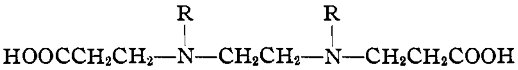
[Contribution from the Department of Chemistry of Clark University]

The Preparation and Properties of Some N,N'-Disubstituted-ethylenediaminedipropionic Acids[1]

By Arthur E. Martell and Stanley Chaberek, Jr.

The N,N'-disubstituted-ethylenediaminedipropionic acids are related structurally to the corresponding diacetic acid derivatives, which have been prepared and studied in this Laboratory, and which form chelate complexes with many metallic ions. Neither the preparation of these dipropionic acid derivatives, nor the effect on complex formation of the substitution of propionic acid groups on ethylenediamine for acetic acid groups, has been studied previously. Therefore, it was undertaken to prepare acids of the type



$$HOOCCH_2CH_2-\overset{\overset{R}{|}}{N}-CH_2CH_2-\overset{\overset{R}{|}}{N}-CH_2CH_2COOH$$

where R may be hydrogen, a propionic acid group or hydrocarbon groups: butyl, cyclohexyl, octyl and benzyl. Two methods of preparation were investigated: (1) the preparation of N,N'-dialkyl-ethylenediaminedipropionitriles by the cyanoethylation of the corresponding diamines, followed by acid hydrolysis; and (2) the condensation of N,N'-dialkyl-ethylenediamines with sodium β-chloropropionate.

The N,N'-dialkylethylenediamines used as starting materials were prepared by the method of Kyrides.[2] The physical constants of these secondary amines and of some of their derivatives may be found in the literature.[3]

The N,N'-dialkyl-ethylenediaminedipropionitriles which were prepared are described in Table I. The compounds decomposed to some extent at temperatures near the boiling points, and this may account for some of the low yields obtained. The low nitrogen values indicate that the nitriles which were purified by distillation, particularly the higher-boiling ones, were impure. However, they were quite satisfactory for further synthetic work. Although the analyses deviated considerably from the calculated values in some cases, they may nevertheless be taken as significant in view of the great difference from the calculated analyses of any other substances that may have been formed, and of the subsequent successful conversion of these compounds to the corresponding amino acids.

Acid hydrolysis of the nitriles progressed smoothly, and yields obtained by this method were generally much higher than those resulting from the reaction of the diamine and sodium β-chloropropionate. The crude acids were generally separated as the hydrochlorides by acidifying a concentrated aqueous solution of the reaction product and allowing it to stand in the cold. The free acids were then prepared by dissolving the resulting precipitate in water, adjusting *p*H to the isoelectric point and recrystallizing from suitable solvents.

Attempts to condense the dioctyl and didodecylethylenediamines with sodium β-chloropropionate resulted in the recovery of 80 to 95% of the diamines, and all attempts to isolate the desired acids from the small amounts of residues were unsuccessful. Acid hydrolysis of dioctylethylenediaminedipropionitrile resulted in decomposition of this compound and in the isolation of dioctylethylenediamine hydrate. Although the yields of β-amino acids were in general rather poor, it is felt that further refinement of the preparative method would effect considerable improvement in most cases. The properties of the amino acids prepared are given in Table II.

Table I

N,N'-Dialkyl-ethylenediaminedipropionitriles

Alkyl	State	B. p., °C.	Mm.	Yield, %	Nitrogen, % Calcd.	Nitrogen, % Found
H	Colorless oil	150–155	20	57	33.71	33.12
CH_2CH_2CN	Colorless oil	176–179	1–2	51	30.86	30.01
C_4H_9	Colorless oil	146–149	3	58	20.13	19.61
$C_6H_5CH_2$	Yellow oil	204–207	3	15	16.17	14.96
C_8H_{17}	Yellow oil	192–194	3	40	14.30	13.05
C_6H_{11}	Colorless solid	M. p. 91.5–92.0		70	16.95	16.68

The complex-forming properties of the disubstituted-ethylenediaminedipropionic acids were studied by two methods. The first was a qualitative titration method which is based upon the fact that if complex formation does occur between the amino acid and the metal ion, an increase in acidity results. This procedure is similar to the quantitative technique used by Schwarzenbach and Ackermann.[4] The titration curves of the dialkylethylenediaminedipropionic acids (Fig. 1) are

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[1] Abstracted from a dissertation presented by Stanley Chaberek, Jr., to the Faculty of Clark University in partial fulfillment of the requirements for the degree of Doctor of Philosophy, August, 1949.

[2] Kyrides, U. S. Patent 2,267,685 (Dec. 23, 1941).

[3] Frost, Chaberek and Martell, This Journal, **71**, 3842 (1949).

[4] Schwarzenbach and Ackermann, *Helv. Chim. Acta*, **31**, 1029 (1948).

TABLE II

N,N'-DIALKYL-ETHYLENEDIAMINEDIPROPIONIC ACIDS

Alkyl	Deriv.	M. p., °C. dec.	Yield, % Method 1	Yield, % Method 2	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found	Mol. wt.[a] Calcd.	Mol. wt.[a] Found
H	2·HCl	194–198	40		34.66	34.65	6.55	6.32	10.11[b]	10.45	240.2	204.0
CH_2CH_2COOH	Free acid	220–225	69	12	48.27	48.30	6.94	6.91	8.04	7.80	348.3	318.7
C_4H_9	Free acid	143–146	25	33	60.73	60.65	10.19	10.42	8.85	8.99	316.4	280.0
C_6H_{11}	Free acid	191–200	18.5	24	65.18	65.09	9.85	10.10	7.60	7.76	368.5	330.0
$C_6H_5CH_2$	Free acid	147–153	22	8	68.72	68.70	7.34	7.10	7.29	7.50	384.5	358.5

[a] All molecular weights were determined potentiometrically. [b] Calcd.: amino N, 0.0. Found: N, 0.0.

characterized by a sharp initial rise in pH during the addition of the first 10 ml. of standard base and by the presence of one inflection point corresponding to the formation of the monosodium salt. The second inflection point is absent, although in the case of the dibenzyl derivative, there is a slight increase in slope in the vicinity of the second equivalence point. It is proposed that the relatively strong tendency for dissociation of the first proton of these dibasic acids, and the extremely low acidity of the second is an indication of the interaction of the two tertiary amino nitrogen atoms to form a hydrogen bridge similar to that already described by Schwarzenbach[4] and Martell and Frost[5] for the corresponding acetic acid derivatives.

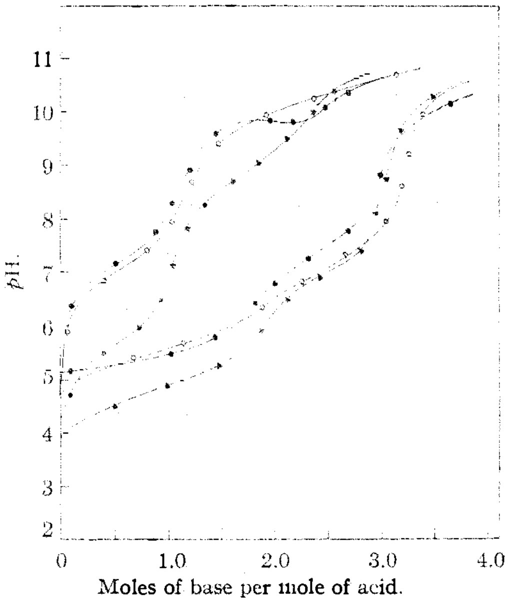

Fig. 1.—Titration of N,N'-disubstituted-ethylenediaminedipropionic acids: —, acid + standard base; - - -, acid and cupric salt + standard base: O, R = butyl; ●, R = cyclohexyl; ▲, R = benzyl.

The addition of cupric ion to solutions of the dibutyl and dibenzyl acids resulted in an acidification of the solution and in the formation of a deep blue color. No acidification was noted when cupric ion was added to a solution of the dicyclohexyl acid. Also, in this case cupric hydroxide precipitated during the titration. The first two acids, therefore, complexed copper, while the third does not. These acids did not complex calcium to any appreciable extent, with the exception that the dibutyl compound seemed to form weak complexes at high pH values.

The titration curves for ethylenediaminetetrapropionic acid and ethylenediaminedipropionic acid dihydrochloride are plotted in Fig. 2. The curves for the acids alone are closely similar to that for ethylenediaminetetraacetic acid. The addition of cupric ions to solutions of these acids resulted in a strong color development and in an acidification effect. The titration curve of the complex solutions was closely similar to that obtained by the neutralization of a strong acid with a strong base, indicating strong complexing of copper.

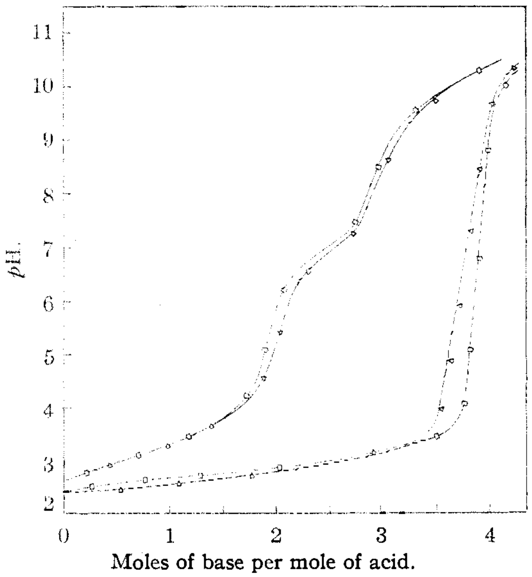

Fig. 2.—Titration of N,N'-ethylenediaminedipropionic acid and of ethylenediaminetetrapropionic acid: —, acid + standard base; - - - -, acid and cupric salt + standard base: □, ethylenediaminedipropionic acid dihydrochloride; △, ethylenediaminetetrapropionic acid.

Further evidence for complex formation between the substituted dipropionic acid derivatives and cupric ions was obtained from the absorption spectra in the region 220 to 350 mμ. The sodium salts of all acids prepared, with the exception of

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(5) Martell and Frost, THIS JOURNAL, **72**, 3743 (1950).

dicyclohexylethylenediaminedipropionic acid, had a slight absorption maximum in the region 255 to 260 mμ. Cupric chloride did not absorb in this region. The presence of cupric ions resulted in a strong intensification of this absorption band over that of the sodium salts of the amino acids present alone, indicating complex formation for these acids. The disodium salt of dicyclohexylethylenediaminedipropionic acid had a weak absorption band at about 280 mμ, and the addition of cupric ions resulted only in weak absorption. Therefore, in view of the titration data obtained in the presence of the cupric ion, it seems that this substance did not complex copper to any appreciable extent. This effect is probably due to the steric hindrance of the cyclohexyl groups and is similar to the results reported by Martell and Frost[5] for the corresponding diacetic acid derivative.

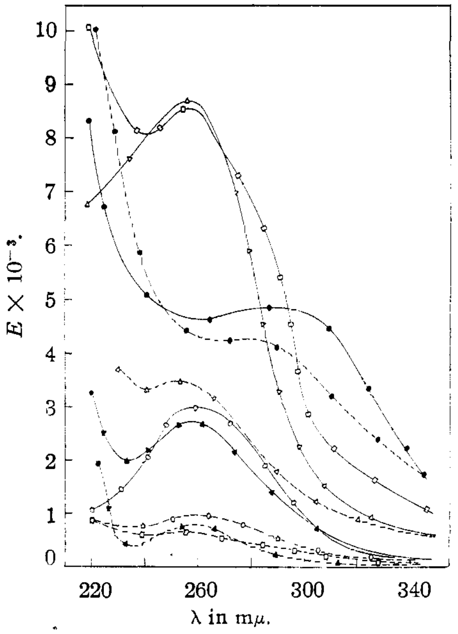

Fig. 3.—Absorption spectra of salts of N,N'-disubstituted-ethylenediaminedipropionic acids: —, cupric salts; ----, sodium salts: O, R = butyl; ●, R = cyclohexyl; △, R = propionic acid; ▲, R = benzyl; □, R = hydrogen.

A comparison with the copper-complexing properties of dibutylethylenediaminediacetic acid prepared by Martell and Frost[5] is given in Fig. 4. The addition of an equimolar amount of cupric ions to the diacetic acid derivative resulted in strong acidification, and the titration curve had a strong inflection point at an equivalence point of 2. On the other hand, the introduction of copper to a solution of the dipropionic acid resulted in much weaker acidification, and although the titration curve showed a slight change in slope at the equivalence point of 2, the strong inflection point occurred in the vicinity of 3 equivalents of base. This shift in inflection point past the 2 equivalents point could possibly be due to the formation of a metallic chelate involving the hydroxide ion. Complex formation seems to be much stronger with the acetic acid derivative.

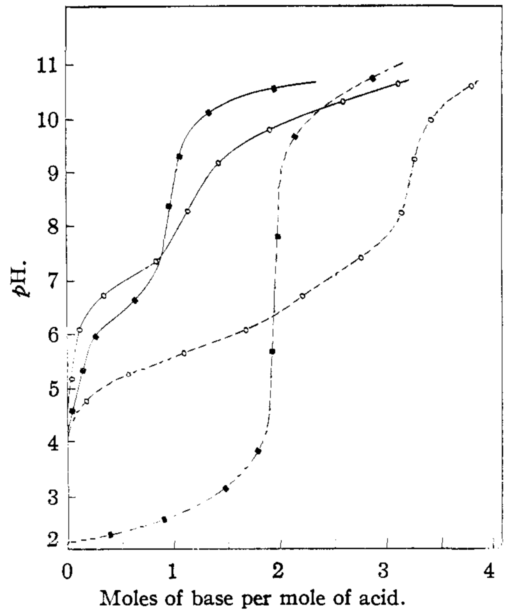

Fig. 4.—Comparison of disubstituted-ethylenediaminedipropionic and diacetic acids: —, titration curve of acid alone; ----, titration curve of acid and cupric ions: O, N,N-dibutylethylenediaminedipropionic acid; ■, N,N'-dibutylethylenediaminediacetic acid.

It is also interesting to compare the calcium-complexing properties of ethylenediaminetetrapropionic acid and ethylenediaminetetraacetic acid (Fig. 5). Although the titration curves for

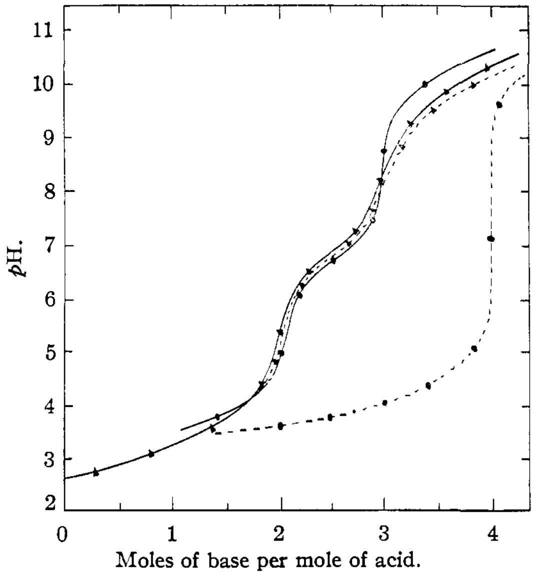

Fig. 5.—Comparison of ethylenediaminetetrapropionic and tetraacetic acids: —, titration curve of acid alone; ----, titration curve of acid and excess calcium ions: ▲, ethylenediaminetetrapropionic acid; ●, ethylenediaminetetraacetic acid.

the free acids are very similar, the curves obtained in the presence of a fifteen-fold excess of calcium ions are totally different. The addition of calcium ions to a solution of the tetraacetic acid derivative resulted in strong acidification, and strong calcium complexing occurred. No appreciable acidification occurred when calcium ions were added to a solution of the tetrapropionic acid, and the resulting titration curve corresponded closely with that obtained by neutralizing the free acid alone. Ethylenediaminetetrapropionic acid does not seem to complex this ion.

Experimental

N,N'-Ethylenediaminedipropionitrile.—To 120 g. (2 moles) of anhydrous ethylenediamine, 212 g. (4 moles) of redistilled acrylonitrile was added dropwise over a period of three hours at room temperature. The solution was stirred at room temperature two hours, refluxed two hours and finally allowed to stand overnight. Distillation under reduced pressure resulted in the separation of the desired product.

Ethylenediaminetetrapropionitrile.—Sixty grams (1 mole) of anhydrous ethylenediamine was added dropwise over a period of two hours to 265 g. (5 moles) of redistilled acrylonitrile and the mixture was refluxed over a water-bath for six hours. The solution was then allowed to stand overnight. Tetracyanoethylethylenediamine was isolated by distillation under reduced pressure.

N,N'-Dialkyl-ethylenediaminedipropionitriles.—To one mole of the symmetrically substituted dialkylethylenediamine, 6 moles of redistilled acrylonitrile was added dropwise over a period of two hours with stirring at 80°. The solution was then refluxed gently for eight hours and was allowed to stand overnight. Excess acrylonitrile was removed by distillation under atmospheric pressure, and all products, with the exception of the dicyclohexyl- derivative, were separated by distillation under reduced pressure. Dicyclohexylethylenediaminedipropionitrile was precipitated by the addition of water to the residue remaining after the removal of excess acrylonitrile, and the purified compound was obtained by recrystallization from 40% aqueous ethanol.

N,N'-Ethylenediaminedipropionic Acid.—To 33 g. (0.2 mole) of rapidly stirred dicyanoethylethylenediamine, 100 ml. of 12 *N* HCl was added dropwise over a period of one hour. The reaction was strongly exothermic, and the flask was cooled in an ice-water-bath. Stirring was continued at room temperature for two hours. Finally the yellow solution was refluxed four hours and allowed to stand overnight. The solution was distilled to dryness under reduced pressure. After the residue was dissolved in distilled water, the resulting solution was made strongly alkaline with aqueous sodium hydroxide and refluxed in a stream of air to remove ammonia. The solution was then acidified to a *p*H of 4.5, distilled to dryness under reduced pressure, and the residue was extracted with 300 ml. of hot absolute ethanol. The hot extract was filtered rapidly to remove sodium chloride, and the solvent was distilled off. A dark yellow viscous mass remained. Attempts to crystallize this residue from ethanol, methanol, butanol, isobutanol or acetone failed. The viscous material was dissolved in a minimum amount of hot distilled water, acidified with an equal volume of 12 *N* HCl and allowed to stand in the cold. Twenty-one grams (40% yield) of ethylenediaminedipropionic acid dihydrochloride separated. This compound was purified by recrystallizing the crude acid five times from hot 80% ethanol.

Ethylenediaminetetrapropionic Acid. Method 1.—Twenty-seven grams (0.1 mole) of ethylenediaminetetrapropionitrile was added to a mixture of 150 ml. of distilled water and 100 ml. of 12 *N* HCl over a period of one hour. The solution was refluxed for six hours and was allowed to stand overnight. The solvent was removed by distillation under reduced pressure, and the residue was made strongly alkaline with aqueous sodium hydroxide. The evolved ammonia was then removed by refluxing the solution in a rapid stream of air. Upon acidification of the solution to a *p*H of 2 and allowing it to stand in the cold, 24 g. of crude ethylenediaminetetrapropionic acid separated. A pure sample was obtained by recrystallizing the crude product four times from hot distilled water.

Ethylenediaminetetrapropionic Acid. Method 2.—To 65 g. (0.6 mole) of β-chloropropionic acid which was neutralized with 24 g. (0.6 mole) of sodium hydroxide in 100 ml. of water, 6 g. (0.1 mole) of anhydrous ethylenediamine was added dropwise over a period of one hour. The solution was then refluxed for six hours and allowed to stand overnight. The yellow solution was acidified to a *p*H of 3, and distilled to dryness under reduced pressure. The brown residue was extracted twice with 300 ml. of absolute ethanol. After filtration to remove the sodium chloride, the ethanol was removed by distillation, and the brown residue was refluxed twice with 200 ml. of ethyl ether for one hour each, in order to remove excess β-chloropropionic acid. The residue was then dissolved in a minimum quantity of hot distilled water, acidified with an equal volume of concentrated hydrochloric acid and allowed to stand in the cold for one week. Four grams, representing 12% of the theoretical amount of crude ethylenediaminetetrapropionic acid was obtained. This compound was purified by recrystallizing it four times from hot distilled water. The pure sample melted at 218–222° with decomposition.

N,N'-Dialkyl-ethylenediaminedipropionic Acids. General Procedure.—The dialkyl-ethylenediaminedipropionitrile (0.1 mole) was dissolved in 150 ml. of 12 *N* HCl, and the solution was refluxed eight hours. The addition of 50 ml. of 95% ethanol was necessary to completely dissolve the dibenzyl-dinitrile derivative in the acid. After standing overnight, this solution was distilled to dryness under reduced pressure. The residue was dissolved in 60 ml. of distilled water, and the solution was made strongly alkaline with aqueous sodium hydroxide. The evolved ammonia was removed from the solution by refluxing it in a rapid stream of air. The solution was then acidified to a *p*H of 4.5, and the solvent was removed by distillation under reduced pressure. The resulting dark residue was extracted with hot absolute ethanol, and the insoluble sodium chloride was filtered off. Removal of solvent resulted in the formation of a viscous brown material that failed to crystallize. The isolation and purification of these acids was accomplished in the following manner:

(a) **N,N'-Dibutylethylenediaminedipropionic Acid.**—The residue was dissolved in 100 ml. of distilled water, and alkalized to *p*H 9.0 with sodium hydroxide; 17 g. (0.1 mole) of aqueous $CuCl_2 \cdot 2\ H_2O$ was added, and the resulting deep blue solution was distilled to dryness under reduced pressure. The remaining dark green residue was extracted with hot absolute ethanol and filtered free of sodium chloride. The ethanol was distilled off, and the green mass was recrystallized from hot absolute butanol. Three recrystallizations failed to remove all traces of chloride ion. The copper complex was then decomposed by precipitation of the copper as cupric sulfide from an aqueous solution of the complex. After filtration, the clear liquid was concentrated by distillation under reduced pressure to approximately 100 ml. and the *p*H was adjusted to 4.7. The distillation residue was extracted with hot absolute ethanol, filtered and cooled. Dibutylethylenediaminedipropionic acid was separated as a white crystalline solid. A pure sample was prepared by recrystallization of the crude acid four times from hot absolute ethanol. Dibutylethylenediaminedipropionic acid is a colorless crystalline solid having a waxy luster.

(b) **N,N'-Dicyclohexylethylenediaminedipropionic Acid.**—The residue was dissolved in distilled water and the *p*H adjusted to 4.8. After distillation to dryness, the residue was refluxed one hour in 100 ml. of acetone, the sodium chloride was filtered off and the hot extract cooled. The crude acid derivative separated as a white crystalline solid containing a trace of sodium chloride. A pure sample, prepared by five recrystallizations from 80% ethanol, was a white crystalline solid with a waxy luster.

(c) **N,N′-Dibenzylethylenediaminedipropionic Acid.**—The residue was dissolved in a minimum amount of hot distilled water and acidified with an equal volume of 12 *N* hydrochloric acid. A white solid separated upon long standing in the cold. This solid was dissolved in distilled water, and the *p*H was adjusted to 4.2. The aqueous solution was distilled to dryness under reduced pressure, the residue was extracted with hot absolute ethanol, and the filtered extract was distilled to dryness. The residue was warmed in 200 ml. of hot redistilled acetone and was allowed to stand in the cold. The acid which separated was purified by recrystallizing the impure acid four times from 90% ethanol and was isolated as a white crystalline solid.

(d) **Acid Hydrolysis of N,N′-Dioctyl-ethylenediaminedipropionitrile.**—Upon alkalizing the acid hydrolysate obtained from the N,N′-dioctylethylenediaminedipropionitrile, the monohydrate of N,N′-dioctylethylenediamine was recovered. Its melting point (44–46°) showed no depression when mixed with an authentic sample of the diamine. The amount recovered represented 80% of the starting material. Manipulation of the residual solution in various ways yielded only a viscous residue, from which no solid material could be crystallized either by strong acidification or by use of various solvents.

N,N′-Dialkylethylenediaminedipropionic Acids. (Method 2). General Procedure.—To 0.1 mole of the stirred dialkylethylenediamine, 0.2 mole of sodium β-chloropropionate dissolved in 200 ml. of water was added, and the mixture was refluxed 12 hours. The solution was then made strongly alkaline and distilled to dryness under reduced pressure. The residue was then refluxed with two 500-ml. portions of ethyl ether for one hour, in order to remove any unreacted diamine. After decantation, the residue was dissolved in a minimum amount of hot distilled water, and the solution was acidified with 12 *N* HCl to a *p*H of 2. Long standing in the cold resulted in the precipitation of a white solid. The free acids were purified by adjusting the *p*H of an aqueous solution of this solid to the value at the isoelectric point, distilling the solution to dryness under reduced pressure, and recrystallizing the residues from suitable solvents in the manner described under method 1.

Titration Method.—Fifty to one hundred mg. of purified amino acid dissolved in 50–100 ml. of water was titrated with sodium hydroxide. The titration was repeated in the presence of equimolar cupric sulfate and in the presence of 15-molar excess of calcium chloride. The *p*H was measured with a glass electrode according to standard practice.

Absorption Spectra Method.—Stock solutions of 0.01 *M* disodium salts of the dipropionic acid derivatives were prepared. A stock solution of 0.001 *M* copper complex was then prepared from the standard solution of the disodium salt and 0.01 *M* cupric chloride. The concentration of the complex solution was then varied by dilution so that the values of the per cent. of transmission at the regions of maximum absorption were within the range of 10 to 80%. Absorption measurements were carried out in the ultraviolet region (220–350 mμ) with a Beckman quartz spectrophotometer, model DU, in quartz cells. Similar measurements were carried out on solutions of cupric chloride and of the disodium salts of the amino acids at the same concentration as those containing the copper complexes.

Acknowledgment.—The authors are indebted to F. C. Bersworth, of Framingham, Massachusetts, for financial support. The choice of topic was made with his coöperation and the work was aided by his advice.

Summary

The preparation of ethylenediaminetetrapropionic acid, N,N′-ethylenediaminedipropionic acid, and a number of N,N′-dialkylethylenediaminedipropionic acids by hydrolysis of the nitriles and by reaction of the corresponding amine with β-chloropropionic acid is described. Potentiometric and spectrophotometric data indicate chelation with cupric ion but little or no chelation with calcium ion, except in the case of N,N′-dicyclohexylethylenediaminedipropionic acid, which showed no appreciable chelation with either ion.

BERKELEY, CALIF. RECEIVED FEBRUARY 25, 1950

[CONTRIBUTION FROM THE RESEARCH LABORATORY OF THE GENERAL ELECTRIC COMPANY]

First and Second Pressure Limits of Explosion of Diborane–Oxygen Mixtures[1]

BY FRASER P. PRICE

Introduction

The ease of ignition of the lower hydrides of boron, sometimes spontaneous and frequently with violent results, has long been known.[2] It was only recently, however, that improved methods for their preparation[3] made them available in sufficient quantity to undertake investigation of their reactions with oxygen.

This paper is the first of a series describing their behavior when mixed with oxygen under a variety of conditions. Diborane was chosen for the initial investigation because it was felt that its reactions would be simplest.

It is reported that diborane reacts with oxygen according to the equation[2]

$$B_2H_6 + 3O_2 \longrightarrow 2H_3BO_3$$

However, when diborane is ignited in air there is always a persistent odor characteristic of boron hydrides. Thus it is very probable that in the heat of an explosion some of the diborane is converted to higher, more stable, hydrides, and that the stoichiometry of the explosions discussed below does not correspond to the above equation

Experimental

Materials.—Diborane was obtained from Mine Safety Appliance Company, Pittsburgh, Pennsylvania, and was purified on the day of use by three successive cycles of freezing in liquid nitrogen, pumping and thawing. Analysis using the mass spectrometer indicated a purity of better than 99% before purification.

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(1) This work done under contract with U. S. Army Ordnance.

(2) Stock, "Hydrides of Boron and Silicon," Cornell University Press, Ithaca, N. Y., 1933.

(3) Schlesinger, *et al.*, in press; Elliott, Boldebuck and Roedel, in press.