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Nuclear Magnetic Resonance and Potentiometric Protonation Study of Polyaminopolyacetic Acids Containing from Two to Six Nitrogen Atoms

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The protonation constants of the higher analogues of ethylenediaminetetraacetic acid (EDTA) have been determined potentiometrically. With the help of NMR measurements, the protonation constants of tetraethylenepentaminehexaacetic acid (TPHA) were determined from potentiometric data. A new ligand, pentaethylenehexamineoctaacetic acid (PHOA), was investigated, and its protonation constants are also given. From the NMR data some new interpretations are made with respect to the sequence of protonation of the various basic sites in triethylenetetraminehexaacetic acid (TTHA), TPHA, and PHOA. An interpretation is given of the variations in the protonation constants for these EDTA analogues.

Introduction

Protonation sites and conformations of aminopolycarboxylic acid compounds in aqueous solutions have been investigated extensively. The literature on both ethylenediaminetetraacetic acid (EDTA) and diethylenetriaminepentaacetic acid (DTPA) is thorough and the interpretations of the data are satisfactory. However this is not the case for triethylenetetraminehexaacetic acid (TTHA) and tetraethylenepentaminehexaacetic acid (TPHA). Letkeman[1] and Martell[2] both studied TTHA with the NMR technique, and the latter supplemented it with infrared data. Both papers postulated essentially identical protonation schemes for the hexabasic anion of TTHA. Close inspection of the chemical shift (of the various nonlabile protons) vs. pH diagrams revealed an apparent "abnormality" in the behavior of the ethylenic (b + c) type protons below pH 4.0. At first this observation was attributed to the nonideality of the assumptions used by Reilley[3] and Chapman[4] in the interpretation of NMR data. Subsequently it occurred to the authors to closely examine the NMR spectra of EDTA below pH 4.0. This had not been done before due to precipitation problems when 0.2 M EDTA solutions were used. The concentration of EDTA was reduced to 0.01 M and a similar "abnormality" was observed for the ethylene protons of EDTA. Unsymmetrical ethylenediaminediacetic acid (EDDA) was chosen as a model compound to further test this abnormal NMR behavior of the ethylenic protons in EDTA and TTHA.

In addition, the available literature[5] on protonation constants for the higher analogues of EDTA was somewhat inconsistent in that various ionic strengths were maintained by different compounds such as KCl and KNO_3. Equilibrium protonation data were sparse for TPHA and nonexistent for pentaethylenehexamineoctaacetic acid (PHOA). Hence a comparative potentiometric study (under idential conditions) was undertaken on the higher analogues of EDTA as indicated below. This equilibrium study made possible a comparison of the protonation constants of the various aminopolycarboxylates and aided in the interpretation of the chemical shift vs. pH data for these compounds.

This quantative study of protonation sites and protonation constants of polyaminopolycarboxylic acids is essential for the interpretation of the equilibria of these ligands with metal ions. Such studies are now being conducted in these laboratories and will be reported later.

Experimental Section

Reagents. Standard base was prepared from "Dilute It" (J. T. Baker) KOH concentrate by dilution under CO_2-free conditions, and the 0.10 M solution was standardized against reagent grade KHP. The KOH solution was stored in a glass bottle protected against the atmosphere with a tube of dry soda lime. Commercial samples of EDTA and DTPA (J. T. Baker) were used after precipitation from water. Unsymmetrical EDDA was prepared by Dr. R. J. Motekaitis in this laboratory and analyzed at 99% purity. TTHA and TPHA were obtained from the Geigy Chemical Corp. (Basel, Switzerland) and used without further purification. The potentiometric titration showed TTHA and TPHA to be 98% and 96% pure, respectively. Pentaethylenehexamineoctaacetic acid (PHOA) was prepared by Dr. I. Murase in this laboratory. The elemental analysis and NMR spectrum confirmed the structure and purity of the acid as $PHOA \cdot 5HCl \cdot H_2O$. A subsequent paper outlines the preparation and analysis of PHOA in full. All other chemicals used in this investigation were of reagent grade purity.

Potentiometric Measurements. Samples of 0.10–0.15 mmol of solid ligand (molecular weight determined by titration) were diluted with 40.0 or 50.0 mL of distilled water in a sealed, thermostated (25 ± 0.05 °C) potentiometric titration vessel equipped with a Sargent blue type glass–calomel combination electrode, N_2 inlet and bubbler outlet, and a graduated (Metrohm) microburet. The test solution, adjusted to 0.10 M in KNO_3, was titrated with 0.10 M standard CO_2-free KOH while $-\log [H^+]$ was measured with a Beckman Research Model 1019 pH meter calibrated with strong acid and strong base so as to read directly in hydrogen ion concentration ($pK_w = -\log [H^+][OH^-]$ was 13.79). The maximum variation between calculated and observed values of pH in this calibration was ±0.01 pH unit throughout the pH range of 2–11. In this paper the term pH is used synonymously with $-\log [H^+]$.

NMR Measurements. The proton nuclear magnetic resonance spectra were recorded with a Varian HA-100 spectrometer at an ambient temperature of 34 °C (±1 °C). The spectral data obtained were average readings of several recordings with a reproducibility of ±0.5 Hz. The values of the chemical shifts were measured with respect to *tert*-butyl alcohol (TBA).

Stock solutions of the various acids (free ligands) were prepared by weighing out the appropriate amounts of solid acid and dissolving them in 10 mL of D_2O. The pH of the stock solution was adjusted by the addition of KOH or HNO_3. A Corning Model 101 pH meter used with a combination microelectrode was calibrated with a standardized acid solution to read $-\log [H^+]$.

Results and Discussion

The potentiometric data were analyzed by computer with a program developed in this laboratory (by Dr. R. J. Motekaitis), which is very similar to the ones summarized and compared in a recent paper by Leggett.[6] Our computer program had the capability of evaluating protonation constants under highly acidic conditions, thus giving a better overall fit for the potentiometric data. The results obtained included slightly lower pK_a values (below pK 3) than those reported in the literature.[5]

The NMR data are given by use of the nomenclature developed by Reilley[3] and Sawyer[7] where the protonation sites are labeled (1)–(6) and the nonlabile protons are lettered (a)–(h) as shown in Figures 1–6. The use of proton magnetic resonance in the study of complexones has been described by Kostromina.[8]

Sudmeier and Reilley[3] studied numerous model compounds and concluded that the protonation shift of methylene protons directly bonded to a tertiary amine was 0.75 ± 0.05 ppm. If

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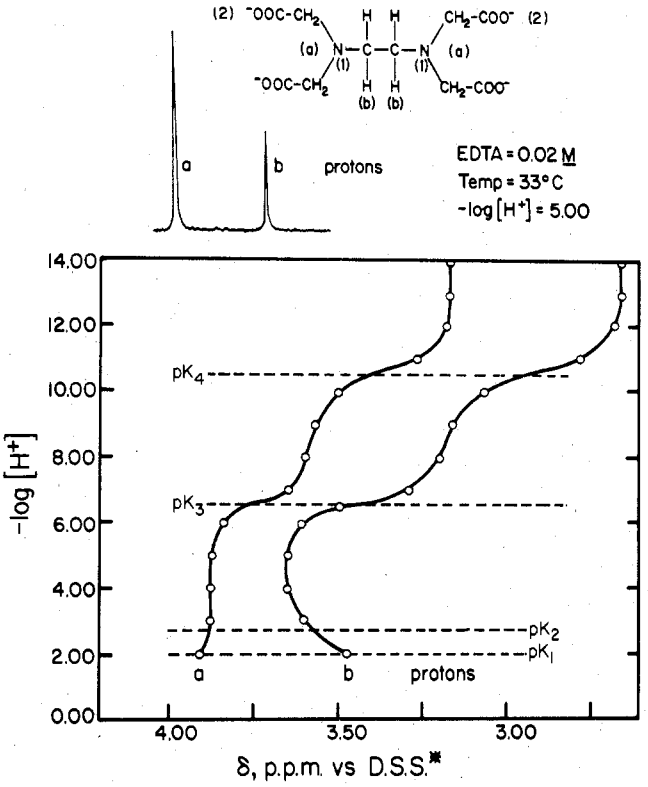


Figure 1. Chemical shift of EDTA vs. pH.

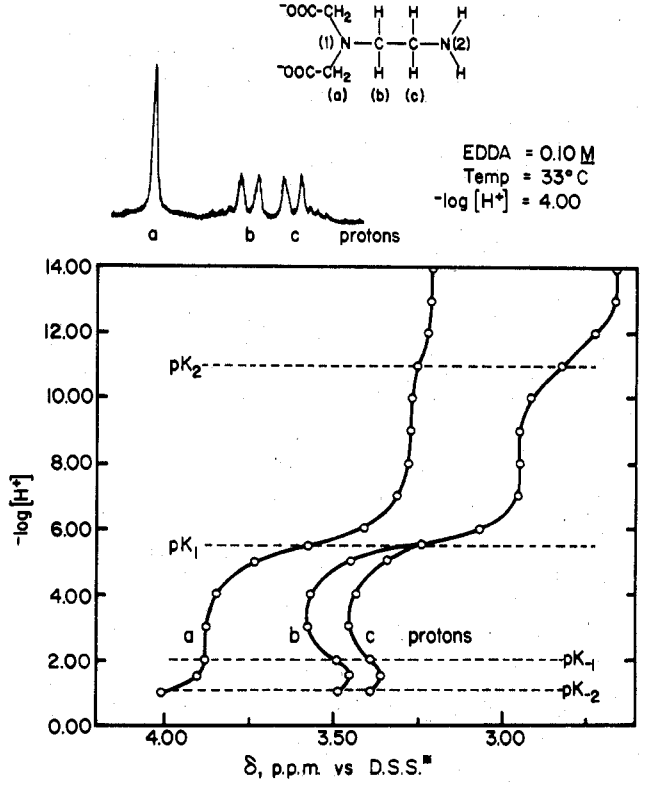


Figure 2. Chemical shift of EDDA vs. pH.

another nitrogen atom were protonated two bonds away (as in EDTA) from the original nitrogen atom, then an additional shift of 0.35 ppm was observed. The protonation shift of methylene protons directly attached to carboxylate groups was only 0.20 ppm, an important feature in distinguishing various protonation schemes. Though the above conclusions work well for many substituted EDTA type compounds, rather large deviations occur when these theoretical shifts are applied to

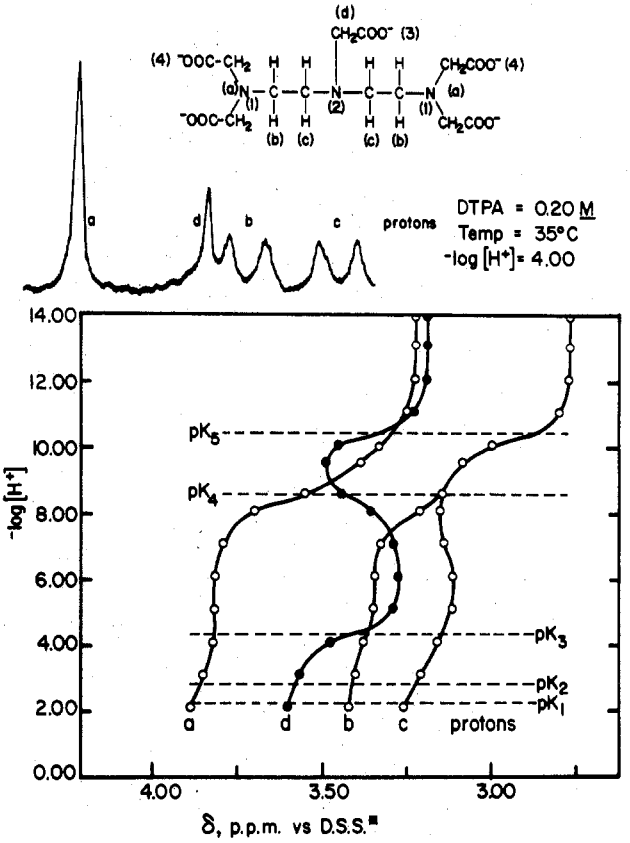


Figure 3. Chemical shift of DTPA vs. pH.

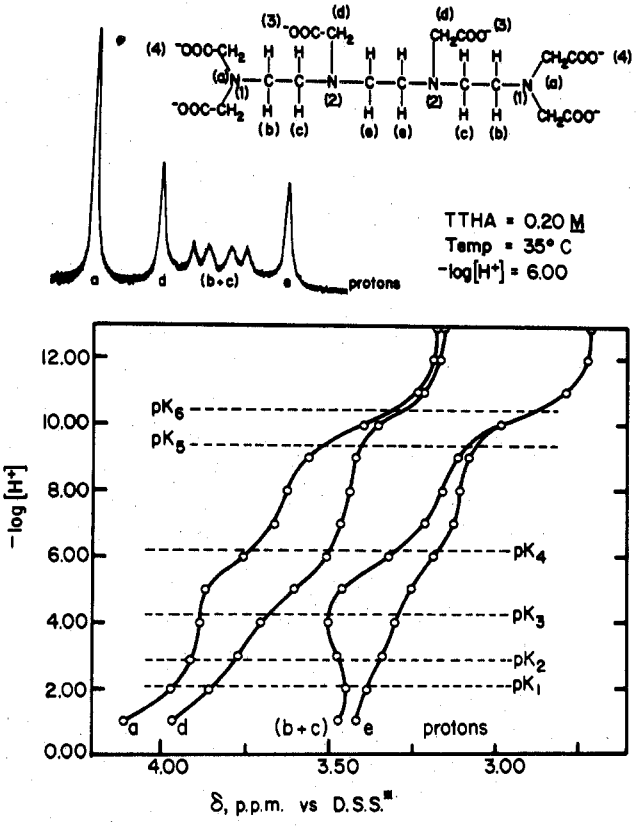


Figure 4. Chemical shift of TTHA vs. pH.

DTPA[3] and to TTHA.[1] In this paper the chemical shift of a given methylene proton deshielded by the protonation of an adjacent basic nitrogen site is defined as

$$\Delta\delta_N = \delta_A - \delta_B \qquad (1)$$

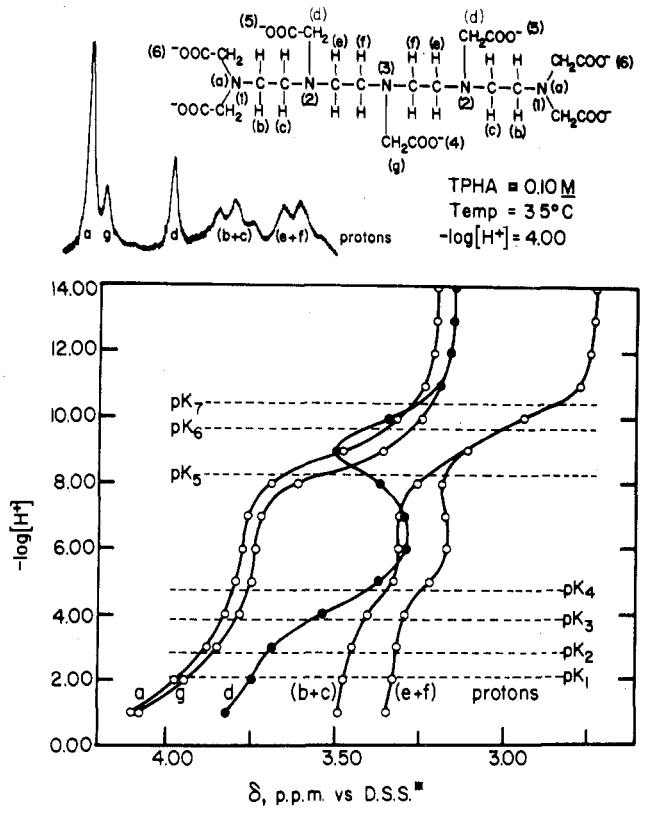


Figure 5. Chemical shift of TPHA vs. pH.

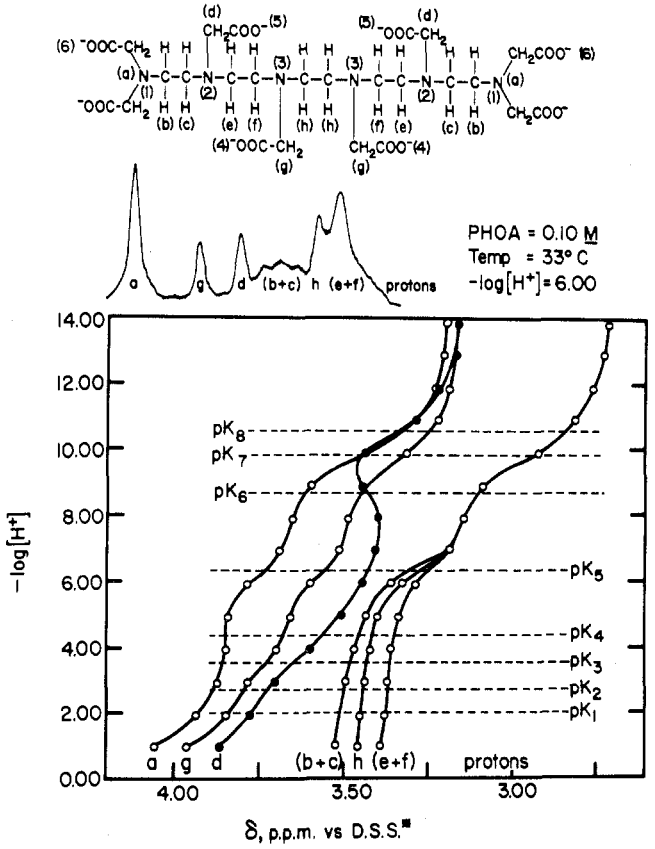


Figure 6. Chemical shift of PHOA vs. pH.

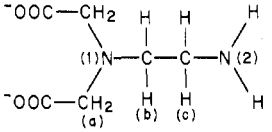
where A and B denote acidic (pH 2.5) and basic (pH 13) conditions, respectively. We recognize that a small error is introduced by setting the acidic limit at pH 2.5 since the protonation of carboxyl groups may start as much as 2 pH units above that value. However the above method is in very good agreement with the more rigorous approach used by Sudmeier and Reilley.[3] In addition, the percent protonation, P, at a given basic site i is defined as

$$P_i = [(\delta_i - \delta_B)/(\delta_A - \delta_B)] \times 100 \qquad (2)$$

and hence the fractional protonation of a basic site, f_i, can be obtained from eq 2. An important relationship ($f_1 + f_2 + \ldots = n$, where n is the number of protons bound to the ligand) as described previously[1] was used extensively in this study. In following the chemical shifts of particular protons, one finds a point of inflection where $\delta = {}^1/_2(\delta_A - \delta_B)$ or where the concentrations of the protonated and nonprotonated forms are equal. At this point then, the pK_a = pH of the solution in question. This is helpful in the postulation of protonation schemes for ligands under various pH conditions and proved to be particularly useful in the determination of pK_a's for TPHA and PHOA.

EDTA, EDDA, and TTHA. Earlier NMR studies of EDTA,[3,7] which ran into precipitation problems below pH 5, were satisfactorily explained up to that pH range. Similarly studies on TTHA,[1,2] though having no precipitation difficulties down to pH 1, were adequately explained with the concepts developed by Chapman[4] and Reilley,[3] except for the behavior of the ethylene protons (b + c type; see Figure 3) below pH 4. Letkeman and Westmore[1] attributed this upfield shift to a deprotonation of the end nitrogen atoms. This was in direct conflict with the explanation offered by Bohigian and Martell[9] in their potentiometric study. Hence, in part, this study was undertaken to resolve the above issue.

The NMR spectra (with a 100 MHz spectrometer) were run for both EDTA and TTHA as shown in Figures 1 and 4. With only 0.02 M EDTA, spectra were recorded down to pH 2.0, and an upfield shift for the ethylene protons showed up below pH 4 very similar to the TTHA case. The obvious explanation would be a deprotonation of the end nitrogen atoms in the ligand except for the fact that the (a) protons should also be affected by such a deprotonation, and yet the (a) protons showed further protonation. This could be partially explained by the fact that if the end carboxyl groups were protonated extensively[1] then the (a) protons would move downfield due to the carboxyl protonation. However the chemical shift due to carboxyl protonation (δ_C 0.20) is only one-fourth the shift of a nitrogen protonation. In search of more information to explain the NMR data, a model compound, unsymmetrical EDDA, was studied. The results are



given in Figure 2. Clearly the first mole of H^+ added to the basic anion of EDDA attaches itself to the $N_{(2)}$ atom and the second mole of H^+ is situated on $N_{(1)}$. The (b) protons are deshielded (under acidic conditions) more than the (c) protons because of their closer proximity to the carboxyl groups. When a third mole of H^+ is added, the ethylenic protons again move upfield as was the case for EDTA and TTHA. In the EDDA case, it is not reasonable to postulate a deprotonation of nitrogen atoms in favor of carboxyl protonation because the chemical shift of (a) protons points toward further deshielding as the pH is lowered. It is well-known that adjacent nitrogen atoms can be protonated to a large extent under acidic conditions as reported by Reilley[3] and Sawyer;[10] see Figure 3. Hence the following model best explains all of the available information.

When only 1 mol of H^+ is added to the anion of EDDA, the end carboxyl groups freely rotate, and an average electrical environment is exposed upon the rest of the molecule. After

Table I

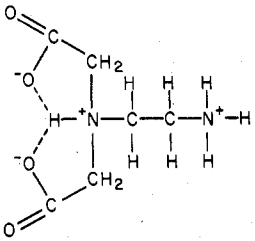
source	pK_1	pK_2	pK_3	pK_4	pK_5	pK_6	pK_7	ionic strength
Dyatlova et al.[14]		2.80	3.82	5.56	8.88	9.95		0.1 M (KCl)
Dyatlova et al.[15]			2.80	3.82	5.56	8.88	9.95	0.1 M (KCl)
Bohigian[16]	1.84	2.30	2.92	3.90	5.33	8.23	9.99	0.1 M (KNO_3)

Table II. Percent Protonation at Various Basic Sites[a]

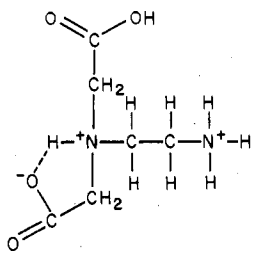
n	$N_{(1)}$	$N_{(2)}$	$N_{(3)}$	$\Sigma f_i = n$
		EDTA $(2f_1 = n)$		
1	50			1.0
2	95			1.9
		DTPA $(2f_1 + f_2 = n)$		
1	25	50		1.0
2	85	20		1.9
3	90	80		2.6
		TTHA $(2f_1 + 2f_2 = n)$		
1	30	25		1.1
2	60	40		2.0
3	90	60		3.0
		TPHA $(2f_1 + 2f_2 + f_3 = n)$		
1	15	25	15	1.0
2	35	50	25	1.9
3	80	25	80	2.9
4	85	60	85	3.8
		PHOA $(2f_1 + 2f_2 + 2f_3 = n)$		
1	20	25	15	1.2
2	40	40	30	2.2
3	65	35	50	3.0
4	85	50	65	4.0

[a] n is the number of moles of H^+ ions added per mole of the ligand anion, and Σf_i is the calculated value of n from the percent protonation given in the table.

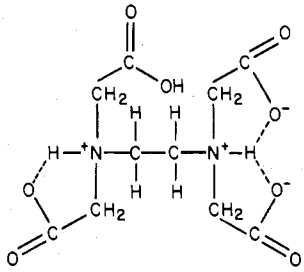
the second mole of H^+ has been added, the carboxyl groups become semistationary due to H-bonding as outlined in a paper by Fujiwara and Reilley,[11] and illustrated below.



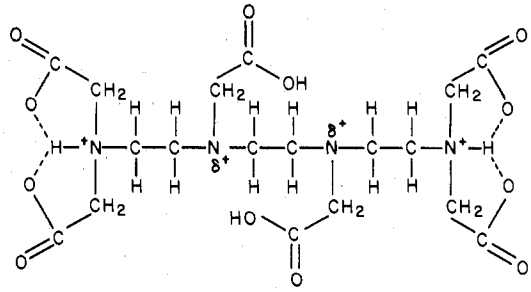
This accents the chemical shift experienced by the ethylenic protons and is exhibited in Figure 2. When the third mole of H^+ is added, one of the carboxyl groups must become protonated thereby destroying the H-bond bridging of the doubly protonated molecule. Then the protonated carboxyl group is repelled from the bridged structure containing a protonated nitrogen atom. The magnetically anistropic COOH group now spends an appreciable amount of time in the vicinity of the ethylene backbone of the molecule as shown below.



It is well-known that the carbonyl group has both a negative and a positive long-range shielding effect depending on the orientation and distance that a hydrogen atom is separated from the carbonyl carbon atom.[12] The classic example of the carbonyl group illustrating a positive shielding effect is the identical chemical shifts of the β methylene group in cyclobutanone. These protons have the same shift as the protons in cyclobutane. It has been shown that the positive shielding region of a carbonyl group is close to the x axis at the "carbon end" of the bond and that above and below the plane of the bond, in the vicinity of the z axis, the shielding is positive as well. In the EDDA and EDTA cases, it is postulated that when a protonated carboxyl group swings away from the protonated nitrogen end of the molecule it will spend most of its time near the ethylene backbone of the molecule. This behavior then will introduce a measure of shielding for the (b) + (c) protons which in turn exhibit a chemical shift upfield under these conditions. The following structures are proposed for EDTA andd TTHA, respectively.



3 mol of H^+ added (H_3A^-)



4 mol of H^+ added (H_4A^-)

In the TTHA case,[1] the end nitrogens are protonated 90% of the time at pH 3.0, whereas the central nitrogens are protonated only 60%. The central carboxyl groups are estimated to be protonated about 50% of the time while the end carboxyl groups are virtually free of protons. Hence the above structure fits the protonation scheme and suggests that the protonated carboxyl groups are responsible for the "abnormal" behavior of the (b) + (c) protons below pH 4.0 as shown in Figure 4.

DTPA and TPHA. DTPA was studied by NMR spectroscopy previously,[3,10] and Figure 3 is given in this paper as an aid for the interpretation of the NMR data for TPHA. Letkeman and Sawyer[13] studied TPHA with NMR spectroscopy and postulated a protonation scheme for this relatively new ligand. They used the protonation constants of TPHA as reported by Dyatlova and Lastovkii[14] in a review paper. Later a detailed literature study revealed that those pK_a's had been typed incorrectly and that the original article[15] quoted them differently. Another unpublished study[16] of TPHA was found which was in close agreement with Dyatlov et al.[15] (see Table I). A number of investigators have studied the metal complexes of TPHA with the above constants of ref 15. However, the protonation scheme for TPHA as outlined by

Table III. Protonation Constants of Some Aminopolycarboxylic Acids[a]

	EDTA	DTPA	TTHA	TPHA	PHOA
pK_{-2}		1.45	1.50	1.40	1.40
pK_{-1}		1.75	1.80	1.70	1.70
pK_1	2.00	2.06	2.10	2.00	2.02
pK_2	2.60	2.73	2.76	2.69	2.52
pK_3	6.11	4.28	4.10	3.78	3.57
pK_4	10.21	8.65	6.18	4.75	4.48
pK_5		10.59	9.62	8.13	6.20
pK_6			10.68	9.87	8.85
pK_7				10.76	9.96
pK_8					10.85

[a] The potentiometric studies were carried out at 25 ± 0.05 °C and at an ionic strength of 0.10 M in KNO_3.

Letkeman and Sawyer[13] assumed a sharp break at 4 mol of base added/mol of acid and not 5 mol of base/mol of acid as the corrected pK_a's would indicate. Thus the logical protonation scheme given by Letkeman and Sawyer was in conflict with the accepted pK_a's of TPHA. This prompted the authors to reexamine both the NMR and potentiometric data for TPHA.

The NMR spectra of DTPA (δ vs. pH) are shown in Figure 3 and turn out to be a classic example of how NMR can provide conclusive information on the sequence of protonation of an aminopolycarboxylic acid. Not only can one clearly differentiate which nitrogen atoms are protonated at a give pH but the sharp break between pK_3 and pK_4 is also evident.

With the method outlined earlier, the preferred protonation sites and the extent of protonation were determined quantitatively for the TPHA anion. Table II shows the extent of protonation of various nitrogen sites for a number of EDTA analogue-type compounds. Figure 5 definitely indicates a sharp break when 4 mol of base has been added to 1 mol of TPHA. The original protonation scheme[13] was the only logical explanation available. Hence a potentiometric study was undertaken on DTPA, TTHA, and TPHA. These results are summarized in Table III. The titration data were analyzed by computer and showed good agreement for DTPA and TTHA with the published values.[5] However our pK_a's for TPHA are substantially different from those of Dyatlova[15] and Bohigian,[16] who both used graphical methods. We can only speculate that either the higher purity of the TPHA or the newer computer methods account for the discrepancy of these values.

Theoretically the addition of 1 mol of acid to 1 mol of TPHA anion should yield a solution of $pH = {}^1/_2(pK_7 + pK_6) \simeq 10.2$. It also follows that $2f_1 + 2f_2 + f_3 = 1.0$ for 1 mol of H^+ added to the TPHA anion. Both of these statements are in good agreement with the experimental data in Figure 5 and the protonation calculations given in Table II. In addition, when 2 mol of acid has been added, the $pH = {}^1/_2(pK_6 + pK_5) \simeq 9.0$ and theoretically $2f_1 + 2f_2 + f_3 = 2.0$. Again the experimental data confirm this. Subsequent addition of a third mole of acid should yield a solution of $pH = {}^1/_2(pK_5 + pK_4) \simeq 6.5$ and $2f_1 + 2f_2 + f_3 = 3.0$. One could go another step in this analysis and find that ${}^1/_2(pK_4 + pK_3) \simeq 4.5$ where $2f_1 + 2f_2 + f_3 = 4.0$ in perfect agreement with the experimental values given in Table II.

It is interesting to note the correlation between the protonation constants of the polyamines[18] with the pK_a's of the carboxylic acid derivatives as tabulated in Table III. It is also noteworthy that the sharp inflection points of the titrations of both the amine and the carboxylic acid occur at the same mole ratio of base to acid; i.e., dien has a break at 2 mol of base/mol of amine, trien is the same, and tetren has a break at 3 mol of base/mol of amine. This corresponds to our potentiometric measurements for TPHA as well as the NMR data and points out convincingly that the protonation constants as given in this paper are the correct ones.

PHOA. The pK_a's of PHOA in Table III indicate a break in the titration curve between pK_5 and pK_6. This corresponds to 5 mol of base added/mol of PHOA. The NMR data also support such a conclusion. A detailed potentiometric study of the free ligand and selected metal–ligand ratios will be published shortly.[17]

Figure 6 shows the chemical shift vs. pH diagram for PHOA. From the NMR data one concludes that the first 2 mol of acid added to 1 mol of the anion of PHOA is distributed almost evenly among the various basic nitrogen sites, with the highest preference of protonation being on $N_{(2)}$ positions, since the (d) protons move downfield faster than either the (a) or (g) protons. When a third mole of H^+ is added, the $N_{(2)}$ positions deprotonate and the $N_{(1)}$ and $N_{(3)}$ are favored for protonation. Further addition of acid shows an almost equal protonation of the various basic nitrogen sites. The above generalizations are supported by summations of fractional protonation, f_i, of the various sites as given in Table II. The correlation between theoretical additions of base, n, and those obtained by adding the various f_i values from experimental data is excellent for $n = 3$ and 4 and not as good for $n = 1$ and 2. The latter values doubtless suffer both from the purity of the PHOA (95% plus) and from the basic assumptions used in this treatment. However on the whole, the NMR data for PHOA compares favorably with that obtained for the other analogues of EDTA and so provides an additional measure of confidence in the new pK_a's of PHOA.

Summary

Table III shows the gradual increase in basicity of the highest pK_a's of the EDTA analogues and a relatively constant value for pK_1 and pK_2. This can be rationalized by the interpretation that the first two protonation constants are due to protonation of carboxyl groups whereas the other protonation constants are a result of the basic nitrogen sites accepting protons. It would appear that the lengthening of the chain (addition of $HOOC-CH_2-N-CH_2-CH_2-$) from EDTA to PHOA causes the highest pK_a's to increase gradually, i.e., become easier to protonate. This correlation can be accounted for by purely electrostatic considerations.

The pK's of the parent polyamines[18] and the protonation constants of the corresponding polyaminopolyacetic acids in Table III clearly indicate the analogous locations of the breaks in the potentiometric curves of these ligands. In retrospect it is evident that earlier studies[14-16] on TPHA should have revealed a break at 4 mol of base/mol of ligand, considering the behavior of tetraethylenepentamine. The above correlations provide further support for the protonation constants assigned to PHOA. The NMR data added valuable information on the protonation sequence of the various basic sites in each ligand and confirmed earlier conclusions that the carboxyl groups in EDTA analogues protonate appreciably only below pH 4.0.

This paper establishes the foundation for subsequent studies of the coordination sites and affinities of polyaminopolyacetic acids with various metal ions. The metal chelating properties of PHOA as well as TPHA are now being studied in this laboratory and should be reported soon.[17]

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Registry No. EDTA, 60-00-4; DTPA, 67-43-6; EDDA, 5835-29-0; TTHA, 869-52-3; TPHA, 3234-59-1; PHOA, 69531-85-7.

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Electron Transfer. 41. Rate Enhancement by Ligands in Which Conjugation Is Interrupted[1]

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Seven new carboxylatocobalt(III) complexes, each with a pyridine ring separated from the $-COOCo^{III}$ group by a saturated unit, have been prepared and their reductions with Cr^{2+} and Eu^{2+} studied. Specific rates are well above those for reduction of the ordinary aliphatic and aromatic carboxylato complexes of $(NH_3)_5Co^{III}$ when, and only when, a $-C(=O)NH-$ group lies in the γ position on the ring. Rate enhancement for the Cr^{2+} reduction of complexes of the type $Inic^+-C-COOCo^{III}$ (II and III), in which a single carbon separates the ring and the carboxyl, are particularly striking, exceeding those reported for a number of complexes in which the two functions are in direct conjugation. The rapid europium(II) reductions exhibit strong autocatalytic components, reflecting catalysis of the primary reactions by the ligand released. In these cases, very nearly linear kinetic decay curves demonstrate the specific rate of the uncatalyzed component to be nearly equal to that for Eu^{2+} reduction of the free ligand, which is the initiation step in the catalytic sequence. The properties of the Cr(III) products from the rapid Cr^{2+} reductions correspond to those of a $-COOCr^{III}$ rather than a $-C(NH_2)=OCr^{III}$ complex, indicating coordination of chromium to the carbonyl of the $-COOCo^{III}$ in the activated complexes and ruling out a two-step internal catalytic mechanism. The structures of the very rapid oxidants preclude rate enhancement by chelation or by conjugation of the usual type but appear to allow intervention of a homoallylic type intermediate such as X (or one featuring through-space interaction), in which chromium or europium is bound both to the lead-in carbonyl and, by π interaction, to the activated pyridine ring. It is further suggested that the latter interaction occurs with preliminary, but reversible, electron transfer to the ring. Similar intermediates may intervene in the Eu(II) reductions of the parent ligands, which have been found to be about 10^2 times as rapid as that of the protonated form of isonicotinamide, in which an ^+NH function replaces $^+N-C-COOH$.

Although an array of diverse systems has been described in which inner-sphere reduction of cobalt(III) is strikingly accelerated by bound carboxylato or a related ligand,[2] virtually all such cases fit one of two descriptions. In the first category are substituents in which a donor substituent is available for chelation with the reducing center; these are thought generally to enhance the electron-transfer process by increasing the association constant of the binuclear precursor complex.[3] In quite another group are ligands in which an unsaturated donor function, such as carbonyl or pyridine nitrogen, lies in conjugation with the coordinated carboxyl; these are presumed to increase the rate of internal electron transfer within the precursor.[4,5] Acceleration may be particularly marked when possibilities for both conjugation and chelation exist in the same ligand.[2c,6]

Quite apart from these effects is the catalysis of electron transfer by noncoordinated conjugated species capable of undergoing one-electron reduction to radicals,[7] which, in turn, are known to react very rapidly with cobalt(III) centers.[8] Earlier communications from this laboratory dealt with such catalytic processes.[7b,c,9]

The present study began as an attempt to design an intramolecular analogue of such catalytic systems in which the catalytic center and the oxidizing center are incorporated into a single molecule or ion. It was expected that initial attack on such difunctional oxidants would occur at the catalytic center, followed by rapid electron transfer to Co(III), and that the overall rate of reduction, which would be determined principally by the rate of initiation, might be substantially greater than that for a complex having no such catalytic site. If mechanistic ambiguity were minimized by precluding conjugative interaction between the two centers, such a reaction sequence should constitute a clear-cut example of the radical-ion or chemical mechanism, which has often been proposed[5,10] but infrequently demonstrated[11] for inner-sphere reductions.

We here report our findings concerning the reductions of such insulated bifunctional complexes, including some rate enhancements which are considerably greater than those anticipated. At the same time, however, our evidence suggests that these rapid reductions proceed not through the expected two-step path but rather by a variation of inner-sphere attack at the bound carboxyl.

Experimental Section

Inorganic Materials. Lithium perchlorate,[12] carbonatopentaamminecobalt(III) nitrate,[13] aquopentaamminecobalt(III) perchlorate,[13] and solutions of Cr(II),[13] Eu(II),[14] and V(II)[15] were prepared as described.

Organic Ligands. 4-Carbamoyl-1-(carboxymethyl)pyridinium perchlorate ($Inic^+CH_2COOH(ClO_4^-)$) was prepared by a method similar to that of Craig and co-workers,[16] in which isonicotinamide was alkylated with iodoacetic acid in water. Iodide and unreacted iodoacetate were removed by stirring with three successive portions of anion-exchange resin (Bio-Rad AG 2-X8) in its HCO_3^- form, after

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