[CONTRIBUTION OF THE DEPARTMENT OF CHEMISTRY OF CLARK UNIVERSITY]

Chelating Tendencies of Aminomethylenephosphonic-N,N-diacetic Acid

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RECEIVED MARCH 4, 1957

The third and fourth acid dissociation constants of aminomethylenephosphonic-N,N-diacetic acid and its chelate stability constants with Mg(II), Ca(II), Sr(II), Ba(II), Mn(II), Cd(II) and Zn(II) ions at 30° and ionic strength 0.1 are reported. The results are interpreted on the basis of the probable structures of the compounds formed.

Recent work of Schwarzenbach and co-workers[1] indicates that the phosphonic acid group may have an effective donor function when substituted in place of carboxyl groups of aminopolycarboxylic acids. In this paper are described the results of a potentiometric investigation of one of the simplest of such compounds, aminomethylenephosphonic-N,N-diacetic acid, in which one carboxyl group of the well-known chelating agent, nitrilotriacetic acid, is replaced by a phosphonic acid group. This report is part of a general research program involving the influence of functional groups on chelating tendencies.

Experimental

Method.—The experimental procedure employed is similar to that described previously.[2] The amino acid was titrated with carbon dioxide-free standard potassium hydroxide prepared according to the method of Schwarzenbach and Biedermann.[3] The molar ratios of metal to ligand employed were 1:1 and 10:1 for all metals investigated. The hydrogen ion function was determined by calibrating the measuring system, consisting of glass and calomel electrodes and a Beckman Model G pH meter, under the reaction conditions to be employed in the measurements. The calibration was made with a cell consisting of a number of hydrogen and silver-silver chloride electrodes, the potential of which was measured with a Leeds and Northrup Type K potentiometer. The experimental solutions were maintained at an ionic strength of 0.100 by the use of potassium chloride as a supporting electrolyte. The pH functions obtained were converted to hydrogen ion concentration by assuming that the value of $\gamma\pm = 0.78$; as reported by Shedlovsky and MacInnes,[4] would hold over a considerable pH range at constant ionic strength and temperature. Carbon dioxide-free nitrogen was bubbled through a presaturator and the cell during all runs. The concentration of the aminophosphonic acid in the experimental solutions was always below 0.002 M. The metal solutions were standardized by chelatometric titration with ethylenediaminetetraacetic acid. The specific procedure employed involved use of the disodium salt for Mn(II), Cd(II) and Zn(II), and the trisodium salt with Ca(II), Mg(II), Sr(II) and Ba(II), with the pH meter as end-point indicator. The amino acid was prepared by the treatment of iminodiacetic acid with chloromethylenephosphonic acid according to the method described by Schwarzenbach and co-workers.[1]

Results

The potentiometric data thus obtained are presented in part in Fig. 1 and 2. In Fig. 1 are shown the values of hydrogen ion concentration as a function of a, moles of standard base added per mole of ligand present in the solution being titrated. In these experiments the molar ratio of metal to ligand was always 1:1. In Fig. 2 a comparison is given between curves obtained when 10:1 and 1:1 ratios of metal to ligand were used. Each curve in Figs. 1 and 2 represents about 40 individual measurements of pH.

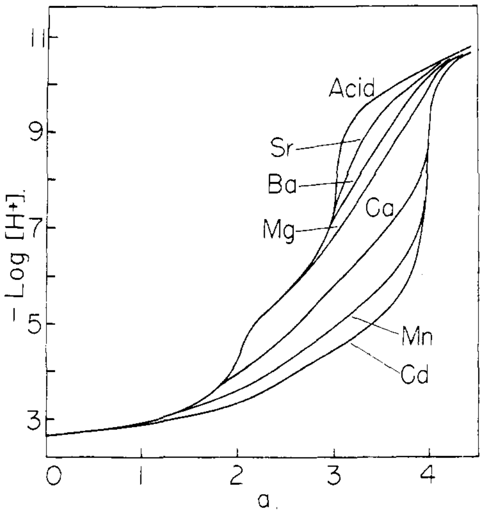

Fig. 1.—Potentiometric titrations for 1:1 molar ratio of metal to ligand: a, moles of potassium hydroxide per mole of amino acid; $t = 30°$, $\mu = 0.1$; initial concentrations of metal ion and ligand $= 3.0 \times 10^{-4}$ M.

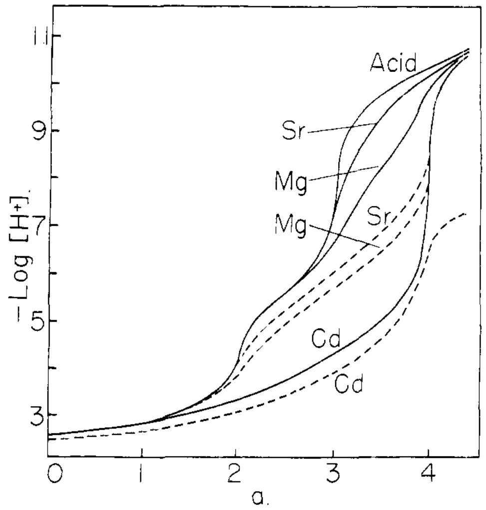

Fig. 2.—Effect of metal concentration on potentiometric measurements: ——— represents 1:1 ratio of metal ion to ligand; -------- represents a 10:1 ratio; a, moles of potassium hydroxide added per mole of ligand; $t = 30°$; $\mu = 0.1$; initial ligand concentration $= 3.1 \times 10^{-4}$ M.

Calculations.—The third and fourth dissociation constants of aminomethylenephosphonic-N,N-diacetic acid may be calculated from the relationships

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[1] G. Schwarzenbach, H. Ackermann and P. Ruckstuhl, *Helv. Chim. Acta*, **32**, 1175 (1949).

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

[3] G. Schwarzenbach and W. Biedermann, *Helv. Chim. Acta*, **31**, 331 (1948).

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

$$K_3 = \frac{[H^+][HX^{-3}]}{[H_2X^{-2}]} = [H^+] \text{ at } a = 2.5$$

$$K_4 = \frac{[H^+][X^{-4}]}{[HX^{-3}]} = \frac{[H^+](C_s - [OH^-])}{[OH^-]} \text{ at } a = 4.0$$

The first two dissociation constants were not determined since they are not needed in the calculations of chelate stability constants. This simplification is due to the fact that the first two acid forms of the ligand are completely dissociated at the lowest *p*H values of the lowest metal titration curves of Figs. 1 and 2. The dissociation constants K_3 and K_4 were calculated not only from the simplified equations given above, but were also checked by the use of additional points along the titration curve.

Two methods were employed for the calculation of metal chelate stability constants. The first is a modified Bjerrum method described by Chaberek and Martell,[2,5] by which the formation function, *n*, defined as the number of moles of ligand bound per metal ion, is plotted against the free ligand concentration. The reciprocal of the ligand concentration at $n = 1/2$ is equal to the chelate formation constant. It was necessary to employ an algebraic method of calculation when the metal ion concentration greatly exceeded total ligand species since under these conditions the formation function could never approach the value $1/2$. The equations employed for this second method of calculation are

$$K_M = \frac{C_x - Y[X^{-4}]}{[X^{-4}](C_M + Y[X^{-4}] - C_x)}$$

where K_M is the chelate formation or stability constant expressed in terms of molar concentration [ ], C_M and C_x are the total concentrations of metal and ligand species, respectively, and Y is defined by the equation

$$Y = \frac{[H^+]^2}{K_3K_4} + \frac{[H^+]}{K_4} + 1$$

The concentration of free ligand anion, necessary for both methods of calculation, was calculated with the relationship

$$[X^{-4}] = \frac{(4 - A)C_A - [H^+] + [OH]}{\frac{2[H^+]^2}{K_3K_4} + \frac{[H^+]}{K_4}}$$

The above equations are simpler than the relationships usually employed[6] in the calculation of formation constants involving tetranegative ligands. This simplification is the result of the elimination of the first two dissociation constants from the calculations for the reasons given above.

Discussion

The metal chelate formation constants and acid dissociation constants of the ligand calculated according to the methods described above, are listed in Table I, along with the values reported previously by Schwarzenbach, *et al.*,[1] for somewhat different experimental conditions.

The acid dissociation constants listed in Table I indicate that the ligand has two groups with appreciable basicity. The most basic functional group is probably the tertiary nitrogen atom.

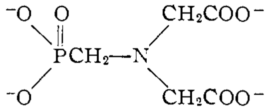
TABLE I

EQUILIBRIUM CONSTANTS

Ion	pK_n or Log K_M Algebraic, 10:1	Algebraic, 1:1	Bjerrum, 1:1	Schwarzenbach[a]
H^+ (K_3)		5.80		5.75
H^+ (K_4)		10.64		10.76
Ba^{++}	5.01	5.06	5.08	5.35
Sr^{++}	5.36	5.41	5.44	5.59
Mg^{++}	5.88	5.96	6.01	6.28
Ca^{++}	7.21	7.12	7.13	7.18
Mn^{++}	7.94	7.98	8.03	
Cd^{++}	8.44	8.50	8.52	
Zn^{++}	8.99	..	..	

[a] Reported by Schwarzenbach, *et al.* (ref. 1), for 20°.

The fact that its basicity is somewhat greater than is usually found in amino groups of α-amino acids is probably due to the large negative charge of the basic anion I. The addition of a second hydrogen ion to the ligand probably results in conversion of the trinegative anion II to a structure III in which the hydrogen ion is associated with the phosphonate group. The second hydrogen ion association cannot take place with one of the carboxyl groups, in view of the known strong acidity of such groups in analogous structures such as nitrilotriacetic acid. Hence it follows that K_3 must correspond to the dissociation of a proton from the phosphonate group. In further support of this conclusion, Schwarzenbach also has pointed out that the third dissociation constant, K_3, is of the same order of magnitude as the second dissociation constants of alkylphosphonic acids. The structures of the three most basic forms of the ligand in the order of decreasing basicity are thus believed to be adequately represented by formulas I, II and III. Formula IV is the probable structure of the neutral acid form, although the contribution of tautomeric forms involving the shift of a hydrogen ion from one of the carboxyl groups is a definite possibility, in view of the strongly-acidic nature of the three groups involved.



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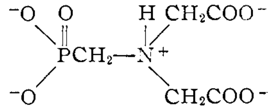
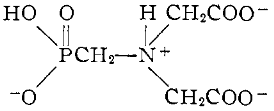
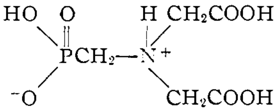


II



III



IV

The chelate stability constants listed in Table I indicate that aminomethylenephosphonic-N,N-diacetic acid is a very effective chelating agent for all the metal ions investigated. The algebraic and Bjerrum methods of calculation gave results which are essentially in agreement, the formation constants in most cases differing by 0.03 log units or less. The stability constants calculated from runs containing a 10:1 molar ratio of metal ion to ligand are about 0.05 log unit lower. This type of behavior is not entirely unexpected since it is known that activity coefficients of ions may change appreciably when the ratios of the constituent ions

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(5) S. Chaberek and A. E. Martell, THIS JOURNAL, **74**, 6228 (1952).

(6) R. Courtney, S. Chaberek and A. E. Martell, *ibid.*, **75**, 4814 (1953).

change, even though the ionic strength remains constant.[7] In this respect, however, the calcium chelate seems to behave somewhat differently than the other metal ions listed.

The equilibrium constants reported for this investigation are somewhat lower than those previously reported by Schwarzenbach. The differences, though small in most cases, are outside experimental error. If the influence of a slight difference in ionic strength is neglected, it seems that the stabilities of these metal chelates decrease with an increase in temperature.

The unusually high metal ion affinity of aminomethylenephosphonic-N,N-diacetic acid is seen from a comparison of stability constants given in Table II. The other chelating agents listed are tetradentate with the exception of ethylenediaminetetraacetic acid, which is usually considered to be a hexadentate ligand. With the data listed in Table II, it is possible to conclude with considerable assurance that the phosphonate compound is also tetradentate. Otherwise it would be difficult to explain why its metal chelates are more stable than those of other tetradentate ligands. Further, a search of the literature has revealed that aminomethylenephosphonic-N,N-diacetic acid is the most effective tetradentate ligand yet found for the binding of alkaline earth and probably also the more basic heavy metal ions in aqueous solution.

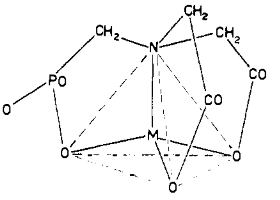
TABLE II

STABILITY CONSTANTS OF AMINOPOLYCARBOXYLATE CHELATES

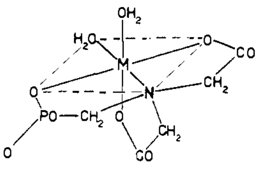
Metal ion	Log K_M			
	NPDA[a]	NTA[b,c]	2-HIMDA[d,e]	EDTA[f,g]
Ba^{++}	5.1	4.8		7.8
Sr^{++}	5.4	5.0		8.6
Mg^{++}	6.0	5.4	3.5	8.7
Ca^{++}	7.1	6.4	4.8	10.6
Mn^{++}	8.0	7.4	5.6	13.4
Cd^{++}	8.5	9.5	7.1	16.4
Zn^{++}	9.0	10.4	8.6	16.1

[a] NPDA = aminomethylenephosphonic-N,N-diacetic acid. [b] NTA = nitrilotriacetic acid. [c] Reported by Schwarzenbach, *et al.* (G. Schwarzenbach and E. Freitag, *Helv. Chim. Acta*, **34**, 1492 (1951)); (also Ref. 1). [d] 2-HIMDA = 2-hydroxyethyliminodiacetic acid. [e] Reported by S. Chaberek, R. Courtney and A. E. Martell, THIS JOURNAL, **74**, 5057 (1952). [f] EDTA = ethylenediaminetetraacetic acid. [g] Reported by Schwarzenbach, *et al.* (G. Schwarzenbach and E. Freitag, *Helv. Chim. Acta*, **34**, 1503 (1951)); H. Ackerman and G. Schwarzenbach, *ibid.*, **32**, 1543 (1949).

On the basis of the demonstrated tetradentate nature of aminomethylenephosphonic-N,N-diacetic acid, it is possible to assign the structures represented by formulas V and VI to its metal chelates. Formula V indicates the nature of the tetrahedral chelate compound formed with a metal ion of coordination number 4, such as the magnesium(II) ion. Formula VI represents the metal chelate compounds formed with the remaining metals investigated, in which four of the six octahedral valences of the metal are satisfied by the ligand and the remainder are solvated.



V



VI

An interesting correlation of the chelate stability constants determined in this investigation with a fundamental property of the metals is given in Fig. 3, in which the logarithms of the stability constants

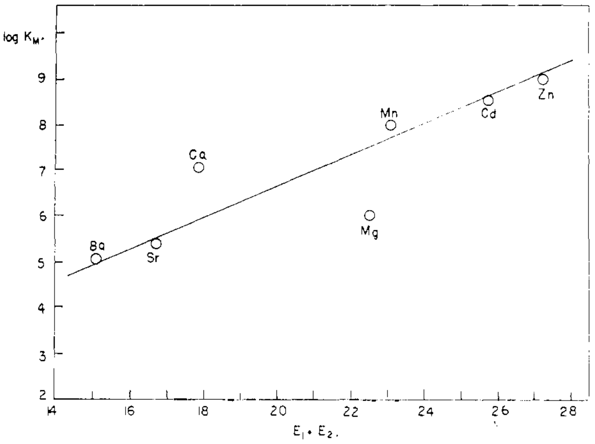


Fig. 3.—Correlation of metal chelate stability constants with the sum of the first two ionization potentials of the metal.

are plotted *vs.* the sum of the first and second ionization potentials. A linear correlation with ionization potential sum has come to be considered normal behavior for the free energies of metal chelate formation in aqueous solution.[8,9] Since the abscissa of Fig. 3 and similar graphs is an electron-binding energy term, such a correlation can only be interpreted in terms of a variation in the energy of the metal–ligand bonds, *i.e.*, the enthalpy of complex formation. Hence adherence of the measured values to the linear correlation of Fig. 3 means that as the energy of binding of two electrons to the metal atom increases, the energy of binding of the ligand increases proportionately. The slope of the line in Fig. 3 thus represents the ratio, Δ enthalpy of bond formation divided by Δ enthalpy of combination of the gaseous ion with two electrons.

If the stability data in Fig. 3 are to be interpreted in this manner, it is necessary that the entropy contributions to free energy remain relatively constant throughout the series of metal ions investigated (or that changes in entropy parallel changes in enthalpy). The fact that most of the points of Fig. 3 lie close to the straight line indicates that the entropy changes may be approximately constant for most of the metal ions investigated. This interpretation is supported by the fact that all of the metal chelate formation reactions may be summarized by the same general equation

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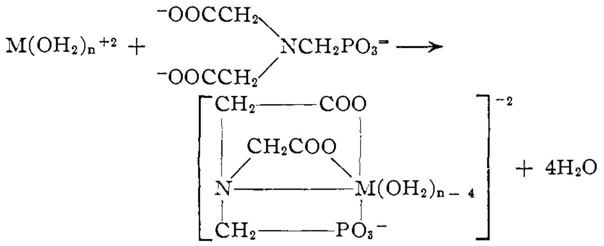
[7] F. Carini and A. E. Martell, THIS JOURNAL, **75**, 4810 (1953).

[8] A. E. Martell and M. Calvin, "Chemistry of the Metal Chelate Compounds," Prentice-Hall, Inc., 1952, pp. 188-190.

[9] M. Calvin in "The Mechanism of Enzyme Action," W. D. McElroy and B. Glass, Editors, John Hopkins University Press, Baltimore, 1954, p. 225.



It can be seen that two metal ions Ca(II) and Mg(II) have stabilities which differ considerably from the normal values. The behavior of the calcium ion is similar to that noted with other aminopolycarboxylic acids capable of forming a number of chelate rings with the metal ion.[10] In such cases the stabilities of the calcium chelates are always much higher than the values predicted by any type of empirical correlation. A plausible explanation for this interesting behavior of the calcium ion has not yet been given.

A reasonable explanation can be offered for the lower-than-normal stability of the magnesium chelate. Since the magnesium ion may be considered as having a coördination number of 4 in its aqueous complexes, the chelate compound would be tetrahedral, with the metal ion ideally at the center of a regular tetrahedron, and with the four electron-donor groups at the corners. For all the other metal ions investigated the coördination compounds have more-or-less octahedral arrangements of donor groups, four positions being occupied by the ligand, and the remaining two *cis*-positions occupied by water molecules.[11] Inspection of formulas V and VI indicates that a ligand which could readily conform to formula VI, would not necessarily be able to provide the distribution of donor groups required by V. An examination of molecular models indicates that this difference in behavior is indeed the case, and that the strain resulting from the formation of the magnesium chelate would consequently involve an energy contribution in the direction of decreased stability.

Acknowledgment.—The authors are indebted to Mrs. Sonya Westerback of Clark University for the synthesis of aminomethylenephosphonic-N,N-diacetic acid.

[10] A. E. Martell and M. Calvin, ref. 8, p. 193.

[11] The authors do not hereby specify a rigid structure for the coördination spheres consisting of ligand groups and solvated water. It is recognized that the tetrahedral and octahedral arrangements represent average or approximate positions as a consequence of the "essentially-ionic" nature of the metal-donor bonds. Such an interpretation is not inconsistent with the correlation of stability with ionization potential described above.

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[CONTRIBUTION FROM THE CHEMISTRY LABORATORIES OF NORTHWESTERN UNIVERSITY]

Mechanism of Racemization of Complex Ions. IV. Effect of Added Large Ions upon the Rates of Dissociation and Racemization of *Tris*-(1,10-phenanthroline)-iron(II) Ion[1,2]

BY ARNE JENSEN, FRED BASOLO AND H. M. NEUMANN

RECEIVED OCTOBER 25, 1957

The rates of dissociation and racemization of tris-(1,10-phenanthroline)-iron(II) have been measured at 25° in aqueous solutions containing various large anions and cations. Lauryl sulfate, *d,l*-10-camphor sulfonate, some alkaloid hydrochlorides and certain polyelectrolytes affect the rates. These effects are attributed to ionic association, and independent evidence for association has been obtained from studies of the ultraviolet spectra and by dialysis techniques. Structural features of the associations are discussed.

Several years ago Rây and Dutt[3] reported that the rates of racemization of aqueous solutions of *dextro-* and of *levo*-tris-(biguanidinium)-cobalt(III) chloride *dextro*-tartrate are slightly different. Davies and Dwyer[4] have observed that the presence of optically active ions have different effects on the rates of racemization of *dextro-* and *levo*-tris-(1,10-phenanthroline)-nickel(II) ions. They also found that the rate of racemization of this complex is likewise altered by the presence of large optically inactive ions.

This behavior of complex ions in the presence of large ions, polyelectrolytes and proteins may in some way be related to the biological activity of these metal complexes. For example it was found that although certain complex cations are stable and probably pass through the body unchanged, they also exhibit marked biological activity.[5] Certain metal complexes, when injected intraperitoneally into mice, cause paralysis and death by respiratory failure suggestive of curariform activity. There is reason to suspect that this activity results from their attachment to active sites in the biological system.

The purpose of this investigation was to make a quantitative kinetic study on the effect of large ions, polyelectrolytes and proteins on the rates of dissociation and racemization of tris-(1,10-phenanthroline)-iron(II) ion. Data are presented to show that the effects are due to inter-ion-associations. Associated species are present even in dilute aqueous solution and even between ions of like charges.

[1] Previous paper in this series, J. E. Dickens, F. Basolo and H. M. Neumann, THIS JOURNAL, **79**, 1286 (1957).

[2] This investigation was supported by a Grant-in-Aid from the National Institute for Health, Grant No. RG-4335 (C).

[3] P. Rây and N. K. Dutt, *J. Indian Chem. Soc.*, **20**, 81 (1943).

[4] N. R. Davies and F. P. Dwyer, *Trans. Faraday Soc.*, **50**, 24 (1954).

[5] For a brief summary and references see F. P. Dwyer, E. C. Gyarfas, R. D. Wright and A. Shulman, *Nature*, **179**, 425 (1957).