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PREPARATION, CATION-EXCHANGE ISOLATION AND SOME PROPERTIES OF N'-METHYLETHYLENEDIAMINE-N,N,N'-TRIACETIC ACID

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SUMMARY

N'-Methylethylenediamine-N,N,N'-triacetic acid has been synthesized for the first time by a classical carboxymethylation procedure (yield 71%) using cation-exchange elution techniques to isolate the amino acid product from a complex reaction mixture, prior to crystallizing from an alcohol-water mixture. The product melted at 204–206° and its pK_a values appear to be about 2.5, 5.4 and 10.3. The tri-negative anion of N'-methylethylenediamine-N,N,N'-triacetic acid forms a very stable complex with cupric ion and a moderately stable complex with calcium.

INTRODUCTION

Search for a selective complexant for tripositive lanthanons which: (1) has high water solubility; (2) forms fairly stable, labile rare-earth chelate species; and (3) exhibits a single (poly)dentate behavior toward all the rare-earth(III) cations, fomented an interest in the investigation of N-alkyl-substituted ethylenediaminetriacetates and N'-methylethylenediamine-N,N,N'-triacetate (MEDTA) in particular. Library search revealed that N'-*n*-butyl, N'-*n*-octyl, N'-*n*-dodecyl, N'-cyclohexyl and N'-benzyl-substituted entities of this kind have been prepared (generally in poor yields)¹ from the corresponding N-substituted ethylenediamines by a classical carboxymethylation reaction, involving formaldehyde and sodium cyanide². BRUNO *et al.*¹ reported increased solubility and decreased yield as the *n*-alkyl substituent decreased in bulk from octyl to butyl (recoveries of purified products were about 15% and 3%, respectively). Only in the case of N'-benzylethylenediamine-N,N,N'-triacetic acid was the yield appreciable (51%).

Carboxymethylation with formaldehyde and sodium cyanide is complicated by evolution of NH_3 , part of which is inadvertently carboxymethylated to nitrilotriacetate (NTA); and subsequent recovery of N'-alkylethylenediamine-N,N,N'-triacetic acids from the acidified reaction mixtures entails recovery of water-soluble products from a

large amount of water-soluble sodium sulfate, as well as from reaction by-products (nitrilotriacetic acid, iminodiacetic acid, etc.). Because the isolation technique of BRUNO *et al.* seemed unnecessarily tedious, it was elected (in the present attempt to synthesize MEDTA) to exploit ion-exchange technology. At the outset it was known that *N'*-hydroxyethylethylenediamine-*N,N,N'*-triacetic acid (HEDTA), a close analogue of MEDTA, readily forms a cationic species, probably H_5A^{2+} , which has considerable affinity for cation-exchange resins³, whereas nitrilotriacetic acid exhibits little, if any, affinity for H^+ -form cation-exchange resin. Furthermore, it was anticipated that protonated species formed in the cases of iminodiacetic acid, *N'*-methylethylenediamine-*N,N,N'*-diacetic acid, etc. (if present as by-products) could be separated via displacement chromatography by eluting the sorbed amino acid mixture down an H^+ -form cation-exchange bed with either dilute aqueous NaOH or NH_4OH .

EXPERIMENTAL

One mole (74 g) of *N*-methylethylenediamine, 250 g of *tert.*-butanol and 250 ml of water were heated to the boiling point in a 3-l, three-necked, round-bottomed flask, equipped with two 500-ml addition funnels, a reflux condenser and a magnetic stirrer. One funnel was filled with a water solution containing 171 g (3.5 moles) of NaCN and 10 g of NaOH; and the other was filled with 500 ml of solution prepared by diluting 296 ml of 37% formaldehyde (3.7 moles) to volume. The mixture in the flask was heated under reflux and swept with air while the NaCN and H_2CO were added slowly. The refluxing and sweeping operations were continued for 24 h (until evolution of NH_3 ceased). The *tert.*-butanol was then eliminated by distillation, the pH was adjusted to 1.2 with H_2SO_4 , and the mixture was again refluxed (3 h). After cooling, the contents of the flask were passed through a column series comprised of three, 2-in.-diameter \times 4-ft.-length cation-exchange beds containing 40–50 mesh, H^+ form, Dowex 50W-X8 resin; and the system was rinsed with distilled water to eliminate H_2SO_4 and NTA. The system was then eluted with 0.1 *N* NaOH. During elution a 2-ft. (lighter colored) displacement chromatographic zone formed and progressed down the columns ahead of the lengthening band of sorbed Na^+ .

The chromatographic zone of sorbed amino acid(s) was collected as it passed off the system in a total of twenty 0.9-l fractions. Samples 1–15 (being colorless and giving similar titration curves) were combined and evaporated to about 400-ml volume and cooled to room temperature. Addition of 200 ml of absolute alcohol induced turbidity which disappeared when the solution was warmed. Further alcohol was added and heating was continued until a total of 800 ml of ethanol had been incorporated and the solution was at its boiling point and permanently turbid. At this point, a further 800 ml of ethanol was added with stirring, and the solution was allowed to cool. The precipitate was recovered by filtration and dried under vacuum, yielding 160 g of product (melting point 204–246°); analysis: 43.4% C, 6.8% H and 11.3% N (theoretical: 43.55% C, 6.50% H, 11.29% N, 38.76% O). The formula weight was ascertained to be 250.2 (theoretical 248.24) by titration. An additional 18 g of product was recovered from fractions 16–19, increasing the overall yield to 71%.

Fig. 1 shows the results of: (1) titrating 200 ml of 0.005 *M* MEDTA with 0.1 *M* KOH; (2) titrating 200 ml of solution made up 0.005 *M* in MEDTA and 0.005 *M* in

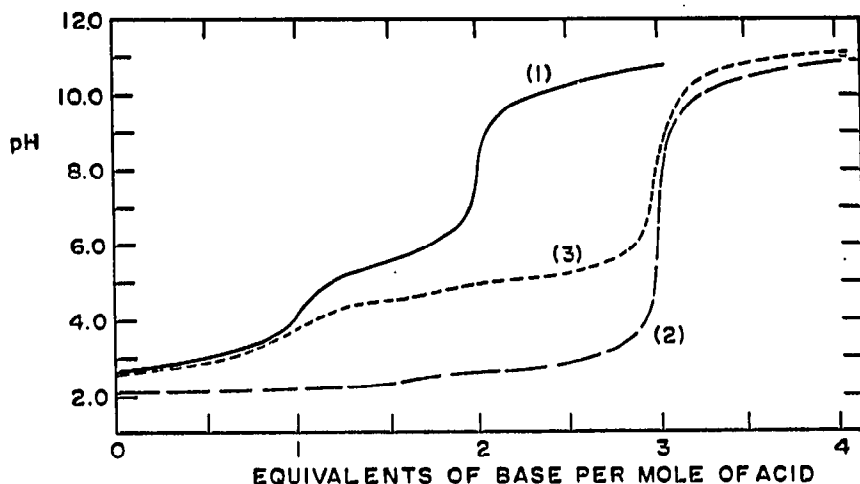


Fig. 1. Titration with base of MEDTA: (1) alone; (2) with equimolar Cu^{2+} ; and (3) with a large excess of Ca^{2+} .

$\text{Cu}(\text{NO}_3)_2$ with 0.1 M KOH; and (3) titrating 200 ml of solution made up 0.005 M in MEDTA and 0.05 M in $\text{Ca}(\text{NO}_3)_2$ with 0.1 M KOH.

CONCLUSIONS

Although MEDTA appears almost infinitely soluble in water, it is only slightly soluble in alcohol. Consequently, MEDTA is readily recovered from concentrated solution (after ion-exchange purification) by adding absolute alcohol. MEDTA is a typical triprotic amino acid ($\text{p}K_a$ values about 2.5, 5.4, and 10.3) which protonates further, forming H_4Ch^+ and H_5Ch^{2+} species of appreciable stability. Comparing the results of titration with base (alone, with equimolar copper nitrate and with a ten-fold concentration of calcium nitrate) to similar data of BRUNO *et al.*¹ revealed that MEDTA forms complexes with Cu(II) and with calcium which compare in stability with those formed by *N'*-benzylethylenediamine-*N,N,N'*-triacetate ($\log K_{\text{CuCh}} = 16.8$; $\log K_{\text{CaCh}} = 6.7$) more closely than with those formed by *N'*-*n*-butylethylenediamine-*N,N,N'*-triacetate ($\log K_{\text{CuCh}} = 12.7$; $\log K_{\text{CaCh}} = 1.6$). Clearly, MEDTA will have complexing properties very similar to those of HEDTA, except that (lacking the hydroxyl donor group) it cannot function hexadentately, as well as pentadentately, as does HEDTA in complexing some rare-earth(III) cations⁴. For this reason, MEDTA is expected to be superior to HEDTA for eluting and separating the middle lanthanons (Sm–Ho) on cation-exchange systems.

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