3})}{(A^{-3})[C_M + \beta(A^{-3}) - C_A]}$$

This relationship may be transformed to the following, which is useful in obtaining values of K_1 from $\bar{n}$ values greater than 0.5

$$K_1 = \bar{n}/(A^{-3})[1 - \bar{n}]$$

This equation gives excellent results at $\bar{n}$ values less than 0.7, and good approximations for $\bar{n}$ values between 0.7 and 0.8.

Discussion of Results

Titration Data.—The experimental data presented in the form of titration curves in Figs. 1–4 also serve the function of indicating the formulas of the metal chelates formed, and give a qualitative picture of the relative stabilities of these chelates. The free acid titration curves shown in Fig. 1 are characterized by rather flat low-*p*H buffer regions followed by a rather strong *p*H rise at two equivalents of alkali hydroxide per mole of metal ion. This indicates considerable overlapping of the first two acid neutralizations for all three propionic acid derivatives investigated. The fact that the high-*p*H buffer regions between two and three equivalents of alkali hydroxide practically coincide indicates that the amino groups have about the same basicity and are considerably hydrolyzed in aqueous solution. The relative positions of the low-*p*H region indicate that the acid strengths of the carboxyl groups decrease in the order NDAP > NDPA > NTP. Since the lowering of the high-*p*H buffer region indicates the relative energies of interaction with magnesium ion, it is apparent that the chelate stability is moderately strong for NDAP, weak for NDPA, and very low for NTP. Since the metal curves do not have sharp inflections at $a = 3$ corresponding to completion of chelate formation, the evidence for the formula of the metal chelate is not completely conclusive. However, the formation of a 1:1 chelate is the only reasonable assumption on the basis of analogous compounds produced by the less basic metals on the evidence provided in Figs. 2–4.

The titration data for the nitrilocarboxylic acids in the presence of Cu^{+2}, Ni^{+2}, Co^{+2}, Zn^{+2} and Cd^{+2} ions, given in Figs. 2, 3 and 4, indicate in most cases a sharp *p*H rise at five equivalents of alkali hydroxide per mole of metal ion. Where it occurs, this inflection is good evidence for the formation of a 1:1 chelate. Three moles of base per mole of metal ion would be required for each mole of chelate formed. However, since the ratio of ligand to metal was originally 2/1, two additional moles of base are required to neutralize the excess amino acid, according to the reaction

$$2H_3A + M^{+2} + 5OH^- \longrightarrow MA^{-1} + HA^{-2} + 5H_2O$$

Beyond the inflection point at $m = 5$ all titration curves have high-*p*H buffer regions somewhat lower than that of the amino acid in the absence of metal ions. By analogy with the behavior of other aminopolycarboxylic acids such as nitrilotriacetic and iminodiacetic acids, this region may be assumed to correspond to the formation of chelates containing two moles of ligand per mole of metal ion. However, because of the uncertainties involved, the calculated values of the corresponding chelate stability constants are not reported.

In the absence of appreciable interaction between metal ion and ligand, the titration curves in Figs. 2–4 would have a strong inflection point at $m = 4$ as a result of neutralization of the amino acid alone. Therefore, the position of the buffer region between $m = 4$ and $m = 5$ constitutes a qualitative measure of the relative stabilities of the 1:1 chelates. Apparently the chelates of high stability are those of NDAP with Cu^{+2}, Ni^{+2}, Co^{+2}, Zn^{+2} and Cd^{+2}, chelates of NDPA with Cu^{+2}, Ni^{+2}, Zn^{+2} and Co^{+2}, and chelates of NTP with Cu^{+2}. All cupric chelates are so stable that appreciable interaction takes place with the amino acid in the absence of added base. The Ni^{+2}, Zn^{+2} and Cd^{+2} chelates of NTP and the Cd^{+2} chelate of NDPA have intermediate stability, while the Cd^{+2}–NTP chelate is obviously very weak.

Formation Functions.—The Bjerrum formation functions for various metal chelates of NDPA and NTP plotted in Figs. 5 and 6, respectively, illustrate the number of moles of ligand bound per mole of metal ion as a function of *p*H. As a measure of the degree of chelation, the formation curves are more reliable than the potentiometric titration curves since they are independent of associated phenomena, such as dissociation and hydrolysis of the unbound amino acid. The corresponding formation functions of NDAP are very similar to those of NDPA shown in Fig. 5, and consequently

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[7] G. Schwarzenbach, A. Willi and R. O. Bach, *Helv. Chim. Acta*, **30**, 1303 (1947).

TABLE I

EQUILIBRIUM CONSTANTS

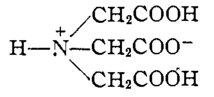
$T = 30°$ $\mu = 0.1$ $\gamma_{H^+} = 0.78$

	NTA[a]		NDAP		NDPA	NTP		IMDA[d,f]	IMPA[d,f]	IMDP[d,f]
	pk		pk		pk	pk		pk	pk	pk
$H^+(pk_1)$	1.9[b]		2.24[e]		3.25	3.67		2.54	3.61	4.11
$H^+(pk_2)$	2.5[b]		3.60[e]		3.98	4.24		9.13	9.46	9.61
$H^+(pk_3)$	9.73[b]		9.35[e]		9.37	9.30		..	..	..
	$\log K_1$[g]	$\log K_1$	$\log K_1$[c]	$\log K_1$	$\log K_1$[c]	$\log K_1$	$\log K_1$[c]	$\log K_1$	$\log K_1$	$\log K_1$
Cu^{+2}	12.7	~11.6	~11.9	~11.6	~11.9	8.8	9.1	10.6	10.5	9.4
Ni^{+2}	11.3	~11.1	~11.4	9.0	9.1	5.8	5.8	8.2	7.4	6.1
Co^{+2}	10.6	9.8	10.1	7.9	7.9	4.8	4.8	7.0	6.2	4.9
Zn^{+2}	10.4	9.8	10.1	7.9	8.0	5.3	5.3	7.0	6.2	5.0
Cd^{+2}	9.8	7.5	7.5	5.6	5.6	3.4	3.4	5.4	4.5	3.5
Mg^{+2}	5.4[b]	5.2[e]	5.2	3.6	3.6	<1	...	3.6	..	...

[a] 20°, $\mu = 0.1$.[2] [b] 20°, $\mu = 0.1$[1] [c] Corrected for hydrogen ion association. [d] Reported by Chaberek and Martell.[3,9] [e] G. Schwarzenbach and P. Ruckstuhl[1] report pk_1 2.1, pk_2 3.69, pk_3 9.66, log K_{MgA} 5.28. [f] IMDA, IMPA and IMDP represent iminodiacetic acid, iminopropionicacetic acid and iminodipropionic acid, respectively. [g] Values of log K greater than 10 are approximations only (about ±0.3 or more). Other values are probably accurate to ±0.1 log K unit.

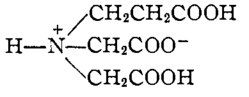
have not been duplicated. With the exception of the Mg^{+2} curve, the sharp inflections of the formation functions for NDPA (and also NDAP) indicate little or no overlapping in the formation of the 1:1 and of the supposed 2:1 chelates. In the case of nitrilotripropionic acid (NTP), Fig. 6 indicates that this type of behavior is true only of the Cu^{+2} ion. Although the degree of formation does not proceed very far for the remaining metals, it is apparent that there is some overlapping for the Ni^{+2} chelate, and probably considerably more for the Co^{+2} chelate.

Equilibrium Constants.—The first and second dissociation constants of the tricarboxylic acids listed in Table I correspond to the dissociation of the carboxylic acid groups of structures I, II, III and IV.



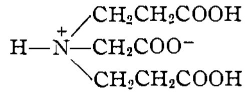
$$H\text{—}\overset{+}{N}(CH_2COOH)(CH_2COO^-)(CH_2COOH)$$

I, NTA



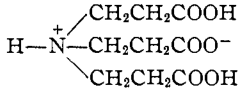
$$H\text{—}\overset{+}{N}(CH_2CH_2COOH)(CH_2COO^-)(CH_2COOH)$$

II, NDAP



$$H\text{—}\overset{+}{N}(CH_2CH_2COOH)(CH_2COO^-)(CH_2CH_2COOH)$$

III, NDPA



$$H\text{—}\overset{+}{N}(CH_2CH_2COOH)(CH_2CH_2COO^-)(CH_2CH_2COOH)$$

IV, NTP

The more strongly acidic carboxyl groups, having pk values in the vicinity of 2–2.5, are evidently the two acetic acid groups on I and the single acetic acid group on II. The remaining carboxyl groups are further removed from the inductive effect of the positive nitrogen atom, and the pK values are correspondingly higher. It is apparent that the pk values for the first two dissociations are not only a function of the distance of the carboxyl from the nitrogen atom, but are also dependent on the position of the negative carboxylate ions already present. Thus pk_1 of NTP is higher than that of NDPA, although both involve the dissociation of a propionic acid group.

For compounds I, III and IV, the first and second dissociating groups are in each case alike, and statistical ratios[8] of the dissociation constants

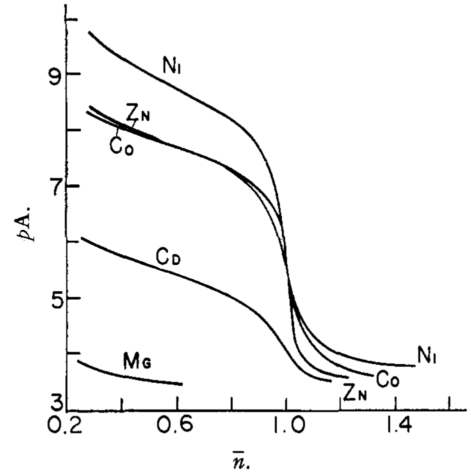


Fig. 5.—Bjerrum formation functions for binding of nitrilodipropionicacetic acid by metal ions; $\bar{n}$ = average moles of ligand anion bound per mole of metal ion; pA = negative logarithm of anion concentration

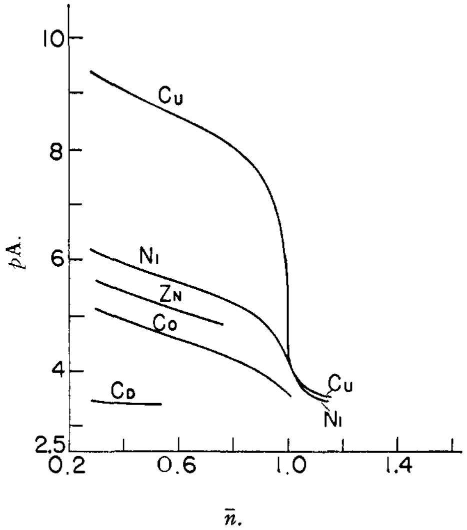


Fig. 6.—Bjerrum formation functions for binding of nitriolotripropionic acid by metal ions; n = average moles of ligand anion bound per mole of metal ion; pA = negative logarithm of ligand anion concentration.

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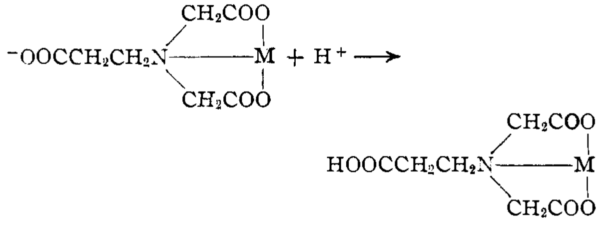
(8) For a discussion of statistical ratios, see ref. 11, p. 80.

(9) S. Chaberek, Jr., and A. E. Martell, THIS JOURNAL, 74, 6021 (1952).

k_1 and k_2 might be expected. Computation of these ratios gives values of k_1/k_2 of 3/1, 4/1 and 3/1 for I, III and IV, respectively. Inspection of the experimental pk values in Table I show that the ratios are in each case only slightly higher than these values, and that the ratio for III is somewhat higher than the others, as it should be. The ratio of k_1 to k_2 for iminodiaceticpropionic acid is comparatively very large in accordance with the fact that the first dissociation involves an aminoacetic acid group, whereas the second involves the comparatively less acidic aminopropionic acid group. It is noteworthy that the basicity of the amino nitrogen atom is the same for each of the propionic acid derivatives investigated, but somewhat lower than that of the nitrilotriacetate anion. One would ordinarily expect a more or less uniform variation in the basicity as the structure is varied from nitrilotriacetate to nitrilotripropionate in a stepwise fashion, as is the case with the corresponding ethylenediamine series.[10]

Because of the possibility of the presence of weakly acidic propionic acid groups in the metal chelates, it was decided to correct the metal chelate formation constants listed in Table I for proton complexing. This may be visualized as taking place with a free propionate ion, according to the reaction scheme



$$K'_1 = \frac{(H^+)(MA^-)}{(MHA)}$$

Although it is not possible to calculate the dissociation constant K'_1 directly from the experimental data, a maximum value of the constant may be taken as the dissociation constant of the same compound with two protons in place of the metal ion. The chelate stability constants in Table I have been corrected for a proton association reaction in this manner. Comparison of the corrected and uncorrected values indicates that in most cases the effect is negligible. For the cobaltous and zinc chelates of NDAP and for the cupric NTP chelate, however, the uncorrected chelate stability constant may be as much as 0.3 log K unit too low.

An unexpected and significant result of this investigation is that there is little decrease in stability of the Cu^{+2}, Ni^{+2}, Co^{+2} and Zn^{+2} chelates on replacement of one acetic acid group of nitrilotriacetic acid by one propionic acid group. This is remarkable in view of the fact that nitrilotriacetic acid is usually considered to be tetradentate and that a 5-membered aliphatic chelate ring is generally more stable than a 6-membered ring.[11] It is possible, however, that the third acetate link is not sterically well disposed toward chelate ring formation, and that a propionate ring in this case would be nearly as stable. Examination of molecular models seems to support this contention.

Similarly, the cupric chelates NDAP and NDPA are equivalent within experimental error. This is explainable on the same basis, except that the ligands can be only tridentate in these chelates because of the square planar requirement of the cupric ion. In this connection it is interesting that the stabilities of the cupric chelates of iminodiacetic acid and iminopropionicacetic acid are also equivalent. These compounds have the same structural differences as those in the NDAP and NDPA–cupric chelates. For all of the remaining metals the chelate stability constant is lowered by a factor of about 10^2 when an acetic acid group of NDAP is replaced by a propionic acid group to give NDPA. Replacement of the last acetic acid group on NDPA by a propionic acid group to give NTP results in a further lowering of the stability of the chelates by 10^2–10^3. The comparison between metal chelate stabilities of nitrilotripropionic acid and iminodipropionic acid listed in Table I reveals that they are practically identical. This indicates that both ligands must be tridentate. On the other hand, the significantly greater stability of the nitrilodipropionicacetic acid chelates (excepting that of Cu^{+2}) over those of iminopropionicacetic acid indicate that the former must be tetradentate.

In the case of the Mg^{+2} ion, it is seen that each successive ring enlargement starting with the nitrilodiaceticpropionic acid chelate results in a decrease in stability of the chelate. Here again, however, the third acetate group on the ligand does not seem to result in greater chelate stability than does a corresponding propionate group.

Acknowledgment.—The authors are indebted to the Bersworth Chemical Company for a grant which made this work possible.

WORCESTER, MASS.

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[10] S. Chaberek, Jr., and A. E. Martell, unpublished work.

[11] A. E. Martell and M. Calvin, "The Chemistry of the Metal Chelate Compounds," Prentice-Hall, Inc., New York, N. Y., 1952, Chapter IV.