[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF CLARK UNIVERSITY]

The Preparation and Properties of N-Substituted Ethylenediaminetriacetic Acids[1,2]

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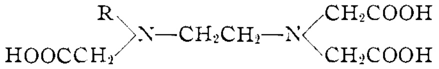
The synthesis of N-substituted N,N′,N′-ethylenediaminetriacetic acids have been prepared with *n*-butyl, *n*-octyl, *n*-dodecyl, cyclohexyl and benzyl groups as substituents. The intermediate N-substituted ethylenediamines are also described. The acid dissociation constants of the amino acids and the corresponding chelate stability constants with calcium(II) and copper(II) ions have been determined, and the results are compared with the hydrogen ion and metal ion affinities of related compounds.

The synthesis of N-substituted ethylenediaminetriacetic acids[3] was undertaken as part of a general investigation of the relationship between ligand structure and chelation tendency. The structures of these substances are intermediate to those of the previously investigated classes of chelating agents, the hexadentate ethylenediaminetetraacetic acid and the tetradentate N,N′-dialkylethylenediaminediacetic acids.[4]

Discussion

The N-substituted ethylenediaminetriacetic acids prepared in this investigation are potentially pentadentate chelating agents having the general structure



$$\begin{matrix}R\\ HOOCCH_2\end{matrix}\!>\!N-CH_2CH_2-N\!<\!\begin{matrix}CH_2COOH\\ CH_2COOH\end{matrix}$$

where R represents butyl, cyclohexyl, octyl, dodecyl and benzyl. The general method of preparation consisted of the synthesis of the N-substituted ethylenediamine, followed by the condensation of the diamine with sodium cyanide and formaldehyde.

Most of the N-alkylethylenediamines were synthesized by the method of Linsker and Evans.[5] However, the separation of the products from the reaction mixtures is considerably different from that employed by these investigators. The N-cyclohexyl derivative was prepared by the method of Pearson, *et al.*,[6] which involved catalytic hydrogenation of the Schiff base prepared by the condensation of cyclohexanone and anhydrous ethylenediamine. Physical properties of the N-substituted diamines are summarized in Table I.

The N-*n*-butyl-, N-benzyl-, N-*n*-octyl- and N-*n*-dodecylethylenediamines were prepared in good yields by the reaction of ethylenediamine with the corresponding alkyl halide at a molar amine/halide ratio of five to one. Optimum yields were obtained when the reactions were carried out at low temperatures using 95% ethylenediamine. The large excess of amine was necessary to minimize the formation of polyalkylethylenediamines.

In the case of the reaction between ethylenediamine and *n*-butyl bromide, the substituted products formed constant-boiling mixtures with the excess ethylenediamine. It was not possible to isolate the pure products in good yield by distillation methods. Separation by extraction methods was achieved only when the reaction was carried out using 95% ethylenediamine. When a more dilute solution of the amine was employed, the products became sufficiently hydrated to cause insolubility of the desired product in non-polar solvents, a property which was also exhibited by the excess reagent. The monosubstituted diamine retained its solubility in non-polar solvents when hydrated to the extent of about 15%, while ethylenediamine containing a few per cent. of water was insoluble in the same solvents.

Corresponding N,N′-dialkylethylenediamines were isolated as by-products from all reaction products. The yields varied from 8.8% for the N-*n*-octyl derivative to 18.6% for the cyclohexyl compound. The identity of these compounds was substantiated by the formation of picrate and phenylurea derivatives, all of which gave nitrogen analyses which checked with the theoretical values which have been reported previously in the literature.

The N-substituted ethylenediaminetriacetic acids were prepared by the carboxymethylation reaction, involving in most cases the use of sodium cyanide and formaldehyde according to the general procedure of Smith, *et al.*[7] The physical constants are summarized in Table II. The final yields of the purified acids were very low, except in the case of the N-benzylethylenediaminetriacetic acid. Considerable amounts of viscous yellow-brown residues were obtained in all reaction mixtures. These residues exhibited complex formation when treated with cupric chloride. Potentiometric titrations based on complex formation of these materials indicated the total yields averaged from 40–70% of the theoretical amounts. The exact nature of the viscous residues is not known. Since the monosubstituted triacetic acids and the residues formed solutions which were exceedingly difficult to separate, it seems quite probable that the by-products are structurally similar to the desired acids. Frost[4] encountered the same difficulty in the preparation of the symmetrical N,N′-dialkylethylenediaminediacetic acids and proposed that the residues were composed of polyamides formed by the reaction of the disubstituted diacetic acid and unreacted diamine. Polyamide formation does not appear to be a feasible explanation in the pres-

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[2] This research was supported by a grant from the Bersworth Laboratories, Framingham, Massachusetts.

[3] The *C. A.* names of these compounds would be acetic acid (N-alkyl-1,2-diaminoethane-N,N′,N′)-tri-. The more common trivial names will be employed throughout this article.

[4] A. E. Frost, Jr., and A. E. Martell, THIS JOURNAL, **72**, 3743 (1950).

[5] F. Linsker and R. L. Evans, *ibid.*, **67**, 1581 (1945).

[6] D. E. Pearson, A. C. Cope and W. H. Jones, *ibid.*, **68**, 1225 (1946).

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

TABLE I

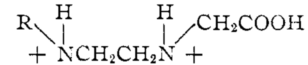
N-SUBSTITUTED ETHYLENEDIAMINES; $R-NHCH_2CH_2NH_2$

R	B.p. °C.	B.p. mm.	Yield, %	Dipicrates M.p.	Dipicrates N, % Calcd.	Dipicrates N, % Found	Diphenylcarbamido derivatives M.p.	Diphenylcarbamido derivatives N, % Calcd.	Diphenylcarbamido derivatives N, % Found
Butyl	77–78[a]	23	66	175–176	19.68	19.57	179	15.81	15.84
Cyclohexyl[j]	109–110[c]	22	58	193–194 dec.	18.65	18.74	213	14.73	14.76
Octyl	105–107[d]	10	64	139–141.5[f]	17.77	17.69	159–160.5	13.65	13.79
Dodecyl	136–140[e]	12	62	133–134[g]	16.18	15.97	146–147	12.01	11.82
Benzyl	102[b]	5	67	222 dec.[h]	18.42	18.77	180[i]	14.42	14.24

[a] J. A. King and F. H. McMillan, THIS JOURNAL, **68**, 1774 (1946), b.p. 71° (13 mm.). [b] L. Bleier, *Ber.*, **32**, 1825 (1899), b.p. 162–165° (20 mm.); J. van Alphen, *Rec. trav. chim.*, **54**, 595 (1935), b.p. 165° (18 mm.); A. L. Wilson, U. S. Patent 2,318,729 (May 11, 1943), b.p. 100° (4 mm.), A. Frost, S. Chaberek and A. E. Martell, THIS JOURNAL, **71**, 3842 (1949), b.p. 155–160° (5 mm.); Z. A. Hicks and G. H. Coleman, *Proc. Iowa Acad. Sci.*, **53**, 207 (1946), b.p. 262° (20 mm.). [c] D. E. Pearson, A. C. Cope and W. H. Jones, ref. 6, b.p. 101–102° (14 mm.). [d] F. Linsker and R. L. Evans, ref. 5, m.p. 29–31°. [e] F. Linsker and R. L. Evans, ref. *d*, m.p. 36–38°. [f] F. Linsker and R. L. Evans, ref. *d*, m.p. 131–132°. [g] F. Linsker and R. L. Evans, ref. *d*, m.p. 141–142°. [h] S. R. Aspinall, THIS JOURNAL, **63**, 852 (1941); A. Frost, Ph.D. Dissertation, Clark University, Worcester, 1949; L. Bleier, ref. *b*, all report m.p. 221° (d.). [i] J. Van Alphen, ref. *b*, m.p. 180°. [j] Dibenzamide derivative, m.p. 198–199.5°; calcd. for $C_{22}H_{26}N_2O_2$: N, 7.82, found: N, 7.68.

TABLE II

N-SUBSTITUTED ETHYLENEDIAMINETRIACETIC ACIDS



$$\mathrm{{}^{-}OOCCH_2\overset{R\ \ H}{\overset{+}{N}}CH_2CH_2\overset{H\ \ CH_2COOH}{\overset{+}{N}}CH_2COO^{-}}$$

R	M.p.,[a] °C.	Mol. wt.[b] Calcd.	Mol. wt.[b] Found	Nitrogen, % Calcd.	Nitrogen, % Found	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found
Butyl	154–156	290	284	9.65	9.51	49.64	49.32	7.63	7.48
Cyclohexyl	206–209	316	319	8.86	8.74	53.15	52.98	7.62	7.53
Octyl	147–148	346	355	8.09	7.85	55.47	55.11	8.73	8.61
Dodecyl	143–145	402	398	6.96	6.79	59.67	59.32	9.51	9.39
Benzyl	130–131	324	336	8.64	8.22	55.55	55.18	6.22	5.97

[a] All compounds melted with decomposition. [b] Determined potentiometrically,

ent case, however, since low temperatures were employed, and the volatile constituents were not allowed to escape. Low recovery of purified products probably may be attributed to two factors. The first is inhibition of crystallization of the amino acid as a result of the presence of by-product formation of compounds such as aminoacetic iminodiacetic, and nitrilotriacetic acids. Smith, *et al.*,[7] noted similar behavior in the isolation of other amino acids. The second factor may be attributed to the necessity of recrystallizing the crude products numerous times to remove the last traces of sodium sulfate. This procedure greatly decreases the yields of pure products. Attempts to minimize this difficulty by the substitution of barium cyanide for sodium cyanide were successful only in the case of N-benzylethylenediaminetriacetic acid.

The N-substituted ethylenediaminetriacetic acids are slightly soluble in non-polar solvents. Variations in aqueous solubility, however, are considerable, the low molecular weight products being much more soluble. The order of solubility, *n*-butyl > benzyl > cyclohexyl > *n*-octyl > *n*-dodecyl, is not unexpected since the N-disubstituted diamines exhibit the same solubility relationships. However, the degree of aqueous solubility is much greater than was anticipated.

The tendencies of the N-substituted ethylenediaminetriacetic acids to form metal chelates were first investigated by potentiometric titration of these acids in the absence and in the presence of copper(II) and calcium(II) ions. Representative examples of the data are presented in Figs. 1 and 2 for the N-*n*-butyl- and N-benzylethylenediaminetriacetic acids, in which the Cu(II) acid and Ca(II) acid ratios are 1:1 and 10:1, respectively. The free acid titration curves are all characterized by the presence of two inflection points at one and two equivalents of hydroxide per mole of acid, corresponding to the formation of the mono- and disodium salts. The neutralization of the first two protons occurs in two definite steps with little overlapping of the acid dissociation constants k_1 and k_2. Thus, if H_3A denotes the free acid, the neutralization process may be summarized by the equations

$$\mathrm{OH^- + H_3A \overset{k_1}{\rightleftarrows} H_2A^- + H_2O}$$

$$\mathrm{OH^- + H_2A^- \overset{k_2}{\rightleftarrows} HA^{-2} + H_2O}$$

The absence of a third inflection at three equivalents of base is no doubt due to high basicity of the species A^{-3} and a correspondingly strong tendency toward its hydrolysis.

$$\mathrm{A^{-3} + H_2O \rightleftarrows HA^{-2} + OH^-}$$

It is interesting to note that the first inflection of the N-benzyl derivative is considerably weaker than those exhibited by the other amino acids. The resulting suppression of the second buffer region to lower *p*H values indicates a comparatively greater acidity of the first ammonium proton which dissociates.

The addition of an equimolar quantity of cupric ions to the N-*n*-butyl-, N-benzyl-, N-cyclohexyl- and N-*n*-octylethylenediaminetriacetic acids results in a general lowering of the second and third acid buffer regions. The resulting titration curves are similar in shape to those obtained in strong acid–strong base neutralization processes, one strong inflection occurring after three equivalents of base have been added. In this region interaction occurs

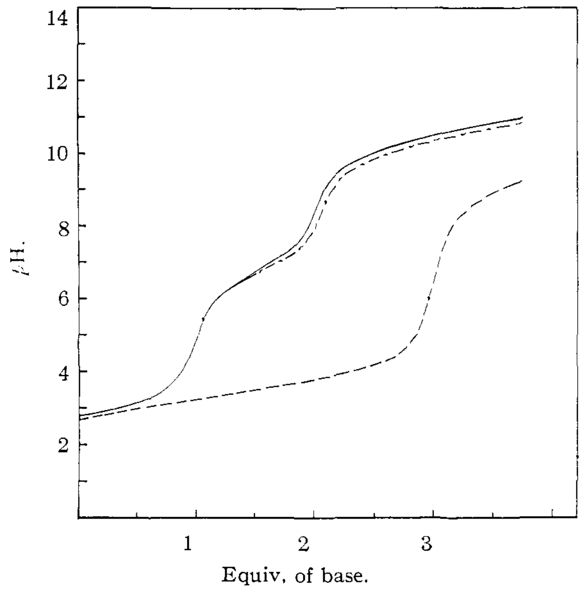


Fig. 1.—Potentiometric titration of N-*n*-butylethylenediaminetriacetic acid at 24.2° and 0.1 ionic strength: —, free acid; —·—·—·—, acid + $CaCl_2$; - - - -, acid + $CuCl_2$.

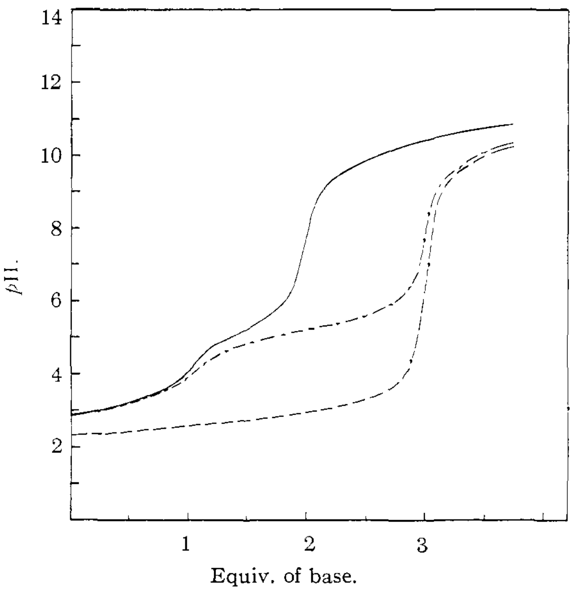


Fig. 2.—Potentiometric titration of N-benzylethylenediaminetriacetic acid at 24.2° and 0.1 ionic strength: —, free acid; —·—·—·—, acid + $CaCl_2$; - - - -, acid + $CuCl_2$.

with both the mono- and dihydrogen acid species to give the metal chelate according to the reactions

$$HA^{-2} + Cu^{+2} + OH^- \longrightarrow CuA^- + H_2O$$

$$H_2A^- + Cu^{+2} + 2OH^- \longrightarrow CuA^- + 2H_2O$$

In the case of the N-benzyl- and N-*n*-octyl derivatives, the addition of cupric ions results also in a repression of the first acid buffer region to lower *p*H values. Complex formation involving these acids occurs also with the undissociated acid species, accompanied by the liberation of three protons. The corresponding neutralization reaction is

$$H_3A + Cu^{+2} + 3OH^- \longrightarrow CuA^- + 3H_2O$$

The absence of an initial acidification with the N-*n*-butyl- and N-cyclohexyl derivatives indicates that little, if any, interaction occurs with the free acid species. The titration of the N-*n*-dodecyl-compound in the presence of cupric ions yielded erratic results, probably as a consequence of the partial separation of a solid phase. That complex formation occurred is evidenced by the fact that deep blue crystals separated from an equimolar mixture of the acid and cupric ions.

The addition of a tenfold excess of calcium ions to a solution of the N-*n*-butyl- and N-cyclohexylethylenediaminetriacetic acids results in a slight acidification effect at high *p*H values. Weak chelation of calcium probably occurs with only one acid species, the anion HA^{-2}. The titration curve, involving calcium ions and the N-benzyl derivative, has two inflections, occurring at one and three equivalents of base. An acidification effect is observed only after one equivalent of alkali has been added. Hence little chelation occurs with the free acid, while considerable interaction proceeds with the mono- and dihydrogen anion species. N-*n*-Octylethylenediaminetriacetic acid shows unexpected behavior in the presence of calcium ions. Although the repression of the second and third acid buffer regions indicates the formation of a rather strong calcium chelate, the presence of an inflection point at approximately 2.5 equivalents of base indicates a complicated type of interaction. This phenomenon may possibly be due to the formation of a polynucleate complex. However, further investigation is necessary to determine the exact nature of metal chelate formation with this ligand. Calcium chelation with the N-*n*-dodecyl derivative also occurred to a limited extent. In this case, however, the separation of a solid phase resulted in erratic titration curves.

The acid dissociation constants and complex formation constants for the cupric and calcium chelates have been calculated at 25° by methods described recently,[8] and are summarized in Table III. The values of *pk*, corresponding to the dissociation of the carboxyl hydrogens, are roughly equivalent. The substitution of an N-benzyl group for N-alkyl substituents increases the acidity of the first ammonium proton (pk_2). Interaction of the N-benzyl derivative with cupric ions is very strong. The stability of the cupric chelate is slightly greater than that of the symmetrical ethylenediaminediacetic acid (log K = 16.2) and less than that for ethylenediaminetetraacetic acid (log

TABLE III

CHELATION TENDENCIES OF N-SUBSTITUTED ETHYLENEDIAMINETRIACETIC ACIDS AT 24.2°

R	Acid dissociation constants pk_1	pk_2	pk_3	Log K Cu(II)	Ca(II)
Butyl	1.8	6.64	10.04	12.7	1.6
Cyclohexyl	1.6	6.47	10.15	11.5	1.7
Octyl	1.9	6.53	9.76	12.5	..
Benzyl	1.9	5.10	9.84	16.8	6.7
Dodecyl	2.0	6.56	9.77	..	..

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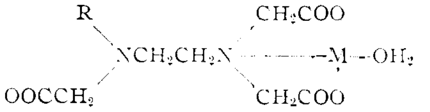
[8] S. Chaberek, Jr., and A. E. Martell, THIS JOURNAL, **74**, 6228 (1952).

K = 18.3). This is not unusual, in view of the square planar structural requirements of the cupric chelate, and likewise the fact that the triacetic acid contains one less acetic acid group than is the case for the tetraacetic acid derivative. It is hence somewhat surprising to find, however, that the corresponding chelate stabilities of the N-butyl- and N-octyl derivatives are considerably weaker, especially since the basicities of these ligands are greater than that of the N-benzyl derivative. Possibly this decreased affinity may be explained on the basis that the large substituents exert a steric effect on the approach of the metal ion to one of the amino nitrogens. An exceptionally strong steric effect could conceivably result in the formation of a copper chelate of the type in which bonding occurs primarily with the terminal imino diacetate group. In this connection it is interesting to note that in the case of the copper–amino acid titration curves of the N-butyl- and N-octyl derivatives, the buffer regions beyond three equivalents of base are displaced to pH values considerably lower than is that involving Cu(II) interaction with N-benzylethylenediaminetriacetic acid. Also, the stabilities of these cupric chelates are intermediate between those involving copper ion interaction with iminodiacetic acid (log K = 10.6) and the symmetrical ethylenediaminediacetic acid (log K = 16.2).



While N,N′-dicyclohexylethylenediaminediacetic acid does not complex cupric ions, appreciable interaction occurs with the N-cyclohexylethylenediaminetriacetic acid. Examination of molecular models of the two compounds indicates that while two cyclohexyl groups inhibit proper alignment of the coördinating groups, the steric effect of a single cyclohexyl group is not sufficient to interfere with formation of chelate rings.

Although the three N-alkyl triacetic acids are very weak calcium chelating agents, fairly stable complexes are formed with the N-benzyl derivative. It is difficult to explain this enhanced affinity. Possibly the addition of calcium ions gives rise to a polarization effect which tends to increase the basicity of the nitrogen attached to the benzyl group. Since the calcium chelates are essentially ionic in character, and since the tendency for electron release is greater for an aromatic substituent than for an alkyl group, then such electron release would account for the increased stability.

Further evidence of complex formation was obtained by a comparison of the ultraviolet absorption spectra of the trisodium salts of the substituted triacetic acids with those obtained in the presence of cupric and calcium ions. Representative examples of the absorption curves are illustrated in Figs. 3 and 4 for the n-N-butyl- and N-benzyl derivatives. Aqueous solutions of cupric chloride and calcium chloride exhibit only slight absorption in this spectral region. The trisodium salts exhibit in general weak absorption consisting of broad bands in the region 245-250 mμ. The absorption of the trisodium salt of the N-benzyl derivative is considerably more intense than is that of the aliphatic derivatives.

The spectra in the presence of cupric chloride show absorption much more intense than those of the trisodium salts alone. This increase in intensity may be interpreted as being due to interaction of the metal ion with the ligand anion. The wave lengths of maximum absorption correspond to those shown by the free trisodium salts except in the case of the N-butyl derivative.

The absorption curves of the trisodium salts in the presence of calcium chloride are very similar to those of the trisodium salts alone. In the case of the N-benzyltriacetic acid derivative the absorption bands are less intense, but the wave length of maximum absorption does not seem to be shifted significantly. The characteristic differences in the nature of the interactions of Cu(II) and Ca(II) ions with the ligands is strikingly illustrated by the absorption curves in Figs. 3 and 4.

The spectra of the trisodium salts and those containing calcium ions do not follow Beer's law. Non-adherence in these cases may be attributed to dissociation changes and the decrease in ionic strength resulting from dilution. The copper chelates follow Beer's law at higher concentration, but exhibit deviations, probably resulting from dissociation, at the low concentration illustrated in Figs. 3 and 4.

Experimental

N-Substituted Ethylenediamines, General Procedure.—Five moles of 95% ethylenediamine was heated to 80° and one mole of the alkyl halide was then added dropwise over a period of 2–3 hours with rapid stirring. Separation of the mixture into 2 phases occurred toward the end of the addition. Heating and stirring were then continued for an additional 4–8 hours. A slight excess of 40% aqueous sodium hydroxide was added, and a third aqueous layer separated out.

In the preparation of N-n-butylethylenediamine and of N-n-benzylethylenediamine, the products were first separated from the excess ethylenediamine by extraction of the mixture with anhydrous benzene. The extract was dried over successive portions of solid potassium hydroxide on a steam-bath, and solvent was distilled off at atmospheric pressure. The residue was dried over metallic sodium and the mono- and symmetrically disubstituted diamines were isolated as water-white liquids by fractionation under reduced pressure over metallic sodium.

In the preparation of N-n-octylethylenediamine, the upper layer of the reaction mixture partially solidified upon cooling as a result of the formation of the hydrate of N,N′-dioctylethylenediamine. This layer was separated and dried over solid potassium hydroxide. Fractionation under reduced pressure and subsequent redistillation over metallic sodium, resulted in the isolation of pure N-n-octyl- and N,N′-dioctylethylenediamines.

The upper layer of the reaction mixture containing N-n-dodecylethylenediamine also solidified upon cooling. Complete separation from ethylenediamine was accomplished by the addition of cold water, filtration and several washings with hot water. The hydrates were extracted with ether, dried over solid potassium hydroxide, and final purification was achieved by fractionation under reduced pressure over metallic sodium.

N-Cyclohexylethylenediamine.—One-half mole of anhydrous ethylenediamine (30 g.) and 0.5 mole (25 g.) of cyclohexanone were mixed and allowed to stand for one hour. The reaction was quite exothermic. The reaction mixture was then added to 0.5 g. of prereduced Adams platinum oxide catalyst in 25 ml. of absolute ethyl alcohol and hydrogenated for two hours at room temperature under an initial hydrogen pressure of two atmospheres. The products were

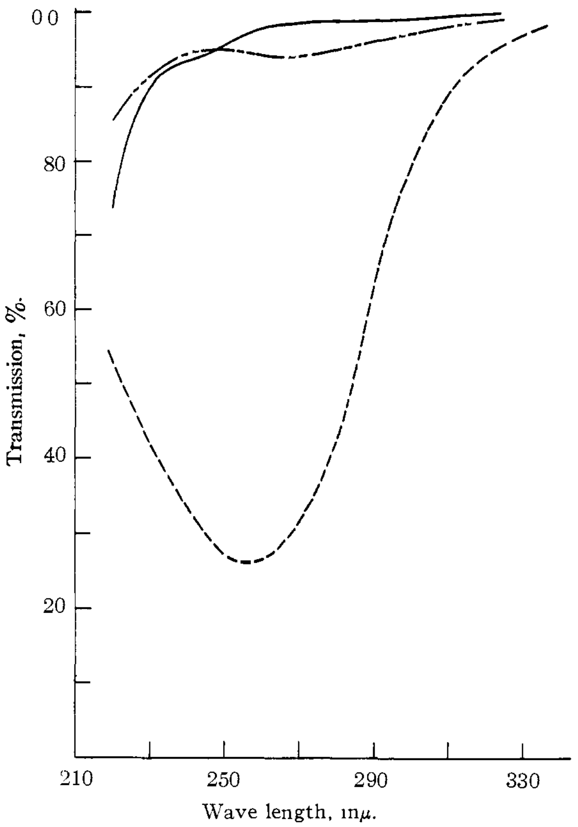


Fig. 3.—Ultraviolet absorption of metal salts and chelates of N-*n*-butylethylenediaminetriacetic acid: —, $5.0 \times 10^{-4}\ M$ trisodium salt; – – – –, $5.0 \times 10^{-4}\ M$ trisodium salt + $5.0 \times 10^{-4}\ M$ CaCl$_2$; - - - -, $1.25 \times 10^{-4}\ M$ trisodium salt + $1.25 \times 10^{-4}\ M$ CuCl$_2$.

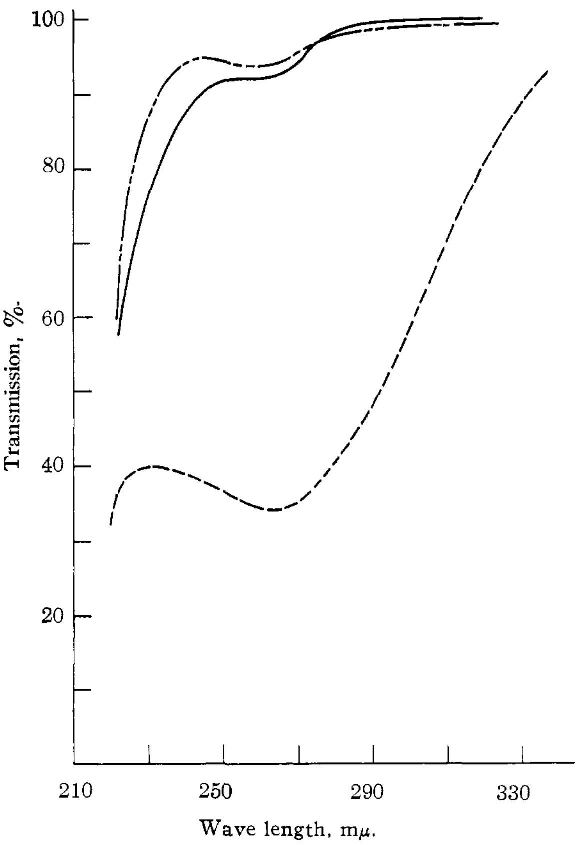


Fig. 4.—Ultraviolet absorption of metal salts and chelates of N-*n*-benzylethylenediaminetriacetic acid: —, $5.0 \times 10^{-4}\ M$ trisodium salt; – – – –, $5.0 \times 10^{-4}\ M$ trisodium salt + $5.0 \times 10^{-4}\ M$ CaCl$_2$; - - - -, $1.25 \times 10^{-4}\ M$ trisodium salt + $1.25 \times 10^{-4}\ M$ CuCl$_2$.

purified by fractional distillation under reduced pressure over metallic sodium.

Synthesis of N-Substituted Ethylenediaminetriacetic Acids. A. Carboxymethylation with Sodium Cyanide and Formaldehyde, General Procedure.—One-tenth of a mole of the N-substituted ethylenediamine, 25 ml. of *t*-butyl alcohol and 25 ml. of water were heated to 80° in a three-neck flask equipped with a mercury seal stirrer, reflux condenser and two dropping funnels. Fifty ml. of an aqueous sodium cyanide solution containing 17.1 g. (0.35 mole) of sodium cyanide, one gram of sodium hydroxide and 29.6 ml. (0.37 mole) of 36.9% aqueous formaldehyde were added dropwise over a period of eight hours. The rates of addition were so regulated that the cyanide was always present in slight excess over the formaldehyde in the reaction mixture. After addition was complete the mixture was then refluxed for 20 hours or until ammonia could no longer be detected, the removal being accelerated by bubbling a stream of air through the reaction mixture.

The *t*-butyl alcohol was then distilled off at atmospheric pressure, and the mixture was acidified to *p*H 1.2 with 30% H$_2$SO$_4$. Heating and stirring were continued for an additional hour, and the mixture was then allowed to cool to room temperature. The desired products were isolated by the following procedures:

(a) **N-*n*-Butylethylenediaminetriacetic Acid.**—Addition of 300 ml. of absolute ethanol to the reaction mixture resulted in the precipitation of a material which was predominantly sodium sulfate, containing a small amount of organic material. Cooling of the filtrate resulted in precipitation of a second batch of sodium sulfate. After this material was filtered off, the alcoholic mother liquor was distilled under reduced pressure. A tan viscous residue remained. The addition to the residue of 100 ml. of *t*-butyl alcohol and 200 ml. of absolute ethanol resulted in the separation of a mass of flocculent yellowish hygroscopic crystals. Decantation of the alcoholic liquor and recrystallization of the solid from hot 90% aqueous ethanol gave a product that could be filtered satisfactorily. Further recrystallization from 90% ethanol until a negative sulfate test was obtained yielded about one gram of the desired triacetic acid.

The organic material which coprecipitated with sodium sulfate was identified as nitrilotriacetic acid. The yield of this material was 1.2 g.

(b) **N-Benzylethylenediaminetriacetic Acid.**—Addition of 200 ml. of absolute ethanol to the reaction mixture resulted in the precipitation of sodium sulfate, which was removed by filtration. The filtrate was then cooled overnight, and a second crop of sodium sulfate was filtered off. The filtrate was again allowed to stand in the cold for three days. Colorless organic crystalline solid, contaminated by traces of sodium sulfate, separated. Three recrystallizations from 90% ethanol yielded 16.5 g. (51% of the theoretical amount) of pure N-benzylethylenediaminetriacetic acid.

No further crystallization occurred from the alcoholic mother liquor. Evaporation of the solvent under reduced pressure resulted in the isolation of a yellow viscous residue, soluble in water and alcohol, and which complexed cupric ions.

(c) **N-Cyclohexylethylenediaminetriacetic Acid.**—Sodium sulfate was fractionally precipitated by the addition of 500 ml. of absolute ethanol and allowing the mixture to stand in the cold for 24 hours. Filtration, followed by refrigeration for two days, resulted in the precipitation of the N-cyclohexyltriacetic acid as white coarse crystals. Recrystallization from 90% ethanol until a negative sulfate test was obtained resulted in the isolation of about 2 g. of the pure acid. The bulk of the reaction product was a viscous brown residue which resisted further separation by extraction techniques. Extraction of the sodium sulfate fraction with cold water, followed by the recrystallization of the residue from hot water gave 2.4 g. of nitrilotriacetic acid.

(d) **N-*n*-Octylethylenediaminetriacetic Acid.**—Sodium sulfate was fractionally precipitated by the addition of 300 ml. of absolute ethanol. The resulting filtrate was then evaporated under reduced pressure to half its original volume and allowed to stand in the cold. The desired triacetic acid, contaminated with a considerable amount of sodium sulfate, precipitated. Twelve recrystallizations from 90% ethanol yield 5 g. (15% of the theoretical amount) of N-*n*-octylethylenediaminetriacetic acid; 3.2 g. of nitrilotriacetic acid was isolated from the alcoholic mother liquor.

(e) **N-*n*-Dodecylethylenediaminetriacetic Acid.**—Sodium sulfate was fractionally precipitated by the addition of 300 ml. of absolute ethanol and allowing the solution to stand overnight in the cold. Further refrigeration of the mother liquor for four days resulted in the precipitation of the crude triacetic acid derivative. Three recrystallizations from a large volume of hot water yielded 3 g. of pure N-*n*-dodecylethylenediaminetriacetic acid. In addition, 3 g. of nitrilotriacetic acid was isolated from the sodium sulfate residues.

B. **Carboxymethylation of N-Benzylethylenediamine with Barium Cyanide.**—One liter of an aqueous solution containing 15 g. (0.1 mole) of N-benzylethylenediamine, 32.2 g. (0.17 mole) of barium cyanide and 31.5 g. (0.1 mole) of barium hydroxide octahydrate was heated to 40° on a water-bath. One hundred milliliters of an aqueous solution containing 0.37 mole of formaldehyde was added dropwise over a period of 20 hours with rapid stirring. A stream of air was bubbled through the reaction mixture to aid in the removal of ammonia.

The mixture was then treated with the stoichiometric amount of 50% H_2SO_4 and heated at reflux temperature for eight hours. The precipitated barium sulfate was allowed to settle overnight and filtered. The filtrate was evaporated to a small volume under reduced pressure and was then diluted with approximately 300 ml. of absolute ethanol. The small amount of barium sulfate which separated after standing overnight was filtered off, and this filtrate was concentrated to a total volume of approximately 150 ml. The N-benzyltriacetic acid separated upon cooling. After three recrystallizations from 90% ethanol a pure product was obtained. A mixed melting point with a sample of the triacetic acid formed by the former procedure showed no depression.

Potentiometric Titration Method.—Titrations were performed in a closed cell which was thermostated at 24.2 ± 0.1°. Presaturated nitrogen was bubbled slowly through the solution to maintain an inert atmosphere. The *p*H values were determined with the aid of a Beckman Model G *p*H meter equipped with glass and calomel electrodes standardized by the use of standard buffer solution. The sodium hydroxide was prepared carbonate free by the usual procedure. Titrations were performed on solutions containing initial amino acid concentrations of 2×10^{-3} *M* both in the absence and in the presence of an equimolar amount of cupric chloride and 10 times the amount of calcium chloride. The titration of the dodecyl derivative was performed on a suspension of the acid in 0.1 *N* KCl.

Spectrophotometric Method.—Measurements were performed in the ultraviolet region (220–350 mμ) with a Beckman model DU quartz spectrophotometer. Quartz cells were used and transmission readings were taken at 5 mμ intervals. All solutions were prepared by diluting a 10^{-3} *M* stock solution to the desired concentrations. The stock solution was prepared by dissolving the weighed quantity of acid in one-half the required volume of water, adding the stoichiometric quantity of standard sodium hydroxide to form the trisodium salt, and diluting to volume. Solution containing copper(II) and calcium(II) chelates were prepared in the same manner. All solutions were filtered before use.

Calculation of Stability Constants.—The calculation of the acid dissociation and complex formation constants was performed by the algebraic method described recently.[8] The final equation for the formation constants may be written

$$K = \frac{C_A - \beta[A^{-3}]}{[A^{-3}]\,(C_M + \beta[A^{-3}] - C_A)}$$

where C_A and C_M are the total concentrations of amino acid and metal ions, respectively, and K is the formation constant. $[A^{-3}]$ was calculated from the expression

$$[A^{-3}] = \frac{(3 - a)C_A - [H^+] + [OH^-]}{\frac{3[H^+]^3}{K_1K_2K_3} + \frac{2[H^+]^2}{K_2K_3} + \frac{[H^+]}{K_3}}$$

where K_1, K_2 and K_3 are the corresponding acid dissociation constants, and a denotes moles of standard base added per mole of amino acid, and

$$\beta = \frac{[H^+]^3}{K_1K_2K_3} + \frac{[H^+]^2}{K_2K_3} + \frac{[H^+]}{K_3} + 1$$

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Derivatives of Sulfenic Acids. XXV. The Kinetics of the Reaction of 2,4-Dinitrobenzenesulfenyl Chloride with Cyclohexene[1]

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Reaction of 2,4-dinitrobenzenesulfenyl chloride and cyclohexene in dry acetic acid yields only the 1:1 adduct, 2-chlorocyclohexyl 2′,4′-dinitrophenyl sulfide, and follows the rate expression, $-d[\mathrm{ArSCl}]/dt = k[\mathrm{ArSCl}]$ [cyclohexene]. The values of k (mole/l.)$^{-1}$ sec.$^{-1}$, are 4.17×10^{-3}, 4.89×10^{-3}, 7.84×10^{-3} and 14.75×10^{-3}, at 15.3°, 17.6°, 25° and 35.2°, respectively. This gives 11.1 ± 0.5 kcal./mole for E_a and −33 cal./deg. for $\Delta S^{\ddagger}$. The values of k, (mole/l.)$^{-1}$ sec.$^{-1}$, for other solvents are 30.2×10^{-3}, 14.6×10^{-3}, 6.5×10^{-3} and 1.08×10^{-5}, for nitrobenzene, *sym*-dichloroethane, chloroform and carbon tetrachloride, in the order listed. These data are consistent with a mechanism previously suggested, which involves formation of a cyclic sulfonium ion intermediate as the rate-determining step.

From previous work it is known that 2,4-dinitrobenzenesulfenyl chloride (I) undergoes a general addition reaction with olefins,[2] that the additions to styrene and *p*-substituted styrenes, in dry acetic acid, are first order with respect to each reactant and are favored by electron-releasing *para* substituents in the styrene,[3,4] that the addition of the sulfenyl chloride to cyclohexene leads to the *trans* adduct[5] and that the reactions, in acetic acid, can be suitably formulated on the basis of a polar mechanism involving formation of an intermediate sulfonium ion as the rate-determining step.[3]

In continuing our studies of the kinetics and mechanism of the sulfenyl halide–olefin reaction, the kinetics of addition of I to cyclohexene, in acetic acid and in other solvents, have now been determined. Cyclohexene was selected for particular

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[1] Carried out under sponsorship of the Office of Ordnance Research, United States Army.

[2] N. Kharasch and C. M. Buess, THIS JOURNAL, **71**, 2724 (1949).

[3] W. L. Orr and N. Kharasch, *ibid.*, **75**, 6030 (1953).

[4] W. L. Orr and N. Kharasch, *ibid.*, **78**, 1201 (1956).

[5] A. J. Havlik and N. Kharasch, *ibid.*, **78**, 1207 (1956).