*The Synthesis of Chelating Agents. II. The Synthesis of Aminoacetone-N,N-diacetic Acid and Its Chelating Behavior with Metal Ions**

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A great deal of work has been done in the preparation of iminodiacetic acid (IDA) derivatives. However, very little has been reported in the literature on the synthesis of derivatives which have a carbonyl group as an additional coordinating site. The only such compound related to the carbonyl derivative is *N*-acetoamidoiminodiacetic acid (*N*-AIDA), which has been reported on by Schwarzenbach and his co-workers.[1]

This paper will report on the synthesis as well as on the chelating behavior of a new chelating agent, aminoacetone-*N*, *N*-diacetic acid (AADA), or 1-amino-2-propanone-*N*, *N*-diacetic acid, which is the first iminodiacetic acid derivative to have a keto group as an additional coordinating site. This compound was prepared by the condensation of monobromoacetone with an iminodiacetic acid dimethyl ester, followed by the hydrolysis of the resulting ester.

By comparing the chelating behavior of AADA with that of similar ligands which do not have an additional coordinating group, we have been able to obtain information on whether or not the aliphatic keto carbonyl group can coordinate to the metal ions of the first transition group or the alkaline earth group.

Schwarzenbach and his co-workers investigated the chelation behavior of various iminodiacetic acid derivatives which have different

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[1] G. Schwarzenbach, G. Anderegg, W. Schneider and H. Senn, *Helv. Chim. Acta*, **38**, 1147 (1955).

additional coordinating groups, they suggested that the coordinating site of the acetoamido group of *N*-AIDA was not the amino group but the carbonyl group.[1] In this connection, it is also of interest to compare the chelating behavior of AADA with that of *N*-AIDA in order to make certain whether or not the coordination of the acetoamido group of *N*-AIDA occurs exclusively of the carbonyl group.

The chelate stability measurements were therefore carried out, by the pH titration method, on solutions with 1 : 1 and 1 : 2 metal ligand ratios in order to determine the first and second stability constants. The metal ions chosen in this study were copper(II). nickel(II) lead(II), zinc(II), cadmium(II), cobalt(II), calcium(II), strontium(II) and magnesium(II).

The results of the stability constant measurements indicate that the chelating behavior of AADA is very similar to that of *N*-AIDA; it is proved that the coordination of the carbonyl group of AADA to metal ions is appreciable, and that the coordination site of the acetoamido group of *N*-AIDA is also the carbonyl group, as has previously been suggested by Schwarzenbach and his co-workers.[1]

Experimental

The Synthesis of AADA.—A solution of 30 g. (1.86 mol.) of an iminodiacetic acid dimethyl ester[2] in 30 ml. of ethylacetate was added dropwise with stirring to a solution of 13.1 g. (0.95 mol.) of monobromoacetone[3] in 90 ml. of ethylacetate, and the mixture was then kept at 60~70°C under reflux for 4hr. After the mixture had cooled, the resulting white crystals of iminodiacetic acid dimethyl ester hydrobromide were filtered off and repeatedly washed with 100 ml. of ethylacetate. About 21 g. of the hydrobromide was recovered.

The mixture of the filtrate and the washing reagent was concentrated to evaporate ethyl acetate under reduced pressure, the temperature of the solution being kept below 50°C. The residue, a pale yellow oil (24 g.), was a crude aminoacetonediacetic acid dimethyl ester containing a small amount of unreacted monobromoacetone. To a solution of this ester in 30 ml. of ethanol, 80 ml. of water and 33 g. of solid $Ba(OH)_2.8H_2O$ were added; the mixture was then refluxed on a boiling water bath for 2 hr. with occasional shaking. After the mixture had cooled, barium sulfate was precipitated by adding a theoretical amount of sulfuric acid. The precipitate was then filtered off with the aid of Celite and repeatedly washed with hot water.

The mixture of the filtrate and the washing reagent was concentrated to 30~40 ml. under reduced pressure, the temperature being kept below 60°C. To the concentrated solution, 200 ml. of ethanol was added, and the mixture was stored in a refrigerator overnight to complete the precipitation of the free acid of AADA; the crude product was then filtered off and recrystallized from 80% methanol five times. Yield, 12.5 g. (70%). Pure AADA consists of white, bulky crystals which decompose at 190~191°C.

Found: C, 44.44; H, 5.86; N, 7.37, 7.29. Calcd. for $C_7H_{11}NO_5$: C, 44.25; H,6.05; N, 7.41%.

AADA is very soluble in water, soluble in boiling methanol and acetone, very slightly soluble in boiling ethanol, and insoluble in benzene and ether. The solid sample is sensitive to acid or alkaline vapor, and it must be stored in a tightly closed container. The aqueous solution gradually decomposes and rapidly turns yellow at a high temperature. The decomposition is also accerelated by an acid or base.

Measurement.—The experimental method and the conditions in this study are similar to those described in a previous paper.[4] A Hitachi-Horiba Model P pH meter equipped with extension glass and calomel electrodes was used to measure the hydrogen ion concentration. The temperature of the titration solutions was kept at 25.0±0.1°C, while the ionic strength was maintained at approximately 0.10 M with potassium nitrate.

The concentration of the ligand for the determination of the acid dissociation constants was about 0.001~0.002 M. For the titration of solutions of 1 : 1 metal ligand ratio, the initial concentrations were about 0.001M of each component. For the 1 : 2 solutions, the concentrations of metal ions and ligand were about 0.001 M and 0.002 M respectively.

Calculations

The equilibrium constants described in this paper may be summarized as follows:

$$pk_1 = -\log\frac{(HA^-)(H^+)}{(H_2A)}$$

$$pk_2 = -\log\frac{(A^{2-})(H^+)}{(HA^-)}$$

$$K_{MA} = \frac{(MA)}{(M^{2+})(A^{2-})}$$

$$K_{MA_2} = \frac{(MA_2{}^{2-})}{(MA)(A^{2-})}$$

The acid dissociation constants were obtained by a direct algebraic method described previously,[4] and the results were checked by a modified Bjerrum method.[5]

The 1 : 1 metal chelate titration curves were used for the calculation of the first stability constants by means of the algebraic method reported on in a previous paper.[4]

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[2] J. V. Dubsky, *Ber.*, **50**, 1694 (1917).

[3] P. A. Levene, "Organic Syntheses," Coll. Vol. II, 88 (1948).

[4] T. Ando, This Bulletin, **35**, 1395 (1962).

[5] S. Chaberek, Jr., and A. E. Martell, *J. Am. Chem. Soc.*, **74**, 5052 (1952).

The data obtained from the 1 : 2 curves for heavy metals were utilized as a basis for the calculation of their first and second chelate stability constants according to the modified Bjerrum method which has been described in detail by Chaberek and Martell.⁵⁾ The final equation which was employed in this paper is:

$$\bar{n}=\frac{1}{C_{\mathrm{M}}}\left[C_{\mathrm{A}}-\left(\frac{(\mathrm{H}^+)^2}{k_1\cdot k_2}+\frac{(\mathrm{H}^+)}{k_2}+1\right)(\mathrm{A}^{2-})\right]$$

where

$$(\mathrm{A}^{2-})=\frac{(2-a)C_{\mathrm{A}}-(\mathrm{H}^+)+(\mathrm{OH}^-)}{2(\mathrm{H}^+)^2/k_1\cdot k_2+(\mathrm{H}^+)/k_2}$$

where C_{A} and C_{M} are the total concentrations of ligand and metal ion species respectively, and where a is the number of moles of sodium hydroxide added per mole of ligand.

However, the exact values of the constants were obtained by the successive approximation procedure developed by Carlson, McReynolds and Verhoek.⁶⁾

Results and Discussion

Titration Curves. — The corrected potentiometric titration curves for AADA with or without an equivalent amount of metal ions are given in Fig. 1. The curve for the free acid is similar in shape to those of IDA and its homologues, but the inflection at one equivalent of the base which corresponds to the formation of the monosodium salt is considerably weaker than those of IDA and its homologues.

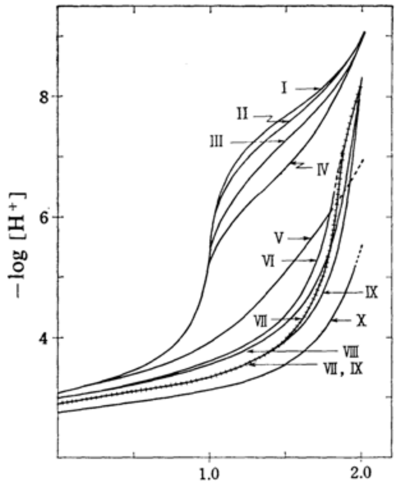

Fig. 1. Titration curves for 1 : 1 solution with 0.1 N NaOH. Concentration of ligand and metal ions……1×10^{-3} M. I, ligand; II, Mg(II); III, Sr(II); IV, Ca(II); V, Co(II); VI, Cd(II); VII, Pb(II); VIII, Zn(II), IX, Ni(II); X, Cu(II). a denotes moles of base added per mole of ligand.

During the titration of the solutions with a 1 : 1 metal ligand ratio, a little pH fluctuation was found in the vicinity of $a=1.8$ for cadmium and cobalt, and in the vicinity of $a=2.0$ for copper, nickel and lead, but no fluctuation was observed in the case of zinc and other metal ions. It is interesting to note on these curves that zinc and cadmium form more stable chelates with AADA than does cobalt in the low pH region. This chelating behavior is rather similar to that of 2-hydroxyethyliminodiacetic acid (2-HIDA) and N-AIDA, but it is different from that of IDA and N-methyliminodiacetic acid (MIDA).

The titration curves for the solutions with a 1 : 2 metal ligand ratio are illustrated in Fig. 2. The curves for alkaline earth metals were not observed, because it is not likely that they form any stable 1 : 2 chelate with this ligand. A similar chelating tendency for zinc and for cadmium was also observed in this case, and a fluctuation of pH was experienced in the case of cadmium and cobalt in the pH region above 7. The curve for zinc apparently shows a considerably strong inflection at three moles of base per mole of metal ion. This indicates that the formation of 1 : 1 and of 1 : 2 chelates occurs in separate pH regions. This two-step reaction may be expressed as follows:

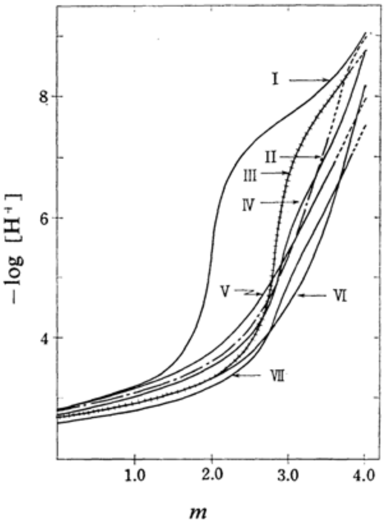

Fig. 2. Titration curves for 1 : 2 solution with 0.1 N NaOH. Concentration of ligand……2×10^{-3} M, metal ion……1×10^{-3} M. I, ligand; II, Cd(II); III, Pb(II); IV, Zn(II); V, Co(II); VI, Ni(II); VII, Cu(II). m denotes moles of base added per mole of metal ion.

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6) G. A. Carlson, J. P. McReynolds and F. H. Verhoek, ibid., 67, 1334 (1945).

the formation of 1 : 1 chelate in the lower pH region :

$$H_2A + M^{2+} + 2OH^- \rightarrow MA + 2H_2O$$

$$H_2A + OH^- \rightarrow HA^- + H_2O$$

the formation of 1 : 2 chelate in the higher pH region :

$$MA + HA^- + OH^- \rightarrow MA_2^{2-} + H_2O$$

A similar inflection was also observed on the curves for copper and cobalt, although it is much weaker.

The curve for lead is so unusual that no decisive interpretation can be made. However, the curve indicates that AADA forms a considerably stable 1 : 1 chelate with lead in the low pH region, and that the chelate changes into a hydroxo-complex or a polynuclear complex in the higher pH region.

Formation Functions.—The Bjerrum formation functions for certain metal chelates of AADA are given in Fig. 3. In the case of copper and nickel, the Bjerrum method could not be employed for the determination of K_{MA} because the values for $-\log(A^{2-})$ were not available at $\bar{n}=0.5$. It was also impossible to determine directly the K_{MA_2} for cadmium from the $-\log(A^{2-})$ value at $\bar{n}=1.5$, for some precipitation occurred in this region. However, K_{MA} at $\bar{n}=0.5$ for nickel was conveniently calculated from the known values of $K_{MA} \cdot K_{MA_2}$ at $\bar{n}=1.0$ and K_{MA_2} at $\bar{n}=1.5$, and the value of K_{MA_2} at $\bar{n}=1.5$ for cadmium, were similarly derived from the values of $K_{MA} \cdot K_{MA_2}$ at $\bar{n}=1.0$ and K_{MA} at $\bar{n}=0.5$.

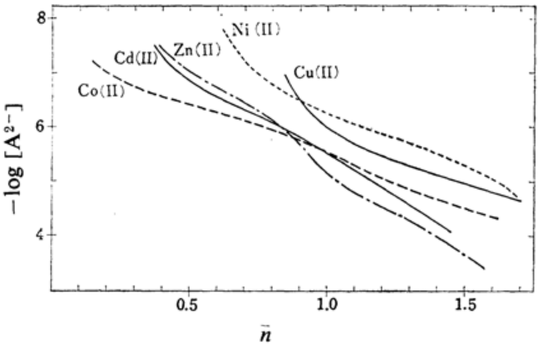


Fig. 3. Formation functions of some divalent metal chelates of AADA. Concentration of ligand……2×10^{-3}, metal ion……1×10^{-3} M ; $t=25°C$; $\mu=0.1$ (KNO_3).

The formation curve for lead was found to be so unusual that the chelating behavior of AADA for lead was thought to be quite different from that of the other IDA derivatives.

Equilibrium Constants.—The acid dissociation and chelate stability constants of AADA are listed in Table I, along with the corresponding values of some IDA derivatives.

The values of the acid dissociation constants determined by the algebraic method agree reasonably well with those obtained by the modified Bjerrum method. The pk_2 value of AADA indicates that the substitution for a methyl group or hydrogen by a acetyl group apparently results in a marked decrease in the basicity of the imino nitrogen. The same effect was also observed with *N*-AIDA.

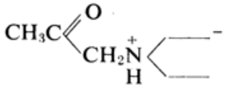
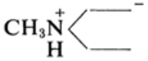
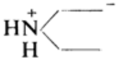
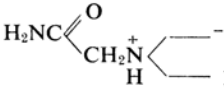
The chelate stability constants calculated by these two methods agree well within the range of experimental error for nickel, zinc and cadmium. However, in the case of cobalt, the K_{MA} value obtained by the algebraic method may be erroneous, for the overlapping of 1 : 1 and 1 : 2 chelate formation in the 1 : 1 titration curve is disregarded in the derivation of the stability constant. Therefore, the agreement of the two values for cobalt is not very good.

The K_{MA} values for lead which were calculated from the data of the titration curve in the range of $a=1.1\sim1.7$ did not agree well. Only if the data from the narrower range of $a=0.8\sim1.1$ were chosen were fairly consistent values obtained ; their mean values are listed in the table for lead chelate. Therefore, this value may not be accurate enough. The determination of K_{MA_2} for lead by the Bjerrum method was unsuccessful, as has been described before. Above a pH of about 3.5, the reaction of AADA with lead seems to be very complicated ; a further investigation will be necessary to analyse the titration curves.

The errors of these stability constants are ±0.1 of log unit. Therefore, the value of two decimal places in the constant means nothing for the below discussion.

The Effect of the Carbonyl Group on the Chelate Stability.—If the carbonyl group is involved in the coordination of AADA to metal ions, it will behave as a quadridentate ligand. Thus, for the metal ions with the coordination number of 4, AADA will form a stable 1 : 1 chelate ; the formation of 1 : 2 chelate will be more difficult than in the case of such tridentate ligands as IDA or MIDA. This will result in a larger difference between $\log K_{MA}$ and $\log K_{MA_2}$. For the metal ions with the coordination number of 6, the situation will also be the same, although the difference between $\log K_{MA}$ and $\log K_{MA_2}$ is smaller than in the former case. The values of the difference for some metal chelates are also shown in Table I. It may be seen from the table that the tendency of AADA to form a 1 : 2 chelate from a 1 : 1 chelate is less marked for zinc and cadmium than for nickel and cobalt. This

TABLE I. ACID DISSOCIATION CONSTANTS OF IDA AND THE DERIVATIVES AND STABILITY CONSTANTS OF THEIR CHELATES (μ=0.10; KNO_3)

Ligand	Acid dissociation constant	Stability constant									
			Cu(II)	Pb(II)	Ni(II)	Zn(II)	Cd(II)	Co(II)	Ca(II)	Sr(II)	Mg(II)
AADA (t=25°C)	pk_1 2.62	log K_{MA}*1	(9.0_5)	(7.7_0)	7.7_4	6.9_6	6.9_2	6.1_7	4.0_8	3.6_2	2.7_2
	pk_2 7.71	log K_{MA}*2			7.3_2	7.0_1	6.8_4	6.4_0			
		log K_{MA_2}	4.9_4		5.2_9	3.6_4	4.1_2	4.5_2			
		Δ log K_D*3	(4.1_1)		2.0_3	3.3_7	2.7_2	1.8_8			
MIDA (t=20°C)	pk_1 2.12	log K_{MA}	10.09		8.37	7.66	6.77	7.62	3.75	2.85	3.44
 1)	pk_2 9.65	log K_{MA_2}	6.83		7.22	6.43	5.75	6.29			
		Δ log K_D*3	3.26		1.15	1.23	1.02	1.33			
IDA (t=30°C)	pk_1 2.54	log K_{MA}	10.55		8.30	7.02	5.30	7.01	2.59*4		2.94*4
 5), 7), 8)	pk_2 9.12	log K_{MA_2}	5.65		6.35	5.14	4.18	5.34			
		Δ log K_D*3	4.90		1.95	1.88	1.12	1.67			
***N*-AIDA** (t=20°C)	pk_1 2.3	log K_{MA}	9.68	8.40	8.02	7.30	7.08	6.91	3.96	3.03	2.47
 1)	pk_2 6.60	log K_{MA_2}	3.26	2.24	3.88	2.24	3.60	3.30			
		Δ log K_D*3	6.42		4.14	5.06	3.48	3.61			

*1 log K_{MA} obtained by algebraic method. *2 log K_{MA} obtained by Bjerrum method. *3 Δ log K_D=log K_{MA}−log K_{MA_2} *4 Determined at 20°C

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7) G. Schwarzenbach, A. Willi and R. O. Bach, *Helv. Chim. Acta*, **30**, 1303 (1945).

8) H. Senn and G. Schwarzenbach, unpublished results (cited from; S. Chaberek and A. E. Martell, "Sequestering Agents," John Wiley & Sons, Inc., New York, (1959) p. 552).

can be understood if one remembers that zinc and cadmium have a coordination number of 4 of tetrahedral configuration, while nickel and cobalt have a coordination number of 6 for a octahedral configuration. A somewhat similar tendency is observed in *N*-AIDA, which is also believed to be a quadridentate ligand for the above-mentioned metal ions, while tridentate ligands such as IDA and MIDA show an ease of 1 : 2 chelate formation.

As has been discussed above, it is quite probable that the carbonyl group is involved in the coordination of AADA to metal ions. If this is the case, this will result in an increase of 1 : 1 chelate stability in comparison with those similar ligands which have no additional coordinating group. In order to examine such an additional stability for the various *N*-substituted IDA derivatives, Schwarzenbach and his co-workers have employed the linear correlation method.[1] According to this method, an increase in the stability which is due to the additional coordinating group is estimated as a difference between the stabilities of the new ligand and of a hypothetical ligand which has no additional coordinating group but which does have the same basicity of imino nitrogen as the new ligand. This comparison can be made by drawing a correlation line of log K_{MA} versus pk_2 for a series of *N*-alkyl substituted iminodiacetic acids, such correlation lines for selected metal ions are shown in Fig. 4. These lines were drawn using the data from the Schwarzenbach's paper.[1] If the stability of the new ligand increases upon the introduction of an additional coordinating group, the plot of log K_{MA} versus pK_2 for such a ligand must be above the correlation line; the degree of deviation from the line is a measure of the additional stability due to the additional coordinating group. The increased stabilities of AADA measured by this method, which is expressed as Δ log K_T, are graphically shown in Fig. 5, along with those of some related IDA derivatives.

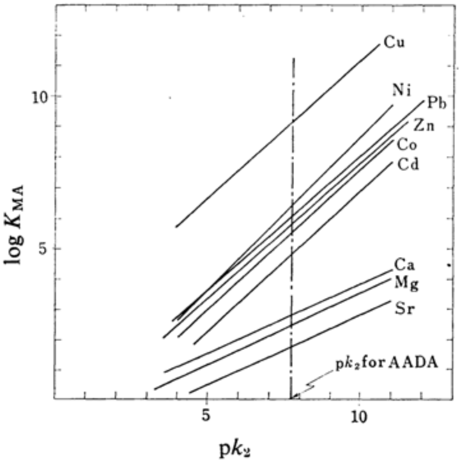


Fig. 4. Correlation lines for the selected metal ions.

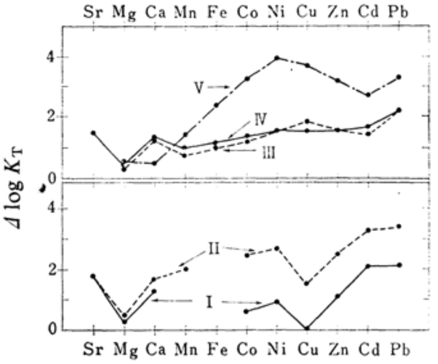
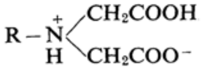


Fig. 5. Increased stability (Δ log K_T) due to an additional coordinating site.

Ligand :

$$R-\overset{+}{\underset{H}{N}}\begin{cases}CH_2COOH\\ CH_2COO^-\end{cases}$$

R

I, CH_3-CO-CH_2-
II, H_2N-CO-CH_2-
III, CH_3-O-CH_2CH_2-
IV, HO-CH_2CH_2-
V, H_2N-CH_2CH_2-

As is clear from curve I of Fig. 5, the contribution of the carbonyl coordination in AADA is appreciable, with the exceptions of magnesium and copper. The chelating tendency of AADA is also found to be very similar to that of *N*-AIDA (curve II); such a resemblance would indicate that the coordination of the acetoamido group of *N*-AIDA occurs exclusively through the carbonyl oxygen, as has previously been suggested by Schwarzenbach. It is interesting to note that, with the exception of copper, the chelating tendencies of AADA and *N*-AIDA are somewhat similar to those of the *N*-hydroxyethyl and *N*-methoxyethyl derivatives of IDA (curves IV and III respectively), both of which have coordinating oxygen. However, they are quite different from that of aminoethyliminodiacetic acid (curve V), which has amino nitrogen as an additional coordinating site.

In the case of copper, no increase in stability is observed at all, probably because the square planar configuration of copper ion is not favorable for the coordination of the carbonyl oxygen of AADA.

It may also be seen from Fig. 4 that the degree of contribution of the carbonyl coordination to the 1 : 1 chelate stability is greater in *N*-AIDA than in AADA. This indicates that the basicity of the carbonyl oxygen in the acid amide group is stronger than in the aliphatic keto group, this situation being consistent with the result from the electronic theory of organic molecules.

Summary

1) Aminoacetone-*N*, *N*-diacetic acid or 1-amino-2-propanone-*N*, *N*-diacetic acid has been synthesized. This is the first iminodiacetic acid derivative to have a keto group as an additional coordinating site.

2) The acid dissociation constant and the chelate stability constants of this ligand have been determined by the pH titration method, at 25°C and 0.10 M ionic strength, for such metal ions as copper(II), lead(II), nickel(II), zinc(II), cadmium(II), cobalt(II), calcium(II), strontium(II) and magnesium(II).

3) It has been proved that the coordination of the carbonyl oxygen of this ligand to metal ions is appreciable, and the increase in the chelate stability has been explained by the contribution of the carbonyl coordination.

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