BULLETIN OF THE CHEMICAL SOCIETY OF JAPAN VOL. 41 838—843 (1968)

Synthesis of Chelating Agents. V.*[1] 1,2,3-Triaminopropanehexaacetic Acid and Its Acid Dissociation Scheme*[2]

Mitsumasa MIYAZAKI,*[3], *[4] Yoshiki MORIGUCHI and Keihei UENO

Department of Organic Synthesis, Faculty of Engineering, Kyushu University, Hakozaki, Fukuoka

(Received October 30, 1967)

1,2,3-Triaminopropane-*N,N,N',N',N'',N''*-hexaacetic acid (TAPHA) was synthesized by the carboxymethylation of 1,2,3-triaminopropane. The acid dissociation scheme of the ligand was studied by means of potentiometric titration, infrared absorption spectroscopy and proton nuclear magnetic resonance spectroscopy. It is found that TAPHA exists as a zwitter ion in aqueous solution, in which protons attach to each nitrogen atom of 1- and 3-carbon, and that the dissociations of first four and the last two steps correspond to the dissociations of carboxylic protons and ammonium protons, respectively. The stepwise proton dissociation constants of the ligand is determined as $pK_1 \approx 2$, $pK_2=2.43$, $pK_3=3.52$, $pK_4=4.30$, $pK_5=8.26$ and $pK_6=9.88$ ($\mu=0.1$, 25°C).

Many multidentate complexanes such as EDTA, DTPA (diethylenetriaminepentaacetic acid)¹⁾ and TTHA (triethylenetetraminehexaacetic acid²⁾ have been synthesized and the relationships between their structures and chelating behaviors have been discussed in various ways. In our laboratories, our efforts have been focused to the syntheses of multidentate complexanes with a hope of finding the ligands with high metal ion specificity, and some of the results have been published in the previous papers of this series.³⁾

This paper is to report on the synthesis of the new ligand, 1,2,3-triaminopropane-*N,N,N',N',N'',N''*-hexaacetic acid (TAPHA), and on the acid dissociation scheme of this ligand. TAPHA has been synthesized in 84% yield from 1,2,3-triaminopropane by the alkaline condensation of three moles of bromoacetic acid per mole of triamine, followed by the repeated carboxymethylation with sodium cyanide and formaldehyde.

Before going into the investigation on the chelating behavior of the ligand, the acid dissociation scheme of TAPHA has been investigated by the conventional potentiometry, the infrared absorption spectroscopy and the proton nuclear magnetic resonance spectroscopy. A microscopic picture of the acid dissociation scheme of this nonadentate hexabasic acid has been establsihed from these results.

During the course of our investigation, a British Patent has been published on the synthesis of TAPHA just after we have succeeded in the synthesis, but no detailed procedure of the synthesis nor detailed chelating behavior of this ligand was available.⁴⁾

Experimental

Synthesis of Ligand. 1,2,3-Triaminopropane-*N,N,N',N',N'',N''*-hexaacetic acid (TAPHA) was synthesized by the carboxymethylation of 1,2,3-triaminopropane.

1,2,3-*Triaminopropane (IV)*.⁵⁾ The triamine was synthesized from allyl chloride (I) *via* allylamine (II)⁶⁾ and 1-amino-2,3-dibromopropane hydrobromide (III)⁷⁾ succesively. The crude triamine was purified by vacuum distillation, bp 89—90°C/15 mmHg. The triamine was identified by the melting point and elementary analysis of tribenzoyl derivative, and IR spectra of free amine. The purity of the triamine determined by the perchloric acid titration in acetic acid, was 97.4%.

TAPHA (VI). The alkaline condensations of chloroacetic acid or bromoacetic acid with triamine (IV) have been tried in various conditions. The reaction

---

[1] Paper IV; N. Okaku, K. Toyota, Y. Moriguchi and K. Ueno, This Bulletin, **40**, 2326 (1967).

[2] Contribution No. 146 from the Department of Organic Synthesis, Kyushu University.

[3] Taken in part from the thesis of Master of Engineering, Kyushu University of M. M.

[4] Present Address: Amagasaki Plant, Dainippon Ink Chem. Ind. Ltd., Amagasaki-shi.

1) a) E. J. Durham and D. P. Ryskiwich, *J. Am. Chem. Soc.*, **80**, 4812 (1958); b) G. Anderegg, P. Nägeli, F. Müller and G. Schwarzenbach, *Helv. Chim. Acta*, **42**, 827 (1959); c) S. Chaberek, A. E. Frost, M. A. Doran and N. J. Bicknell, *J. Inorg. Nucl. Chem.*, **11**, 184 (1959).

2) a) J. H. Grimes, A. J. Huggard and S. P. Wilford, *J. Inorg. Nucl. Chem.*, **25**, 1225 (1963); b) T. A. Bohigian and A. E. Martell, *Inorg. Chem.*, **4**, 1264 (1965).

3) N. Okaku, K. Toyota, Y. Moriguchi and K. Ueno, This Bulletin, **40**, 2326 (1967).

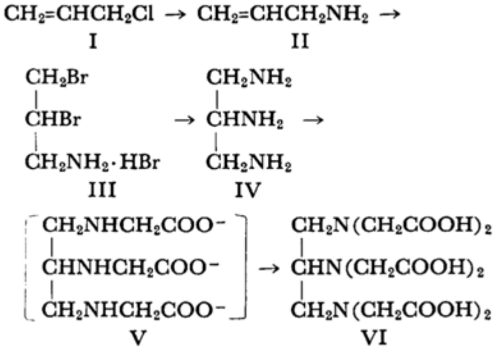
4) J. R. Geigy A. G. Brit. Pat. 926351; *Chem. Abstr.*, **59**, 11264f (1963).

5) J. E. Sutton, *Roy. Australian Chem. Inst. J. & Proc.*, **17**, 232 (1900).

6) A. Clavier, *Bull. Soc. Chim. France*, **1954**, 646.

7) C. Paal and C. Hermann, *Ber.*, **22**, 3076 (1889).

with chloroacetic acid gave no desired product, but gave unidentified partially carboxylated products. The reactions with bromoacetic acid gave TAPHA in very low yield (less than 3.5%). The repeated carboxymethylation of triamine with sodium cyanide and formaldehyde[8] gave also TAPHA, but still in low yield (less than 6.1%). The best result was obtained by the alkaline condensation of three moles of bromoacetic acid with one mole of triamine, followed by the repeated carboxymethylation with sodium cyanide and formaldehyde. The condition of the typical run is as follows.



$$\underset{\text{I}}{CH_2{=}CHCH_2Cl} \rightarrow \underset{\text{II}}{CH_2{=}CHCH_2NH_2} \rightarrow$$

$$\underset{\text{III}}{\begin{array}{l} CH_2Br \\ | \\ CHBr \\ | \\ CH_2NH_2\cdot HBr \end{array}} \rightarrow \underset{\text{IV}}{\begin{array}{l} CH_2NH_2 \\ | \\ CHNH_2 \\ | \\ CH_2NH_2 \end{array}} \rightarrow$$

$$\underset{\text{V}}{\left[\begin{array}{l} CH_2NHCH_2COO^- \\ | \\ CHNHCH_2COO^- \\ | \\ CH_2NHCH_2COO^- \end{array}\right]} \rightarrow \underset{\text{VI}}{\begin{array}{l} CH_2N(CH_2COOH)_2 \\ | \\ CHN(CH_2COOH)_2 \\ | \\ CH_2N(CH_2COOH)_2 \end{array}}$$

Plate 1

In a 300 m*l* reaction flask, a solution of 94.2 g (1.0 mol) of monochloroacetic acid in 70 m*l* water was neutrized to phenolphthalein with 10 N sodium hydroxide solution below 15°C. To this solution, 17.8 g (0.20 mol) of triamine (IV) was added with stirring, and the mixture was heated to 30—45°C. The pH of the mixture was maintained at 10—11 (red to phenolphthalein) by adding sodium hydroxide solution intermittently. It took 25—35 hr to consume theoretical amount of alkali. After then, another 5 m*l* of 10 N sodium hydroxide solution was added and the reaction mixture was heated at 45°C for an additional hour. In a 500 m*l* three-necked flask fitted with a stirrer, a dropping funnel and a distilling column, the above reaction mixture (V) was placed with 6.8 g of sodium hydroxide and 43.6 g (0.89 mol) of sodium cyanide. To this solution, 70 m*l* of aqueous solution containing 0.10 mol of formaldehyde was dropped continuously with stirring at 25°C for 5 hr. After the addition of formaldehyde, the reaction mixture was distilled at reduced presure below 60°C. After 70 m*l* of distillate was obtained, 100 m*l* of water was added to the residue and the distillation was continued under the same condition until 100 m*l* of water distilled. Then the reaction mixture was cooled to 25°C and another formaldehyde solution was dropped slowly into it. After addition of formaldehyde the distillation was repeated again. This process was repeated for eight times. The total amount of formaldehyde added was 0.80 mol. Finally, the pH of the reaction mixture was adjusted to about 1 with 6 N HCl. After keeping the solution in an refrigerator overnight, the white precipitate was separated by filtration, washed with water and was dried at reduced pressure overnight (55.7 g). An additional amount (20.6 g) of the product was obtained by concentrating the filtrate. Total yield 76.3 g (84% for triamine (IV)). The crude product was purified by repeated recrystallization from hot water. When it was dried in vacuum over phosphorus pentoxide or silica gel at 120°C overnight, monohydrate was obtained as white crystalline powder that was slightly soluble in cold water and decomposed at 233.5—230°C.

Found: C, 39.85; H, 5.51; N, 9.16%; mol wt, 458 (Neut. equiv.). Calcd for $C_{15}H_{25}O_{12}N_3\cdot H_2O$: C, 39.56; H, 5.53; N, 9.23%; mol wt, 455.

Measurement of Infrared Absorption Spectra. The spectra were recorded with a Nippon Bunko Model DS 301 double-beam spectrophotometer equipped with sodium chloride optics. The spectra of free ligand as well as its sodium salts were studied in solid phase by Nujol mull method (Fig. 1). The spectra were also measured in a deuterium oxide solution as a function of pD using a cell with calcium fluoride windows. The p*d* of the solution was adjusted by adding sodium deuteroxide solution which was prepared by dissolving metallic sodium in deuterium oxide. Three characteristic absorption bands of 1720, 1625—1630, 1590 cm^{-1} were assigned to $=NCH_2COOH$, $=N^+HCH_2COO^-$, $=NCH_2COO^-$ respectively,[9] and their spectra at various pD values are reproduced in Fig. 2.

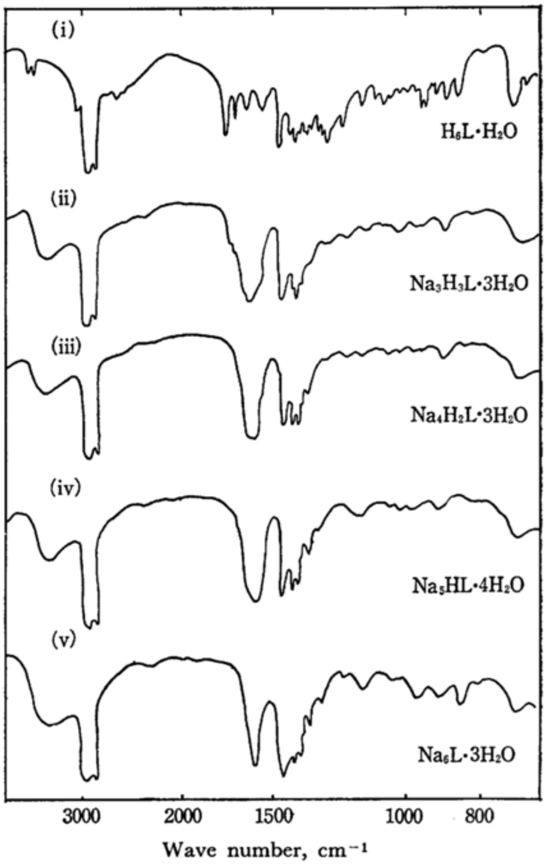


Fig. 1. Infrared spectra of TAPHA free acid and its sodium salts in Nujol mull.

---

[8] R. Smith, J. L. Bullock, F. C. Bersworth and A. E. Martell, *J. Org. Chem.*, **14**, 355 (1949).

[9] Y. Tomita, T. Ando and K. Ueno, *J. Phys. Chem.*, **69**, 404 (1965).

Measurements of Proton Nuclear Magnetic Resonance Spectra. The spectra were studied as a function of pH with a Varian A-60 high resolution spectrometer equipped with a 60 Mc oscillator. *t*-Butylalcohol was used as an internal reference (τ= 8.78 ppm). The pH of the aqueous solution was adjusted by the careful addition of 5 N nitric acid to 1 m*l* of 0.5 M TAPHA stock solution (pH≒12), which was prepared by dissolving free acid in aqueous potassium hydroxide solution. The pH of sample solutions was measured with a Hitachi-Horiba Model P pH meter equiped with a micro glass electrode.

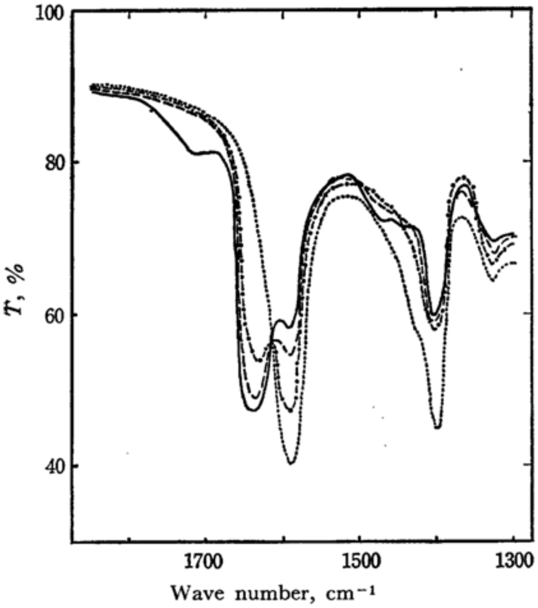


Fig. 2. Infrared spectra of TAPHA in D_2O at various pD values; ——, pD=4.4; - - -, pD= 5.8; -·-·-, pD=8.4; ····, pD≒14.

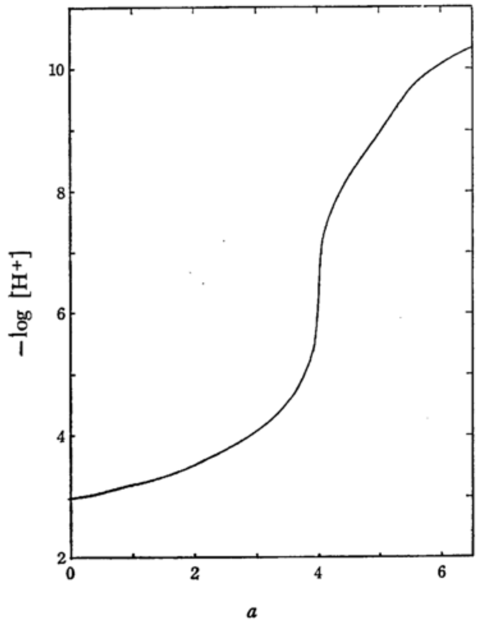


Fig. 3. pH titration curve of TAPHA (5×10^{-4} M) at 25°C in 0.1 M KNO_3.

Measurements of Acid Dissociation Constant. The same apparatus as described in our previous paper was employed.[3] The measurements were carried out at 25±0.1°C in aqueous solution of ionic strength μ=0.1 with KNO_3. For the determination of acid dissociation constant, a 200 m*l* of 5—6×10^{-4} M solution of the ligand was titrated with carbonate free 1×10^{-1} N potassium hydroxide solution. The pH meter was a Hitachi-Horiba Model P and was calibrated under a constant ionic stregnth (0.1) by refering to hydrogen ion concentration calculated from the acetic acid - potassium hydroxide system. A typical result of the titration is shown in Fig. 3.

Calculation of Acid Dissociation Constants

It is seen from Fig. 3 that the dissociations of first four steps are clearly separated from the last two steps. Thus, the calculation of dissociation constants of first four steps and last two steps can be conducted separately.

In general, when the successive acid dissociation constants of *m*-basic acid are defined by Eq. (1), these constants can be calculated from a set of *m* equations as expressed by Eq. (2) using *m* numbers of data of a pH titration curve.[10]

$$\left.\begin{aligned} K_1 &= [\mathrm{H}][\mathrm{H}_{m-1}\mathrm{L}]/[\mathrm{H}_m\mathrm{L}] \\ K_2 &= [\mathrm{H}][\mathrm{H}_{m-2}\mathrm{L}]/[\mathrm{H}_{m-1}\mathrm{L}] \\ &\;\vdots \qquad \vdots \\ K_m &= [\mathrm{H}][\mathrm{L}]/[\mathrm{HL}] \end{aligned}\right\} \quad (1)$$

$$(1-n_i)[\mathrm{H}]_i/K_m + (2-n_i)[\mathrm{H}]_i{}^2/K_mK_{m-1} + \cdots + (m-n_i)[\mathrm{H}]_i{}^m/K_mK_{m-1}\cdots K_1 - n_i = 0 \quad (2)$$

where

$$n_i = m - a_i + ([\mathrm{OH}]_i - [\mathrm{H}]_i)/L_t \quad (3)$$

and a_i and L_t represent the moles of alkali added per mole of ligand at *i*th datum in a pH titration curve and total concentration of ligand respectively. In this paper, the equation for solving Eq. (2) is expressed as the matrixes of Eqs. (4) and (5) and the calculation were carried out at the Computation Center of Kyushu University with a program of Gauss-Jorden method.

$$\begin{vmatrix} J_{11} & J_{12} & J_{13} & J_{14} & n_1 \\ J_{21} & J_{22} & J_{23} & J_{24} & n_2 \\ J_{31} & J_{32} & J_{33} & J_{34} & n_3 \\ J_{41} & J_{42} & J_{43} & J_{44} & n_4 \end{vmatrix} \qquad a_i \leqq 4 \quad (4)$$

$$\begin{vmatrix} J_{11} & J_{12} & n_1 \\ J_{21} & J_{22} & n_2 \end{vmatrix} \qquad 4 < a_i \leqq 6 \quad (5)$$

in which, elements of the matrixes are expressed by Eqs. (3) and (6).

---

[10] G. Schwarzenbach, *Helv. Chim. Acta*, **33**, 947 (1948).

TABLE 1. ACID DISSOCIATION CONSTANTS OF TAPHA AND RELATED COMPLEXANES
$\mu=0.1$ (KNO_3), 25°C

	pK_1	pK_2	pK_3	pK_4	pK_5	pK_6	Ref.
TAPHA	≈2	2.43 ±0.14	3.52 ±0.01	4.30 ±0.01	8.26 ±0.02	9.88 ±0.03	
EDTA	1.99	2.67	6.16	10.23			12
TMDTA	2.0	2.67	7.91	10.27			11
DTPA	1.6	2.64	4.27	8.60	10.58		1b
TTHA	2.42	2.95	4.16	6.16	9.40	10.19	2b

TMDTA: Trimethylenediaminetetraacetic acid
DTPA: Diethylenetriaminepentaacetic acid
TTHA: Triethylenetetraaminehexaacetic acid

$$J_{ij} = (j-n_i)[H]^i \qquad (6)$$

For Eq. (4), $m=4$; $i, j=1, 2, 3, 4$

For Eq. (5), $m=6$; $i, j=1, 2$

The results are shown in Table 1 along with those of other complexanes of related structure.

Results and Discussion

As shown in Fig. 3, there is a marked pH jump at $a=4$, so it is expected that the nature of the acid dissociation of the first four steps are quite different from those of the last two steps, and that TAPHA exists as zwitter ion in aqueous solution. If one compares the acid dissociation constants of TAPHA with those of the other complexanes (Table 1), it is clear that the first four and the last two steps correspond to the dissociations of the carboxylic protons and ammonium protons respectively.

This view is also confirmed from the pD dependence of infrared absorption spectra of TAPHA in deuterium oxide solution. The characteristic absorption bands of TAPHA in deuterium oxide solution over a range of 1800—1300 cm^{-1} are reproduced in Fig. 2. Three bands at 1720, 1630—1625 and 1590 cm^{-1} can reasonably be assigned to $\bar{\nu}_{C=O}$ of $=NCH_2COOH$, $=\overset{+}{N}HCH_2COO^-$ and $=NCH_2COO^-$ groups respectively.[9] In the pD region which corresponds to the pH region on the titration curve at $a>4$, a weak band at 1720 cm^{-1} disappeared completely, indicating the dissociation of carboxylic proton. It was also noticed that a strong band at 1630 cm^{-1} increased in its intensity with an increase of pD, indicating the deprotonation from ammonium nitrogens at higher pH region. Because of the poor solubility of TAPHA in water at low pH region, the dissociation in acidic solution could not be followed by the solution spectra. However, these results show that the acid dissociations of the first four steps correspond to those of carboxylic protons and the last two dissociation steps are related with the deprotonation from ammonium groups.

Thus, it may be concluded that, in aqueous solution, TAPHA takes a zwitter ion structure, in which only two of three basic nitrogens exist as protonated state. Then, we can write two possible structures for TAPHA, the one having two α-ammonium carboxylate groups at 1- and 2-positions (VIIb) and the other having two α-ammonium carboxylate groups at 1- and 3-positions (VIIa). These two structures resemble with EDTA and TMDTA (trimethylenediaminetetraacetic acid) respectively with regard to their relative positions of protonated nitrogen atom.

Now, it has been known that $\Delta pK_{4-3}(=pK_4-pK_3)$ of TMDTA (2.36)[11] is smaller than that of EDTA (4.07),[12] while the pK_4 values being about the same. This indicates that the dissociation of third step, which is a deprotonation from one of two protonated nitrogen atoms, occurs more easily in EDTA than in TMDTA. This effect can be explained by the electrostatic repulsion between protons on two positive nitrogens, which are closer in EDTA, receiving stronger repulsive force between them. The similar effect has been also observed for trimethylenediamine (1,3-diaminopropane) and 1, 2-diaminopropane. ΔpK_{2-1} for trimethylenediamine (1.76)[13] is smaller than that of 1,2-diaminopropane (2.87).[14] If one compares these values with ΔpK_{6-5} of TAPHA which corresponds to ΔpK_{4-3} of EDTA or TMDTA, and ΔpK_{2-1} of the diamines, the value for TAPHA (1.62) is rather closer to those of TMDTA and trimethylenediamine than those of EDTA and 1,2-diaminopropane. This result may suggest that TAPHA will take the structure VIIa rather than VIIb.

A more direct confirmation on the zwitter ion structure of TAPHA in aqueous solution was undertaken by the proton nuclear magnetic spectroscopy. The pH dependence of chemical shift

---

[11] G. Schwarzenbach and H. Ackermann, *ibid.*, **31**, 1029 (1948).

[12] G. Schwarzenbach and H. Ackermann, *ibid.*, **30**, 1798 (1947).

[13] G. Schwarzenbach, B. Maissen and H. Ackermann, *ibid.*, **35**, 2333 (1952).

[14] F. Basalo, R. K. Murmann and Y. T. Chen, *J. Am. Chem. Soc.*, **75**, 1478 (1953).

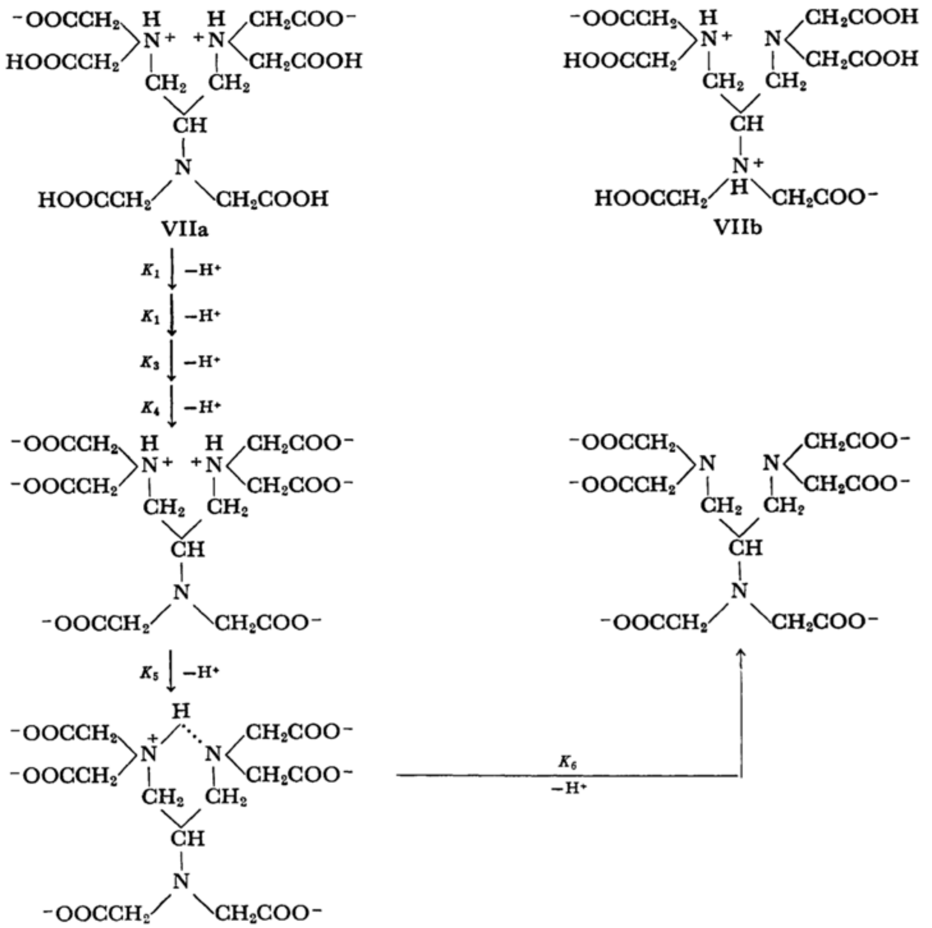


Plate 2

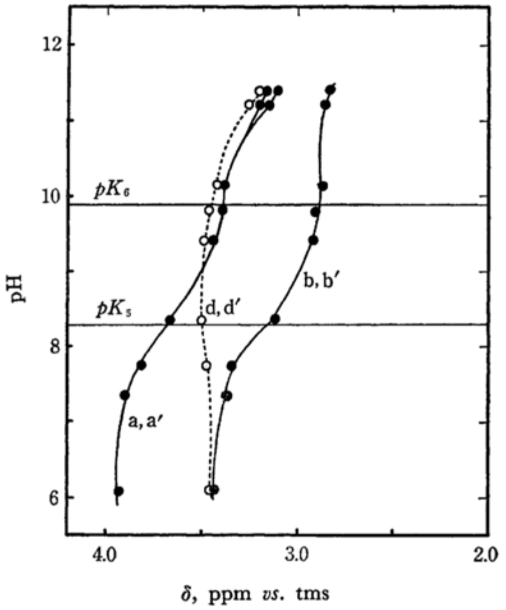
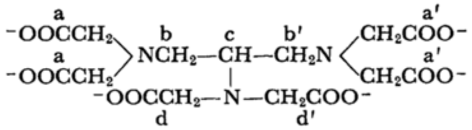


Fig. 4. Chemical shifts of TAPHA at various pH values.

(δ) of TAPHA is shown in Fig. 4. The spectra were assigned by refering to the data of various complexanes which were reported by Reilley *et al.*[15]



As TAPHA is not soluble enough in water at pH lower than 6, the deprotonation process from carboxyl groups could not be followed. The assignment of methyne proton (–CH–) at c-position was also difficult because the corresponding peak was too weak to be distinguished from noise at the concentration level investigated.

As shown in Fig. 4, the peak of methylenic protons at a, a′ and b, b′ position shift markedly over the pH range of 8—10. On the other hand, a very slight shift was observed for the peak of d, d′ methylenic protons. As it is expected that the chemical shifts of a(a′), b(b′) and d(d′)

---

[15] J. L. Sudmeier and C. N. Reilley, *Anal. Chem.*, **36**, 1698 (1964).

methylenic protons are mainly influenced by protonation to its neighboring basic nitrogen atom or carboxylate ion, a most reasonable conclusion is that, when the pH of solution increased from 8 to 10, the deprotonation occures on the nitrogen atoms attached to 1- and 3-carbons. It is also expected from the NMR spectra that TAPHA takes VIIa structure, since the peaks of a- and a'-protons could not be differentiated and no splitting was observed on this peak. If TAPHA would take VIIb structure, which is no longer symmetric with regard to 2-carbon, the peaks due to a, a' and d, d' protons probably split each other.

In view of above facts, the most reasonable scheme of the acid dissociation of TAPHA may be expressed as shown in Plate 2.

Authors are grateful to the Ministry of Eductation for its financial support.