

UNIVERSITY OF ILLINOIS

February 22, 89
..... 19.....

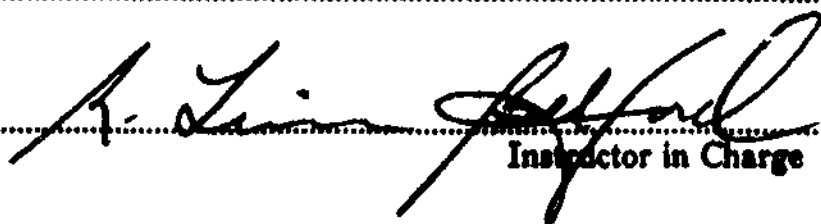
THIS IS TO CERTIFY THAT THE THESIS PREPARED UNDER MY SUPERVISION BY

Marielle Brinkman
.....

Gadolinium EDTA and DTPA Chelate Compounds
ENTITLED.....

IS APPROVED BY ME AS FULFILLING THIS PART OF THE REQUIREMENTS FOR THE

Bachelor of Science in Chemistry
DEGREE OF.....

.....
.....

Instructor in Charge

APPROVED:.....

HEAD OF DEPARTMENT OF... CHEMISTRY.....

**Gadolinium EDTA and DTPA
Chelate Compounds**

By

Marielle Brinkman

Thesis

for the

Degree of Bachelor of Science

in

Chemistry

College of Liberal Arts and Sciences

University of Illinois

Urbana, Illinois

1969

Table of Contents

	Page
Introduction	1
Results	5
Discussion	8
Conclusion	15
Experimental	16
Bibliography	20
Appendix A Purification of EDTA and DTPA	1-A
Appendix B Tables	1-B
Appendix C Figures	1-C
Appendix D Historical Summary of LnEDTA Literature	1-D

**This thesis is dedicated to my parents,
Nancy and Robert Brinkman,
with whom I have spent
many late nights talking.**

Introduction

Magnetic resonance imaging (MRI) is currently in clinical use as a powerful diagnostic probe. The images of living tissue produced by this technique are largely composites of NMR signals from the multitude of water protons contained within the body. The image clarity is dependent upon long nuclear relaxation times, termed "high relaxivities." Not all tissue, because of low relaxivity problems, produces a coherent, clear magnetic resonance image. This problem is solved by a proposed class of compounds called MRI contrast agents. MRI contrast agents are designed to decrease the relaxation times of nearby nuclei via dipolar interactions, thereby intensifying the nuclear magnetic resonance image. The pathway for electronic relaxation of an ion with a half-filled f-shell is inefficient,¹ hence promoting extended electronic relaxation times. The gadolinium (III) cation has a $7s^24f^7$ electronic configuration (Table 1). Its seven unpaired f-electrons, and spherical electronic distribution are characteristics that result in gadolinium having a high relaxivity.²

Besides having a high relaxivity, an MRI contrast agent must also be a stable compound so as not to toxically interact itself, or dissociate, producing constituents that go on to form toxic compounds in the body. Coordinating a multidentate ligand to a metal ion more or less surrounds the metal with the ligand ring structures (Figs. 1-5), thereby repressing characteristic reactions (possible toxicity) of the metal.³ Complexes involving rare earth metal ions owe the stabilities they possess to ionic dipole-dipole attractions, not covalent bonding.⁴ This allows the rare earth chelates to influence and lengthen proton

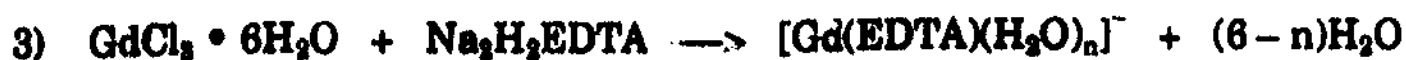
relaxation behavior by virtue of its own high relaxivity via dipole interaction, without forming covalent bonds.

The trivalent gadolinium cation forms stable complexes with two such multidentate ligands: ethylenediaminetetraacetic acid (abbreviated henceforth as EDTA), and diethylenetriaminepentaacetic acid (abbreviated henceforth as DTPA). Another important characteristic of an MRI contrast agent, termed selectivity, is its ability to localize in certain areas of the body, thus highlighting a target tissue. The structures of both $[\text{Gd}(\text{EDTA})(\text{H}_2\text{O})_n]^-$ (abbreviated henceforth as GdEDTA) and $[\text{Gd}(\text{DTPA})(\text{H}_2\text{O})]^{2-}$ (abbreviated henceforth as GdDTPA) (Figs. 1–5) show the many carboxylate groups that make these complexes hydrophilic. The presence of these charged or hydrogen-bonding groups, coupled with the lack of any large hydrophobic groups, ensure their interaction with plasma proteins, other macromolecules, and membranes will be minimal.² These types of compounds have a non-selective cellular distribution, meaning their localization in tissues does not reflect specific cellular processes.² Hence these compounds show no special selectivity. However, their extracellular distribution (lack of selectivity) does not mean these complexes have no use as MRI contrast agents. Studies have been done using GdDTPA to allow imaging of the kidneys for structural and functional information,^{5, 6} the status of blood flow to a tissue,^{7, 8} brain lesions,⁹ and the imaging of tissues that have an increased extracellular volume, e.g. tumors and abscesses.^{6, 9, 10} Several studies have been done comparing the formation constants of the metal chelates,^{3, 24-27} and more specifically, the rare earth chelates^{15, 17, 28-31} of the DTPA and EDTA ligands. After its introduction in the 1940s¹¹, the EDTA ligand gained interest ten years later, when it was

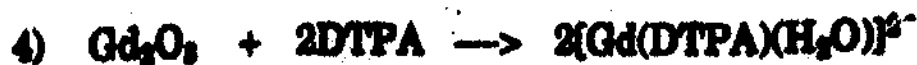
discovered that EDTA brought about improved separations of the rare earth metal ions by precipitation procedures,¹²⁻¹⁴ and by ion-exchange techniques.¹⁴⁻¹⁹ Papers reporting the NMR spectra of metal EDTA chelates,²¹ and the EPR spectra of GdEDTA²² have been published. Its sodium salts are referred to in the literature by several trade names: Versene, Sequestrene, Trilon B, Complexone II, III or IV.³

This paper describes the synthesis and characterization of two gadolinium chelate compounds, GdEDTA, 1-3; GdDTPA, 4; and the tetrasodium salt of the EDTA ligand, Na₄EDTA, 5. The synthesis of Na₄EDTA is presented as a reference for possible future deuterated studies.

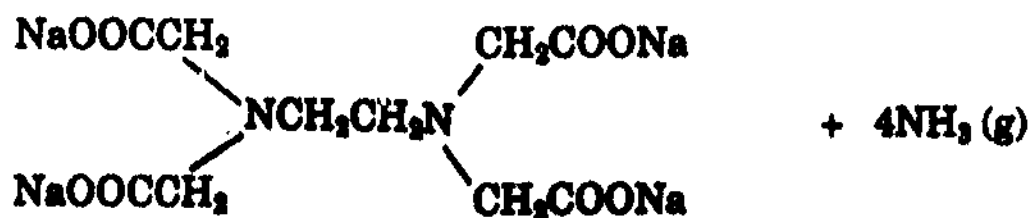
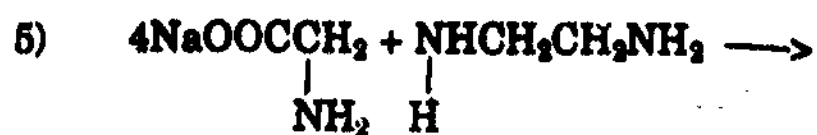
The syntheses of GdEDTA were carried out in aqueous solution using three different sources of Gd (III) cation; the oxide, nitrate, and chloride. The reactions were as follows:



The synthesis of GdDTPA was carried out in aqueous solution using the oxide as the source of Gd (III) cation:



The air-sensitive synthesis of Na_4EDTA was carried out by combining the alkali metal salt of an alpha amino acid (glycine) and ethylenediamine:



Results

The reaction of gadolinium oxide with ethylene-diaminetetraacetic acid, combined in a 1:1 molar ratio of metal ion to ligand, in a refluxing 0.075 M aqueous solution for 45 hours resulted in a white-beige precipitate, $[\text{Gd}(\text{EDTA})(\text{H}_2\text{O})_1]^-$, 1, in 73.79% yield after drying at 110°C. The microanalytical results (Fig. 6) were slightly low for hydrogen, but otherwise compared well with similar preparations (Table 2). The smaller amounts of hydrogen than evidenced in the literature may be explained by fewer water molecules in the primary coordination sphere. The infrared spectrum was recorded (Fig. 13) and showed a strong, broad band at 1584 cm^{-1} which was attributed to the complexed carboxyl groups (Figs. 1-3); and a much weaker band at 1719 cm^{-1} which was attributed to uncomplexed carboxyl groups (Fig. 2, 3).

The reaction of gadolinium nitrate with an equimolar amount of the disodium salt of ethylenediaminetetraacetic acid in refluxing 0.10 M aqueous solution for 18 hours resulted in a white precipitate, $[\text{Gd}(\text{EDTA})(\text{H}_2\text{O})_n]^-$, 2, in 57.67% yield after drying at 110°C. The microanalytical results (Fig. 7) were slightly low for hydrogen, but otherwise compared well for similar preparations (Table 2). The smaller amounts of hydrogen may be explained by fewer molecules in the primary coordination sphere. The infrared spectrum was recorded (Fig. 14) and showed a strong, broad band at 1588 cm^{-1} which was attributed to complexed carboxyl groups (Figs. 1-3), and a much weaker band at 1715 cm^{-1} which was attributed to uncomplexed carboxyl groups (Figs. 2, 3).

The reaction of gadolinium chloride with an equimolar amount of the disodium salt of ethylenediaminetetraacetic acid in refluxing 0.10 M aqueous

solution for 18 hours resulted in a white precipitate, $[\text{Gd}(\text{EDTA})(\text{H}_2\text{O})_n]^-$, 3, in 65.04% yield after drying at 110°C. The microanalytical results (Fig. 8) were slightly high in carbon and nitrogen and low in hydrogen when compared to similar preparations (Table 2). The numbers presented in Table 2 are atomic ratios based on the atomic ratio for gadolinium being 1.00. Therefore, a high ratio for gadolinium could masquerade as high ratios for carbon and nitrogen. This believed excess in gadolinium could indicate the presence of 4:3 or 2:1 metal ion to ligand polynuclear contaminants. The smaller amounts of hydrogen may be explained by fewer water molecules in the primary coordination sphere. The infrared spectrum was recorded (Fig. 15) and showed a medium, broad band at 1583 cm^{-1} , which was attributed to complexed carboxyl groups (Figs. 1-3); and a very weak band at 1714 cm^{-1} which was attributed to uncomplexed carboxyl groups (Figs. 2, 3).

The reaction of gadolinium oxide with diethylenetriaminepentaacetic acid, combined in a 1:1 molar ratio of metal ion to ligand, in a refluxing 0.16 M aqueous solution for 11.5 hours resulted in a white precipitate, $[\text{Gd}(\text{DTPA})(\text{H}_2\text{O})]^{2-}$, 4, in 97.42% yield after drying in vacuo for three days. The microanalytical results (Fig. 9) show a slight excess of carbon and nitrogen (Table 2). As indicated, the atomic ratios in Table 2 are based on gadolinium's being equal to 1.00. Hence, the high values for carbon and nitrogen are interpreted as actually being escalated values for gadolinium. This excess in gadolinium may be attributed to the presence of 2:1 metal to ligand polynuclear contaminants. The infrared spectrum was recorded (Fig. 16) and showed a strong, broad band at 1588 cm^{-1} which was attributed to complexed carboxyl groups (Figs. 4, 5), and a much weaker band at 1715 cm^{-1} which was attributed

to uncomplexed carboxyl groups (Fig. 5). The results of the syntheses and characterization of compounds 1-4 are summarized in Table 5.

The reaction of ethylenediamine in a four molar excess of the sodium salt of glycine in a 30% aqueous solution under positive nitrogen gas flow resulted in the evolution of ammonia gas and a white precipitate, Na_4EDTA , 5, in 37.50% yield after being dried in vacuo for three days. The microanalysis (Fig. 10) is considerably low in carbon (22.51% error) and extremely high in nitrogen (97.69% error) indicating the presence of high concentrations of other species. The infrared spectrum reflects this (Fig. 17). Medium absorbance bands were recorded at 3367 cm^{-1} , 3332 cm^{-1} , 3275 cm^{-1} , and 3198 cm^{-1} ; a strong, broad band was recorded at 1585 cm^{-1} , a medium band at 1343 cm^{-1} , and a broad band stretching across $897\text{-}833\text{ cm}^{-1}$. These bands reflect possible primary amine, and amide formation (Table 4).

The infrared spectra of both the purified EDTA and DTPA ligands were recorded for reference (Figs. 18, 19) and as an aid to spectra interpretation. Both compare well with findings in the literature (Table 3). The resulting crystal structures of the two uncomplexed ligands, EDTA and DTPA, are also provided for reference (Figs. 20, 21).

Discussion

The microanalyses for all of the GdEDTA compounds were all slightly low for hydrogen in comparison to similar preparations in the literature (Table 2). However, the comparative literature preparations were carried out at room temperature, not in a 98-100°C refluxing, aqueous solution. Temperature-dependent electronic absorption spectra for the metal-EDTA complexes of Sm^{3+} , Eu^{3+} , and Gd^{3+} recorded by Geier, Karlen and Zelewsky³² were interpreted as showing that the number of coordinated water molecules decreases at higher temperatures. It is on the basis of this study, that the lower values of hydrogen are thought to correspond to fewer water molecules in the primary coordination sphere.

The microanalyses of GdEDTA, 3, and GdDTPA, 4, both showed a slight excess of gadolinium. Electronic absorption studies indicate the formation of (2:1)^{28, 29, 33-37} and (4:3)^{29, 33} rare earth (metal:EDTA) complexes, although they are reported to be much less stable than the 1:1 complex. Specifically for the analogue complexes of neodymium,²⁹ the bimetallic complexes form in two distinct solution types: (1) concentrated acidic (1.7 M, pH = 5 for Nd_2EDTA) and (2) dilute alkaline (0.035 M, pH = 12.5 for Nd_2EDTA ; 0.03 M, pH = 9.8 for Nd_2DTPA). Hydroxide ions promote the opening of part of the chelate rings. The presence of the negatively charged OH^- group in the coordination sphere of the rare earth metal leads to partial neutralization of the positive charge of Gd^{3+} , and therefore weakens the electrostatic interaction between Gd^{3+} and the ligand. Hence, the bond between the metal ion and the ligand is labilized, and the formation of bimetallic compounds becomes possible.²⁹ The concentrations

of the solutions for preparations 3 and 4 were 0.10 M and 0.16 M respectively; i.e., less than the concentrations for solution (1) by a factor of 10, and thus not providing the high concentration environment that promotes the formation of bimetallic compounds. Unfortunately, the pH of the solutions was not measured – a large oversight – so it is not known if conditions similar to solution (2) existed. Despite the fact that it is not known whether the appropriate conditions for the formation of bimetallic compounds existed, the formation of bimetallic chelate compounds for Ln_2EDTA ,^{29, 33} ($\text{Ln} = \text{Lanthanide}$) and Ln_2DTPA ,^{23, 28, 29, 34-37} is well documented, and the formation of trace amounts of Gd_2EDTA and Gd_2DTPA in preparations 3 and 4, respectively, definitely provides an explanation for the high amounts of gadolinium found in the microanalyses of compounds 3, and 4. Careful monitoring of the pH of the reaction solution will help prevent the formation of these bimetallic compounds. Suggested conditions²⁹ for GdEDTA involve a 0.035 M solution, pH = 3–6; for GdDTPA , a 0.030 M solution, pH = 2–8.

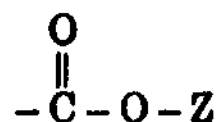
The infrared spectra for GdEDTA compounds 1–3 and GdDTPA , 4, (Table 5) all evidence two distinct absorptions in the carbonyl region. In 1953, Busch and Bailar³⁸ synthesized one hexadentate and two pentadentate Co(III)EDTA compounds, and recorded their individual infrared spectra. The hexadentate complex showed only one, strong absorption band in the carbonyl region. However, both pentadentate complexes exhibited two bands in the carbonyl region; absorption in the 1650-1620 cm^{-1} region, and a weaker, shoulder-type band in the 1730-1710 cm^{-1} region. Busch and Bailar assigned the two types of bands present for pentadentate complexes to complexed carboxyl groups (the stronger, larger band), and uncomplexed carboxyl groups (the

weaker band) (Figs. 1-5). The differing intensities of the bands indicate that there are more complexed than uncomplexed carboxyl groups present in the compounds. Comparing the spectra of GdEDTA compounds 1-3 to that of EDTA (Table 5), complexing of the carboxyl groups shifts the carbonyl band toward lower frequencies, from 1692 \rightarrow 1583-1588 cm^{-1} ; while the band associated with the free carboxyl group is shifted to higher frequencies 1692 \rightarrow 1714-1719 cm^{-1} . Comparing the spectra GdDTPA, 4, to that of DTPA (Table 5), complexing of the carboxyl also shifts the carbonyl band to lower frequencies, from 1693 \rightarrow 1588 cm^{-1} ; while the band associated with the free carboxyl group is also shifted to higher frequencies, from 1693 \rightarrow 1715 cm^{-1} . Complex formation is thought to result in a greater localization of electrons in the carbonyl group, thereby shifting the characteristic infrared absorption band toward longer wavelengths (shorter frequencies).³² One year later, Moeller, Moss and Marshall³³ published infrared absorption studies of LnEDTA chelates (Ln = Nd, Y, Sm) exhibiting the same set of two types of bands in the carbonyl region. Their results, compared with the infrared absorption bands recorded for compounds 1-4, are presented in Table 5. They also attributed the bands to coordinated (1610-1600 cm^{-1}), and uncoordinated (1715-1690 cm^{-1}) carboxyl groups, and go on to make the assumption that the sixth coordination position of Ln^{3+} is occupied by a water molecule. These studies, and the fact that the infrared spectrum presented for compounds 1-4 (Figs. 13-15) exhibit the same phenomenon, are strong evidence for the presence of uncomplexed carboxyl groups in the GdEDTA and GdDTPA compounds prepared. However, the findings presented in this paper are by no means conclusive that the compounds prepared have a penta- or tetradentate structure. The crystal

structure for the analogous NdDTPA complex indicates that the ligand is pentadentate, leaving one coordination site open to be filled by a water molecule.³⁹

However, the structure of GdEDTA compounds is not well defined. As already mentioned, the infrared studies^{33, 38, 40, 43} give evidence of two types of carboxyl groups. However, an X-ray study⁴¹ of LnEDTA complexes indicates that GdEDTA is hexadentate, and transitional in coordination between a nine-coordinate SmEDTA having three water molecules in the primary coordination sphere, and an eight-coordinate TbEDTA having only two water molecules in the primary coordination sphere. This study indicates that the ligand's number of attachments to the metal is not affected by the loss or gain of water molecules, since it predicts that not only do the four carboxyl groups fit around the rare earth metal ion, but up to three water molecules as well (Fig. 22). This X-ray study presents no explanation for the wealth of infrared data indicating the presence of two types of carboxyl groups, already mentioned. It is not clear what the exact structure of GdEDTA is. The infrared spectra presented in this paper, along with the correlated literature,^{33, 38, 40, 42, 43} give strong evidence that one or more of the carboxyl groups is not bonded to the metal. The thermodynamic,^{2, 44, 45, 56} polarographic,³ absorption,³² infrared,^{33, 38, 40, 42, 43} and formation constant¹⁵ data give strong evidence that the number of coordinated water molecules, n , is either two or three – one study indicating that $n = 2$ at high temperatures, and $n = 3$ at lower temperatures.⁵² For a more thorough, historical summary of the research on the structure of GdEDTA, see Appendix D.

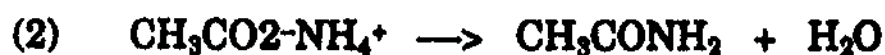
The lowering of the C=O stretching frequency was interpreted by Morris and Busch,⁴⁰ as an indication of covalent, or ionic bonding. According to their studies, if a carboxyl group is linked to some group, Z (in this case, Z = Gd):



the carboxylate resonance will increase as the ionic character of the O - Z link increases. Since an increase in carboxylate resonance imparts enhanced single-bond character to the carbonyl group, it causes a lowering of the frequency of the C=O stretching vibration. Sawyer and McKinnie⁴³ went further and quantified this relationship by stating that chelates with complexed C=O stretching frequencies of 1610 cm⁻¹ or less are considered to be ionically bonded. The complexed carboxylates of compounds 1-4 all absorb at frequencies lower than 1610 cm⁻¹, indicating the bonding in these compounds is ionic in nature.

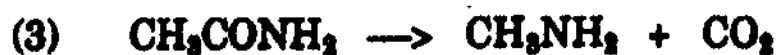
The microanalysis of compound 5 (Fig. 10) clearly indicates that Na₄EDTA was not the only product formed in appreciable amounts. The infrared spectrum (Fig. 17) also clearly shows this. There are two possible interfering side reactions proposed to explain the infrared spectral results.

The first involves the reaction of the carboxyl group with the evolving ammonia gas, producing ammonium methanoate, reaction (1), which upon heating, results in the elimination of water and the formation of the amide, reaction (2):^{11, 46}



The infrared spectrum of compound 5 shows three distinct bands in the 3367-3275 cm^{-1} region. The infrared spectra of amides⁴⁸ exhibit three bands in this region: the asymmetric N-H stretch 3550-3420 cm^{-1} , the symmetric N-H stretch 3200-3050 cm^{-1} , and the hydrogen-bonded N-H stretch 3200-3050 cm^{-1} (Table 4, compare row 1 with row 4). Amide infrared spectra also contain a strong absorption band at 1690-1650 cm^{-1} , corresponding to the C=O stretch. Figure 17 shows a very strong band at a much lower frequency of 1585 cm^{-1} . However, the broadness of the band could possibly obscure the C=O band of amides at the higher frequency. Adding sufficient sodium hydroxide to adjust the pH of the aqueous solution of the sodium salt of glycine to approximately 9.5 will help to prevent the formation of amides.¹¹

Figure 17 also shows strong evidence for a second interfering side reaction, primary amine formation. The broad band from 897-833 cm^{-1} is easily recognizable as the strong, broad absorbance band characteristic of out-of-plane bending in primary amines⁴⁹ (Table 4, compare row 1 with row 2). Also, the strong absorbance previously mentioned at 1585 cm^{-1} falls into the 1640-1560 cm^{-1} strong absorbance region attributed to in-plane bending in primary amines. The primary amine could form from the amide according to reaction (3), a Hofmann rearrangement:⁴⁷



The weak band at 3198 cm^{-1} (Fig. 17) could be attributed to water of crystallization, evidenced in the infrared spectrum of $\text{Na}_4\text{EDTA}^{60}$ (Table 4, compare row 1 with row 6). Other Na_4EDTA bands that compare well with the absorptions present in Figure 17 are 1597 cm^{-1} ($\text{O}=\text{C}=\text{O}$) and 1325 cm^{-1} (CO_2^-).

Two precursors' infrared spectra – ammonium ion⁴⁹ (row 3), and ethylenediamine⁵¹ (row 5) – are also listed in Table 4 and could be responsible for the bands in the $3300\text{-}3030\text{ cm}^{-1}$ region ($^+\text{NH}_4$ stretch vibration) and $3340, 3280\text{ cm}^{-1}$ region ($-\text{NH}_2, -\text{CH}_2$).

Conclusion

GdEDTA and GdDTPA compounds were prepared by the reactions of the oxide, nitrate, and chloride of the Gd^{3+} cation with EDTA acid, or its disodium salt, and the gadolinium oxide with DTPA acid. The hydrogen content of the GdEDTA compounds was lower than that of literature preparations that were carried out at room temperature, evidence for fewer water molecules in the primary coordination sphere. The microanalyses for GdEDTA, 3, and the GdDTPA, 4, compounds show evidence of the formation of bimetallic contaminants. The infrared spectra of the GdEDTA and GdDTPA compounds all strongly indicate the presence of two different types of carboxyl group in the structure of each separate compound. The infrared spectra also indicates the bonding in these compounds is ionic in nature. The air-sensitive preparation of the tetrasodium salt of EDTA by the reaction of the sodium salt of glycine with ethylenediamine resulted in the extensive formation of contaminants. The infrared spectrum of the products obtained from this reaction showed evidence of amide and primary amine formation.

Experimental

The synthesis of ethylenediaminetetraacetic acid tetrasodium salt was conducted under a positive flow of nitrogen using a mercury/mineral oil bubbler. All water used in syntheses and purifications was freshly boiled using the distillation apparatus shown in Figure 23.

Gadolinium (III) chloride hexahydrate, gadolinium (III) nitrate pentahydrate, gadolinium (III) oxide, glycine sodium salt hydrate (all Aldrich), ethylenediamine (Mallinckrodt), and ethylenediaminetetraacetic acid disodium salt (Sigma) were used without further purification.

Ethylenediaminetetraacetic acid (Aldrich) was purified by dissolving in concentrated ammonium hydroxide, precipitating with dilute acid, boiling in distilled water and recrystallizing,⁵² (see Appendix A, section I for further details of this purification). Triethylenediaminepentaacetic acid (Aldrich) was recrystallized from distilled water⁵³ (see Appendix A, section II for further details of this purification).

Melting point determinations were performed on a Buchi Glasapparate-fabrik Flawil melting point apparatus. All infrared spectra were performed on a Perkin Elmer 599B Infrared Spectrophotometer as nujol mulls on sodium chloride plates. Microanalyses were performed by the UIUC School of Chemical Sciences Microanalytical Laboratory.

Infrared band descriptions include the following abbreviations:

(sh) = sharp, (st) = strong, (m) = medium, (w) = weak, (b) = broad.

Ethylenediaminetetraacetato-n-aquogadolinium(III). 1: gadolinium

(III) oxide (5.4351 g, 0.01499 mol) was put in a 600 ml round bottom flask along with 400 ml of water. EDTA (8.7674 g, 0.03000 mol) was added to the flask to provide a 1:1 mole ratio gadolinium tripositive ion:EDTA ligand. The flask was equipped with a magnetic stir bar and a reflux condenser, placed in a mineral oil bath, and allowed to reflux at 98-100°C for 45 hours. The milky-beige solution was distilled down to ca. 50 ml and then placed in an ice bath. The beige-white precipitate was vacuum filtered using a fine glass frit, and washed with three 30 ml aliquots of cold water. The product was dried in a 110°C oven overnight. Yield: 73.79%. Anal. Calcd: C, 25.86; H, 3.25; N, 6.03; Gd, 33.85. Found: C, 26.47; H, 3.32; N, 6.13; Gd, 35.56.

IR (nujol): (CO_{complexed}) 1584 cm⁻¹ (st, b); (CO_{uncomplexed}) 1719 cm⁻¹ (w).

Ethylenediaminetetraacetato-n-aquogadolinium(III). 2:

extremely hygroscopic gadolinium (III) nitrate pentahydrate crystals (13.0027 g, 0.03000 mol) were combined with 300 ml of water in a 500 ml round bottom flask. An equimolar amount of EDTA disodium salt (10.0867 g, 0.03000 mol) was added to the flask along with a magnetic stir bar. The flask was equipped with a reflux condenser, placed in a mineral oil bath, and allowed to reflux at 98-100°C for 18 hours. The cloudy white solution was concentrated down to ca. 30 ml and placed in an ice bath. The product was vacuum filtered using a fine glass frit, washed with three 30 ml aliquots of cold water, and dried in a 110°C oven overnight, after which it displayed a yellowish cast to it. Yield: 57.67%.

Anal. Calcd: C, 25.86; H, 3.25; N, 6.03; Gd, 33.85. Found: C, 26.66; H, 3.07; N,

6.20; Gd, 34.82. IR (nujol): (CO_{complexed}) 1588 cm⁻¹ (st, b);

(CO_{uncomplexed}) 1715 cm⁻¹ (w).

Ethylenediaminetetraacetato-n-aquogadolinium(III).3: extremely hygroscopic, yellowish-clear gadolinium (III) chloride hexahydrate crystals (11.1660 g, 0.03004 mol) were combined with 300 ml of water in a 500 ml round bottom flask. An equimolar amount of Na₂EDTA ligand (10.0904 g, 0.03001 mol) was added. The flask was equipped with a magnetic stir bar and a reflux condenser, placed in a mineral oil bath and allowed to reflux at 98-100°C for 18 hours. The milky-white solution was concentrated to ca. 30 ml and allowed to cool in an ice bath. The white powder was filtered using a fine glass frit, washed with three 30 ml aliquots of cold water, and dried in a 110°C oven overnight. Yield: 65.04%. **Anal.** Calcd: C, 25.86; H, 3.25; N, 6.03; Gd, 33.85. Found: C, 28.44; H, 3.23; N, 6.59; Gd, 34.81. IR (nujol): (CO_{complexed}) 1583 cm⁻¹ (st, b); (CO_{uncomplexed}) 1714 cm⁻¹ (w).

Diethylenetriaminepentaacetatoaquogadolinium(III).4: gadolinium (III) oxide (2.9682 g, 0.008188 mol) and 100 ml of water were combined in a 500 ml round bottom flask equipped with a magnetic stir bar. To provide a 1:1 ratio Gd³⁺ ion:DTPA ligand, diethylenetriaminepentaacetic acid (6.3989 g, 0.01627 mol) was added to the flask. The flask was equipped with a reflux condenser and allowed to reflux at 98-100°C for 11.5 hours. The solution was concentrated down to a white sludge; and vacuum dried, while gently warming, until the compound was completely dry (ca. 3 days). Yield: 97.42%. **Anal.** Calcd: C, 29.73; H, 3.92; N, 7.43; Gd, 27.80. Found: C, 28.82; H, 3.93; N, 8.13; Gd, 26.56. IR (nujol): (CO_{complexed}) 1588 cm⁻¹ (st, b); (CO_{uncomplexed}) 1715 cm⁻¹ (w).

Ethylenediaminetetraacetatotetrasodium(I). 5: a 3-necked round bottom flask, equipped with a magnetic stir bar, reflux condenser, gas inlet, and subaseal, was placed in a mineral oil bath (Fig. 24). The flask was flushed with nitrogen gas for ca. 10 min. while warming. 500 ml of a 30% glycine sodium salt hydrate (14.5691 g, 0.1501 mol) aqueous solution was added to the flask and stirred under positive pressure. The solution was allowed to begin refluxing. Using a syringe, ethylenediamine (2.51 ml, 0.03754 mol) was injected into the reaction flask through the subaseal. $\text{NH}_{3(g)}$ evolved out of the reaction flask through the mercury bubbler without any visible indication. The reaction was allowed to reflux for 9 hours under a steady stream of nitrogen gas. The solution was then vacuum distilled (Fig. 25) to a white sludge. The reflux condenser and subaseal were replaced with glass stoppers, and the gas inlet attached to a vacuum equipped with a liquid nitrogen trap. The product was vacuum dried to a fine white silt (ca. 3 days). Yield: 37.50%. **Anal.** Calcd: C, 31.59; H, 3.18; N, 7.37. Found: C, 24.48; H, 3.85; N, 14.57. IR (nujol): 3367 cm^{-1} (m, sh); 3332 cm^{-1} (m); 3275 cm^{-1} (m); (complexed water) 3198 cm^{-1} (w); (CO) 1585 cm^{-1} (st, b); 1343 cm^{-1} (m); (NH) 897-833 cm^{-1} (st,br) --see Table 4 for a thorough analysis of the IR spectrum.

Bibliography

- 1) Martynenko, L.I.; Artyukhina, G.A.; Bogdanovich, N.G.; Spitsyn, V.I. *Russ. J. Inorg. Chem.* 1970, 7, 783.
- 2) Lauffer, R.B. "Paramagnetic Metal Complexes as Water Proton Relaxation Agents for NMR Imaging: Theory and Design," Massachusetts General Hospital and Harvard Medical School. 1987, 1-138.
- 3) Pecsok, R.L. *J. Chem. Educ.* 1952, 29, 597.
- 4) Moeller, T. *Rec. Chem. Prog.* 1953, 14(2), 69.
- 5) Wolf, G.L.; Fobben, E.S. *Invest. Radiol.* 1984, 19, 324.
- 6) Brasch, R.C.; Weinmann, H.J.; Wesbey, G.E. *Amer. J. Roentg.* 1984, 142, 625.
- 7) McNamara, M.T.; Tscholakoff, D.; Revel, D.; et. al. *Radiology* 1986, 158, 765.
- 8) Liu, P.; Villringer, A.; Lauffer, R.B.; et. al. *Radiology* in press.
- 9) Tweedle, M.F.; Brittain, H.G.; Eckleman, W.C. "Magnetic Resonance Imaging," 2nd Ed. (Partain, C.L. et. al, eds.); W.B. Saunders Co.: Philadelphia, 1987.
- 10) Wolf, G.L.; Burnett, K.R.; Goldstein, E.J.; Joseph, P.M. "Magnetic Resonance Annual" (Kressel, H., ed.); Raven Press: New York, 1985, 231.
- 11) US Patent 2,387,976 Oct. 30, 1945.
- 12) Marsh, J.K. *J. Chem. Soc.* 1950, 1819.
- 13) Marsh, J.K. *J. Chem. Soc.* 1951, 3057.
- 14) Vickery, R.C. *J. Chem. Soc.* 1951, 1817.
- 15) Wheelwright, E.J.; Spedding, F.H.; Schwarzenbach *J. Am. Chem. Soc.* 1953, 75, 4196.
- 16) Vickery, R.C. *J. Chem. Soc.* 1953, 421.
- 17) Vickery, R.C. *J. Chem. Soc.* 1953, 1695.
- 18) Holloway, J.H.; Reilley, C.N. *Anal. Chem.* 1930, 32, 249.
- 19) Vickery, R.C. *J. Chem. Soc.* 1954, 385.
- 20) Prik, G.A. *Russ. J. Inorg. Chem.* 1963, 9(9), 1097.
- 21) Kula, R.J.; Sawyer, D.T.; Chan, S.I.; Finley, C.M. *J. Am. Chem. Soc.* 1963, 85, 2930.

- 22) Al'tshuler, T.S.; Garifyanov, N.S. *J. Struc. Chem. (Russ.)* 1968, 9(6), 867.
- 23) Krumina, V.T.; Astakhov, K.V.; Barkov, S.A. *Russ. J. Phys. Chem.* 1969, 43(5), 665.
- 24) Kornev, V.I.; Astakhov, K.V.; Rybina, V.I. *Russ. J. Phys. Chem.* 1967, 41(2), 208.
- 25) Schwarzenbach, G.; Heller, J. *Helv. Chim. Acta.* 1951, 34, 576.
- 26) Vandegaer, J.; Chaberek, S.; Frost, A.E. *J. Inorg. Nucl. Chem.* 1959, 11, 210.
- 27) Zhirnova, N.M.; Astakhov, K.V.; Barkov, S.A. *Russ J. Phys. Chem.* 1965, 39(5), 647.
- 28) Harder, R.; Chaberek, S. *J. Inorg. Nucl. Chem.* 1959, 11, 197.
- 29) Martynenko, L.I.; Varlamova, G.L.; Kupriyanova, G.N.; Pechurova, N.I.; Tugusheva, G.K. *Russ. J. Inorg. Chem.* 1971, 16(5), 669.
- 30) Moeller, T.; Thompson, L.C. *J. Inorg. Nucl. Chem.* 1962, 24, 499.
- 31) Martell, A.E.; Plumb, R.C. *J. Phys. Chem.* 1952, 56, 993.
- 32) Geier, G.; Karlen, V.; Zelewsky, A.G. *Helv. Chim. Acta.* 1969, 52, 1967.
- 33) Moeller, T.; Moss, F.A.J.; Marshall, R.H. *J. Am. Chem. Soc.* 1954, 77, 3182.
- 34) Ternovaya, T.V.; Kostromina, N.A.; Kundrya, V.T. *Russ. J. Inorg. Chem.* 1975, 20(11), 1636.
- 35) Krumina, V.T.; Astakhov, K.V.; Barkov, S.A. *Russ. J. Phys. Chem.* 1969, 43(5), 665.
- 36) Galaktinov, Y.P.; Astakhov, K.V. *Russ. J. Inorg. Chem.* 1963, 8(11), 1306.
- 37) Galaktinov, Y.P.; Astakhov, K.V. *Russ. J. Inorg. Chem.* 1963, 8(6), 724.
- 38) Busch, D.H.; Ballar, J.C.Jr. *J. Am. Chem. Soc.* 1953, 75, 4574.
- 39) Spirlet, M.R.; Rebizant, J.; Desreux, J.F.; Loncin, F. *Inorg. Chem.* 1984, 23, 4278.
- 40) Morris, M.L.; Busch, D.H. *J. Am. Chem. Soc.* 1956, 78, 5178.
- 41) Hoard, J.L.; Lee, B.; Lind, M.B. *J. Am. Chem. Soc.* 1965, 87, 1612.
- 42) Sawyer, D.T.; Tackett, J.E. *J. Am. Chem. Soc.* 1963, 85, 2390.
- 43) Sawyer, D.T.; McKinnie, J.M. *J. Am. Chem. Soc.* 1960, 82, 4191.
- 44) Betts, R.H.; Dahlinger, O.F. *Can J. Chem.* 1959, 37, 91.

- 45) Moeller, T.; Ferrus, R. *Inorg. Chem.* 1961, 1, 49.
- 46) Streitwieser, A.; Heathcock, C.H. "Introduction to Organic Chemistry," 2nd Ed. 1981, Macmillan Publishing Co., Inc. p. 515.
- 47) *Ibid.*, p. 715
- 48) Conley, R.T. "Infrared Spectroscopy," 1966, Allyn & Bacon, Inc., p. 164.
- 49) *Ibid.*, p.134-136.
- 50) Chapman, D. *J. Chem. Soc.* 1955, 1766.
- 51) Svatos, G.F.; Curran, C; Quagliano, J.V. *J. Am. Chem. Soc.* 1955, 77, 6159.
- 52) Perrin, D.D.; Armarego, W.L.F.; Perrin D.R. "Purification of Laboratory Chemicals," 1966, Pergamon Press Ltd. New York, p. 163.
- 53) *Ibid.*, p. 136.
- 54) Nakamoto, K.; Morimoto, Y.; Martell, A.E. *J. Am. Chem. Soc.* 1963, 85, 309.
- 55) Bowers; *Owen Reports Prog. Physics* 1955, 18, 304.
- 56) Mackey, J.L.; Powell, J.E.; Spedding, F.H. *J. Am. Chem.Soc.* 1962, 84, 2047.
- 57) Kolat, R.S.; Powell, J.E. *Inorg. Chem.* 1962, 1, 293.

Appendix A
Purification of EDTA and DTPA

I. Purification of ethylenediaminetetraacetic acid

All water used in these purifications was freshly boiled using the distillation apparatus shown in Figure 23. Concentrated ammonium hydroxide and concentrated nitric acid (both Mallinckrodt) were used without further purification.

A sample of EDTA (16.6522g, 0.05698 mol) was put in a 250 ml erlynmeyer flask and dissolved in a minimum of concentrated ammonium hydroxide (11.5 ml, 0.1725 mol). Water (200 ml) was added to concentrated nitric acid (35.3 ml, 0.5648 mol) to produce a 2.824 M solution of aqueous nitric acid. 25 ml of 2.824 M HNO_3 was added to the flask to precipitate the EDTA sample out of solution. The EDTA was vacuum filtered using a fine glass frit. The filtrate was saved and treated with 10 ml of 2.824 M HNO_3 . The resulting precipitate was filtered and the filtrate was again treated with 10 ml of 2.824 M HNO_3 . This method of filtration, then precipitation, was repeated twice until all the EDTA was precipitated out of solution. The EDTA was again dissolved in a minimum of concentrated NH_4OH (12.4 ml, 0.1860 mol) and precipitated out stepwise with 2.824 M HNO_3 as already detailed. The EDTA was then placed in a 250 ml round bottom flask along with 100 ml of water and a magnetic stir bar and allowed to reflux for 30 hours to remove any mineral acids. The sample was filtered and recrystallized from water (the solubility of EDTA in boiling water was recorded to be ca. 0.025 M). The resulting beige powder was vacuum filtered using a fine glass frit, washed with 50 ml of cold water, and dried in a 110°C oven overnight. Recovery: 91.47% Anal. Calcd: C, 41.10; H, 5.52; N, 9.58. Found: C, 41.06; H, 5.54; N, 9.53. IR (nujol):(associated

OH) 2653 cm^{-1} (w); (C=O type A) 1692 cm^{-1} (m); (CO₂H) 1345 cm^{-1} (w),
1313 cm^{-1} (w).

II. Purification of diethylenetriaminepentaacetic acid

DTPA (11.7229 g, 0.02978 mol) was put in a 1-liter round bottom flask along with water (500 ml), and a magnetic stir bar and allowed to reflux overnight. The solution was distilled down to ca. 30 ml, placed in an ice bath and the resulting white powder vacuum filtered using a fine glass frit. The sample was dried in a 110°C oven overnight. Recovery: 87.69% Anal. Calcd: C, 42.75; H, 5.89; N, 10.68. Found: C, 42.29; H, 5.75; N, 10.55.
IR (nujol): (C=O type A) 1730 cm^{-1} (w), 1693 cm^{-1} (w); (C=O type B) 1631 cm^{-1} (m).

**Appendix B
Tables**

Table 1

Atomic size relationships and electronic configurations of the lanthanides, plus scandium and yttrium. This table illustrates the "Lanthanide Contraction," i.e., in the lanthanide series, as atomic number increases, atomic radii decreases (ref. 4).

Name	Symbol	Experimental Configuration	Atomic Number	Radius of Ln ³⁺	
				Empirical	Calculated
Scandium	Sc	3d ¹ 4s ²	21	0.83	0.68
Yttrium	Y	4d ¹ 5s ²	39	1.06	0.82
Lanthanum	La	5d ¹ 6s ²	57	1.22	1.00
Cerium	Ce	4f ² 6s ²	58	1.18	0.93
Praseodymium	Pr	4f ³ 6s ²	59	1.16	0.91
Neodymium	Nd	4f ⁴ 6s ²	60	1.15	0.90
Samarium	Sm	4f ⁶ 6s ²	62	1.13	0.87
Europium	Eu	4f ⁷ 6s ²	63	1.13	0.87
Gadolinium	Gd	4f ⁷ 5d ¹ 6s ²	64	1.11	0.86
Terbium	Tb	4f ⁹ 6s ²	65	1.09	0.84
Dysprosium	Dy	4f ¹⁰ 6s ²	66	1.07	0.83
Holmium	Ho	4f ¹¹ 6s ²	67	1.05	0.82
Erbium	Er	4f ¹² 6s ²	68	1.04	0.81
Thulium	Tm	4f ¹⁴ 6s ²	69	1.04	0.81
Ytterbium	Yb	4f ¹⁴ 6s ²	70	1.00	0.79
Lutetium	Lu	4f ¹⁴ 5d ¹ 6s ²	71	0.99	0.78

Table 2
Comparison of experimental atomic ratios of GdEDTA and GdDTPA with theoretical, and literature values

Compound	C	H	N	Gd
GdEDTA, 1	9.75	14.58	1.94	1.00
GdEDTA, 2	10.04	13.78	2.01	1.00
GdEDTA, 3	10.72	14.50	2.13	1.00
NdEDTA ³³	10.0	17.4	2.05	1.0
	10.03	16.4	1.96	1.0
SmEDTA ³³	9.8	17.1	1.91	1.0
	9.8	16.0	1.92	1.0
YEDTA ³³	9.26	16.2	1.73	1.0
	9.67	15.8	—	1.0
GdEDTA theoretical Fig. 1	10	18	2	1
GdDTPA, 4	14.20	23.07	3.43	1.00
GdDTPA theoretical Fig. 5	14	22	3	1

Table 3
Experimental and literature Infrared absorption bands for purified ligands, EDTA and DTPA.

Compound	IR exper (cm⁻¹)	IR liter. (cm⁻¹)	Assignment
EDTA	2653	2659	associated OH⁵⁰
	1692	1704	CO Type A⁵⁴
	1345	1345	CO₂H⁵⁰
	1313	1318	CO₂H⁵⁰
DTPA	1730	1731	CO Type A⁵⁴
	1693	1700	CO Type A⁵⁴
	1631	1634	CO Type B⁵⁴

Table 4

Graphical analysis of the infrared spectrum obtained from the obviously contaminated Na_4EDTA sample.

	3500 cm^{-1}	3000 cm^{-1}	2500 cm^{-1}	2000 cm^{-1}	1500 cm^{-1}	1000 cm^{-1}	500 cm^{-1}
1 Sample	3367 3332 3275 3198				1585 1343	897-833	
2 R-NH_2 primary amine ⁴⁹	3550-3420 3450-3320				1640-1560	990-650	
3 $+\text{NH}_4$ ammonium ion ⁴⁹		3300-3030					
4 $\text{R}-\overset{\text{O}}{\parallel}{\text{C}}-\text{NH}_2$ amide ⁴⁹	3550-3420 3450-3329				1640-1600 1420-1405		
5 $\text{NH}_2\text{CH}_2\text{CH}_2\text{NH}_2$ ethylenediamine ⁵¹	3340 3280						
6 Na_4EDTA ⁵⁰	3434				1597 1325		

Table 5

Summary of the synthesis and characterization results, with literature comparisons. The infrared bands of purified EDTA and DTPA are provided for reference.

Compound	Source of Gd	Ligand	Reaction Time	Yield	Infrared Data
GdEDTA, 1	Gd ₂ O ₃	EDTA	45 hours	73.79%	(CO complexed) 1584 cm ⁻¹ (st, b) (CO uncomplexed) 1719 cm ⁻¹ (w)
GdEDTA, 2	Gd(NO ₂) ₃ · 5H ₂ O	Na ₂ EDTA	18 hours	57.67%	(CO complexed) 1588 cm ⁻¹ (st, b) (CO uncomplexed) 1715 cm ⁻¹ (w)
GdEDTA, 3	GdCl ₃ · 6H ₂ O	Na ₂ EDTA	18 hours	65.04%	(CO complexed) 1583 cm ⁻¹ (st, b) (CO uncomplexed) 1714 cm ⁻¹ (w)
GdDTPA, 4	Gd ₂ O ₃	EDTA	11.5 hours	97.42%	(CO complexed) 1588 cm ⁻¹ (st, b) (CO uncomplexed) 1715 cm ⁻¹ (w)
Na ₄ EDTA, 5	-na-	-na-	9 hours	37.50%	- see table 6 -
NdEDTA ³³					(CO complexed) 1600 cm ⁻¹ (CO uncomplexed) 1672 cm ⁻¹
YEDTA ³³					(CO complexed) 1610 cm ⁻¹ (CO uncomplexed) 1715 cm ⁻¹
EDTA					(CO Type A) 1692 cm ⁻¹
DTPA					(CO Type A) 1693 cm ⁻¹

Appendix C
Figures

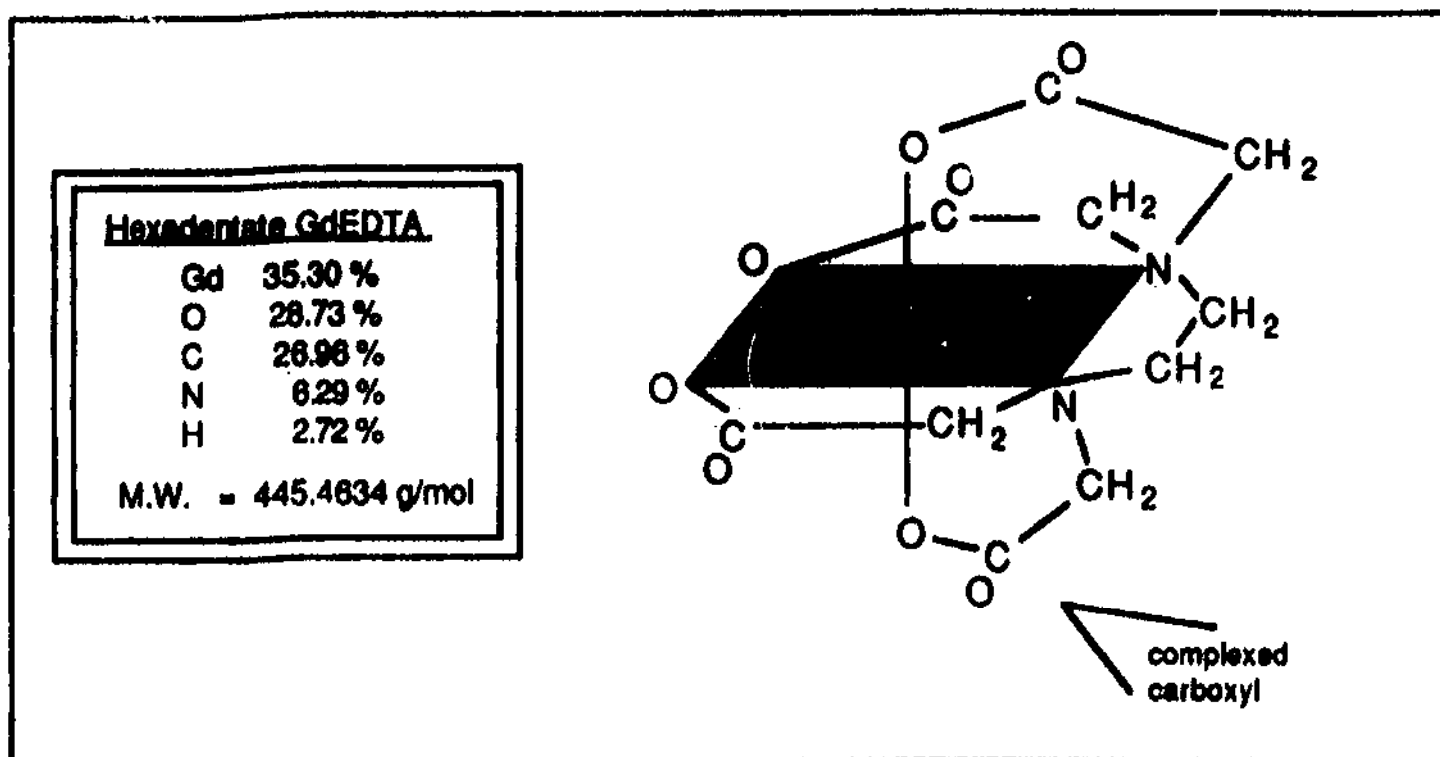


Figure 1

Hexadentate configuration of GdEDTA and corresponding elemental percent composition. All of the carboxyl groups in this configuration are complexed; an example is labeled (ref. 31).

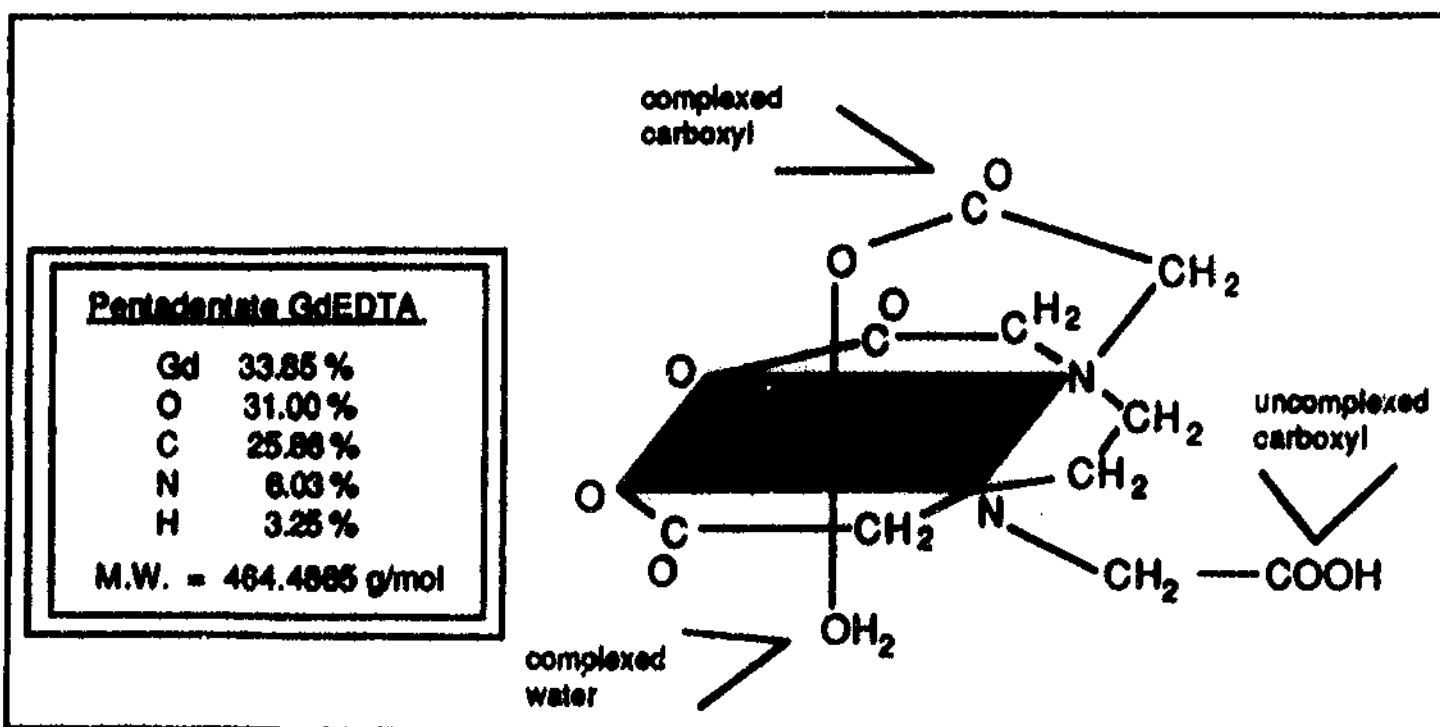


Figure 2

Pentadentate configuration of GdEDTA and corresponding elemental percent composition. Examples of complexed and uncomplexed carboxyl groups, and a complexed water molecule are labeled (ref. 31).

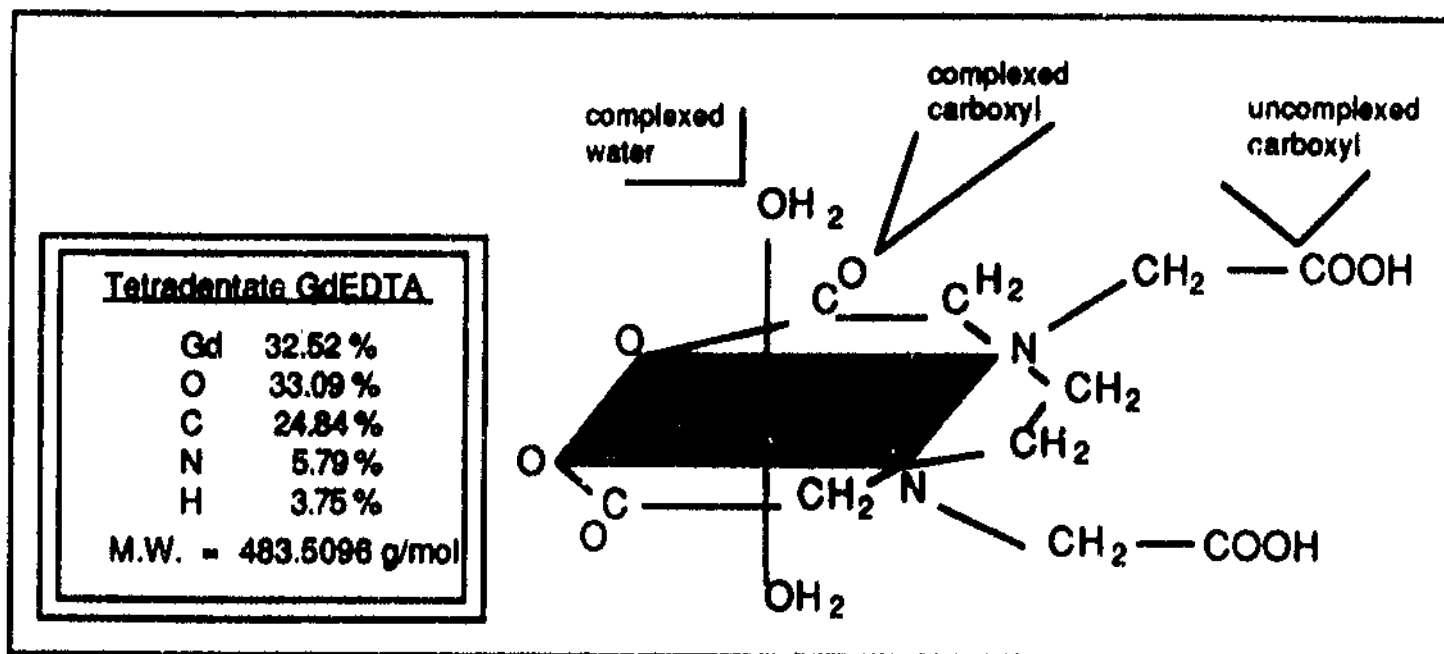


Figure 3

Tetradentate configuration of GdEDTA and corresponding elemental percent composition. Examples of complexed and uncomplexed carboxyl groups, and complexed water molecules are labeled (ref. 31).

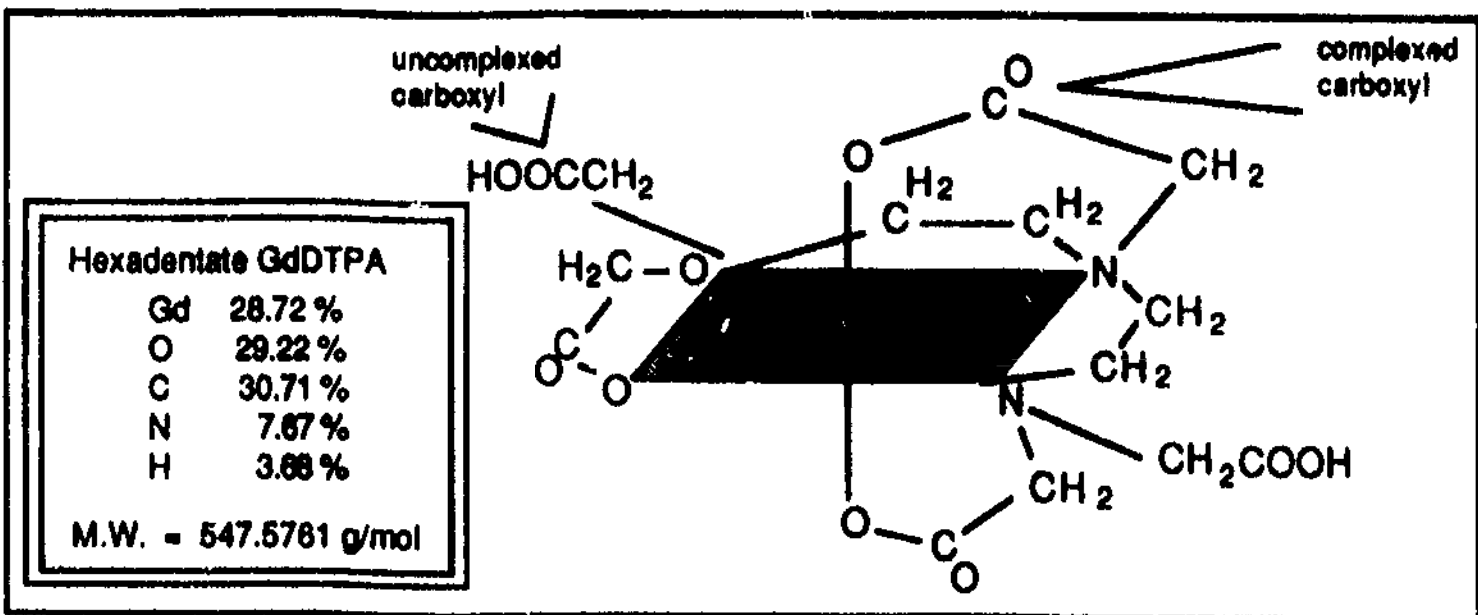


Figure 4

An example of the hexadentate configuration of GdDTPA and corresponding elemental percent composition. Examples of complexed and uncomplexed carboxyl groups are labeled (ref. 26).

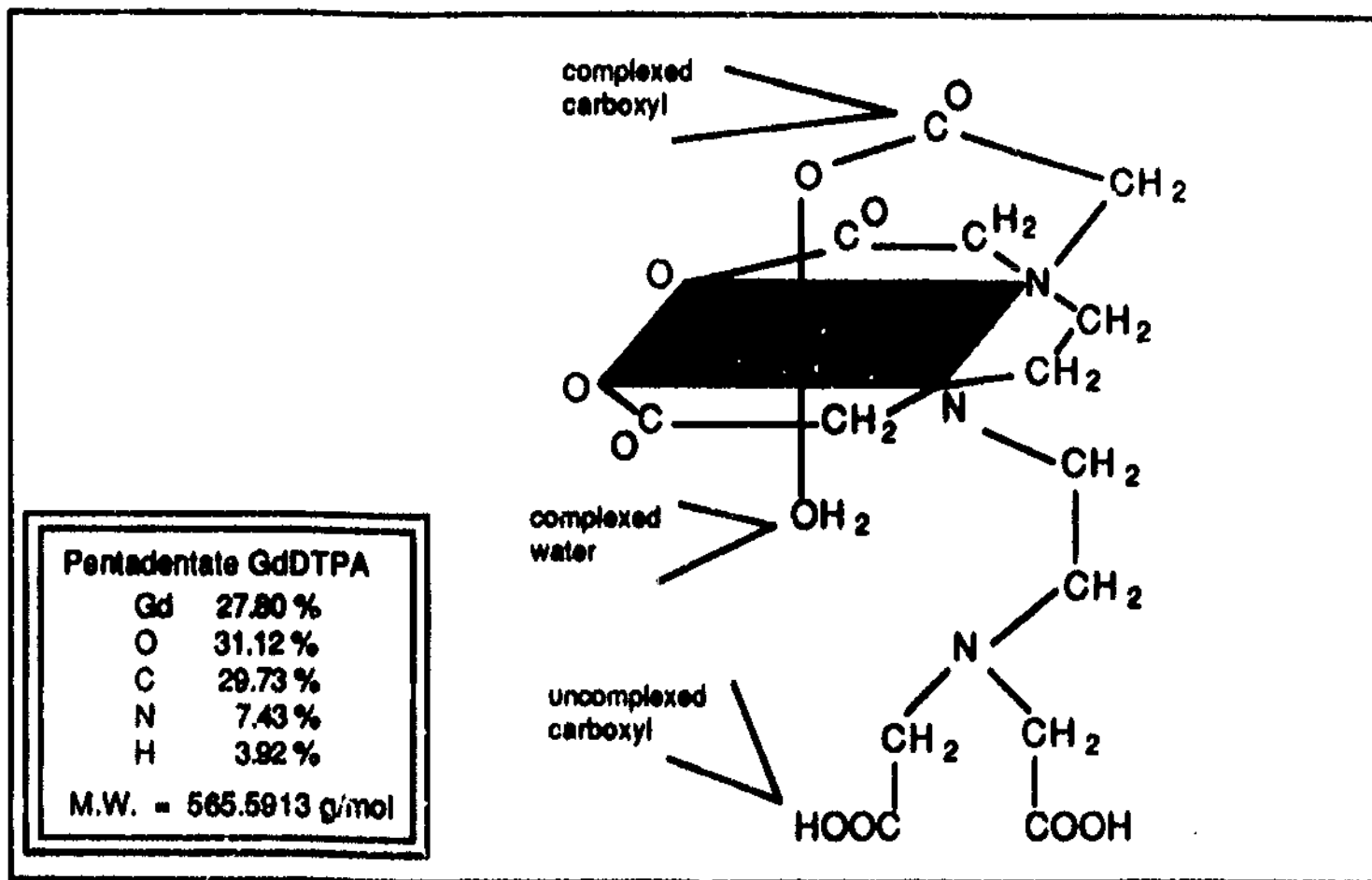


Figure 5

Pentadentate configuration of GdDTPA and corresponding elemental percent composition. Examples of complexed and uncomplexed carboxyl groups, and a complexed water molecule are labeled (ref. 26).

AUG 28 1967

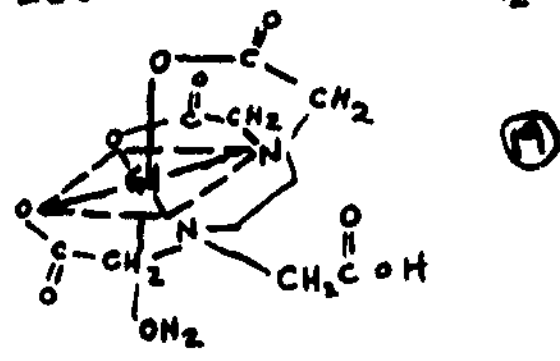
SCS — Microanalytical Record Card

Name M. Brinkman Room/Bldg. 367 Noyes Date 8/28/67

Sample No. 19D Hygroscopic (Yes) Explosive no Toxic no

Elements Present (Formula) GdC₁₀O₉H₁₅N₂ Analyze For C, H, N, Gd

B.P./M.P. _____ Solvent(s) Used H₂O Sensitive To _____

Theory	Found	Structure, Reaction, And Remarks
<u>25.86</u> %C	<u>26.47</u>	$\text{Gd}_2\text{O}_3 + 2\text{EDTA} \rightarrow \text{GdEDTA} \cdot \text{H}_2\text{O}$ 
<u>3.25</u> %H	<u>3.32</u>	
<u>6.03</u> %N	<u>6.13</u>	
<u>33.85</u> %Gd	<u>35.56</u>	
_____ %	_____	
_____ %	_____	

Account # 2525062 Senior Staff Member R. Zeller 134-1-87-44849

Figure 6

Analysis of the product GdEDTA obtained from the following reaction:



SCS — Microanalytical Record Card **FEB 17 1988**

Name M. Brinkman Room/Bldg. 363 Noyes Date 2/19/88

Sample No. (28) Hygroscopic YES Explosive NO Toxic NO

Elements Present (Formula) Gd, C, H, N, O Analyze For Gd, C, H, N

B.P./M.P. _____ Solvent(s) Used H₂O Sensitive To air

Theory	Found	Structure, Reaction, And Remarks
25.86 %C	26.66	$\text{Gd}(\text{NO}_3)_3 \cdot 5\text{H}_2\text{O} + \text{Na}_2\text{EDTA} \rightarrow \text{GdEDTA} \cdot \text{H}_2\text{O}$
3.25 %H	3.07	
6.03 %N	6.20	
33.85 %Gd	34.82	
_____ %	_____	
_____ %	_____	

Account # 2525062 Senior Staff Member [Signature] SM-3-87-66849

Figure 7
 Analysis of the product GdEDTA obtained from the following reaction:
 $\text{Gd}(\text{NO}_3)_3 \cdot 5\text{H}_2\text{O} + \text{Na}_2\text{EDTA} \rightarrow \text{GdEDTA}$

FEB 17 1968

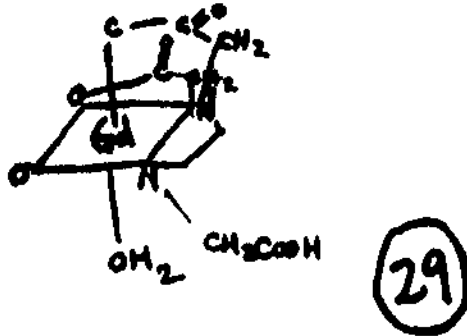
SCS — Microanalytical Record Card

Name M. Brinkman Room/Bldg. 363 N.Y.S.S. Date 2/11/68

Sample No. (29) Hygroscopic yes Explosive no Toxic no

Elements Present (Formula) Gd, C, H, N, O Analyze For Gd, C, H, N

B.P./M.P. _____ Solvent(s) Used H₂O Sensitive To air

Theory	Found	Structure, Reaction, And Remarks
<u>25.86</u> %C	<u>28.44</u>	$\text{GdCl}_3 \cdot 6\text{H}_2\text{O} + \text{Na}_2\text{EDTA} \rightarrow \text{GdEDTA} \cdot \text{H}_2\text{O}$ 
<u>3.25</u> %H	<u>2.23</u>	
<u>6.03</u> %N	<u>6.59</u>	
<u>33.85</u> %Gd	<u>34.81</u>	
_____ %	_____	
_____ %	_____	

Account # 2525062 Senior Staff Member [Signature] SM-3-67-64849

Figure 8

Analysis of the product GdEDTA obtained from the following reaction:



SCS — Microanalytical Record Card

Name M. Brinkman Room/Bldg. 363 Noyes Date JAN 13 1988
 Sample No. (21) Hygroscopic no Explosive no Toxic no
 Elements Present (Formula) GdDTPA · H₂O Analyse For C, H, N, Gd
 B.P./M.P. _____ Solvent(s) Used H₂O Sensitive To _____

Theory	Found	Structure, Reaction, And Remarks
<u>29.73</u> %C	<u>28.82</u>	<p><u>GdDTPA · H₂O</u> (pentadecahydrate) $Gd_2O_3 + 2DTPA \rightarrow GdDTPA$</p> <p style="text-align: right;">21</p>
<u>3.92</u> %H	<u>3.93</u>	
<u>7.43</u> %N	<u>8.13</u>	
<u>27.80</u> %Gd	<u>26.56</u>	
_____ %	_____	
_____ %	_____	

Account # 2525062 Senior Staff Member R. Brinkman SM-3-87-66849

Figure 9
 Analysis of the product GdDTPA obtained from the following reaction:
 $Gd_2O_3 + 2DTPA \rightarrow 2GdDTPA$

SCS — Microanalytical Record Card

Name N. Brinkman Room/Bldg. 363 Hayes Date JAN 13 1988

Sample No. 23 Hygroscopic yes Explosive no Toxic no

Elements Present (Formula) Na₄EDTA Analyze For C, H, N, Na

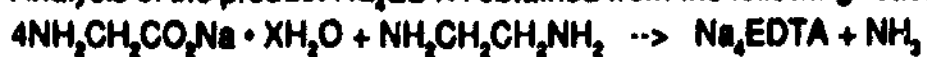
B.P./M.P. _____ Solvent(s) Used H₂O Sensitive To air

Theory	Found	Structure, Reaction, And Remarks
<u>31.59</u> %C	<u>24.48</u>	$\text{HC} \begin{array}{c} \\ \text{NH}_2 \end{array} \text{HCOONa} + \text{NH}_2\text{CH}_2\text{CH}_2\text{NH}_2 \rightarrow \text{Na}_4\text{EDTA}$
<u>3.18</u> %H	<u>3.85</u>	
<u>7.37</u> %N	<u>14.57</u>	$(\text{NaOOCCH}_2)_2\text{NCH}_2\text{CH}_2\text{N}(\text{CH}_2\text{COONa})_2$
<u>24.19</u> %Na		
_____ %	_____	
_____ %	_____	
_____ %	_____	23

Account # 25 25062 Senior Staff Member N. Brinkman SM-107-66849

Figure 10

Analysis of the product Na₄EDTA obtained from the following reaction:



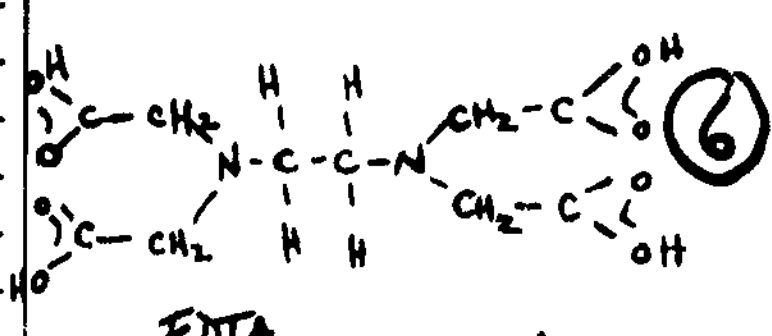
SCS — Microanalytical Record Card AUG 14 1987

Name M. Brinkman Room/Bldg. 363 N. yes Date 8/14/87

Sample No. 6 Hygroscopic no Explosive no Tests LA

Elements Present (Formula) C, H, N, O Analyse For C, H, N

B.P. 352 °C Solvent(s) Used H₂O Sensitive To _____

Theory	Found	Structure, Reaction, And Remarks
4.10 %C	41.06	 <p style="text-align: center;">EDTA</p>
5.52 %H	5.54	
9.58 %N	9.53	
_____ %	_____	
_____ %	_____	
_____ %	_____	

Account # 2525062 Senior Staff Member R. B. [Signature] SM-3-87-44849

Figure 11
Analysis of EDTA after purification.

SCS — Microanalytical Record Card **AUG 18 1987**

Name M. Brinkman Room/Bldg 363 Noyes Date 8/18/87

Sample No. (10) Hygroscopic no Explosive no Toxic no

Elements Present (Formula) C, H, N, O Analyze For C, H, N

B.P./M.P. 219-220 Solvent(s) Used H₂O Sensitive To _____

Theory	Found	Structure, Reaction, And Remarks
<u>42.75</u> %C	<u>42.29</u>	<p>DTPA</p> $\begin{array}{c} \text{HooCCH}_2 \text{---} \text{N---CH}_2\text{---CH}_2\text{---N---CH}_2\text{CH}_2\text{---N} \\ \qquad \qquad \qquad \qquad \qquad \qquad \\ \text{HooCCH}_2 \qquad \qquad \text{CH}_2 \qquad \qquad \text{CH}_2\text{COOH} \\ \\ \text{C} \\ \\ \text{Hoo} \\ \\ \text{H} \end{array}$ <p style="text-align: right;">(10)</p>
<u>5.89</u> %H	<u>5.75</u>	
<u>10.68</u> %N	<u>10.55</u>	
_____ %	_____	
_____ %	_____	

Account # 25 25062 Senior Staff Member N. Bellard JM-5-87-66849

Figure 12
Analysis of DTPA after purification.

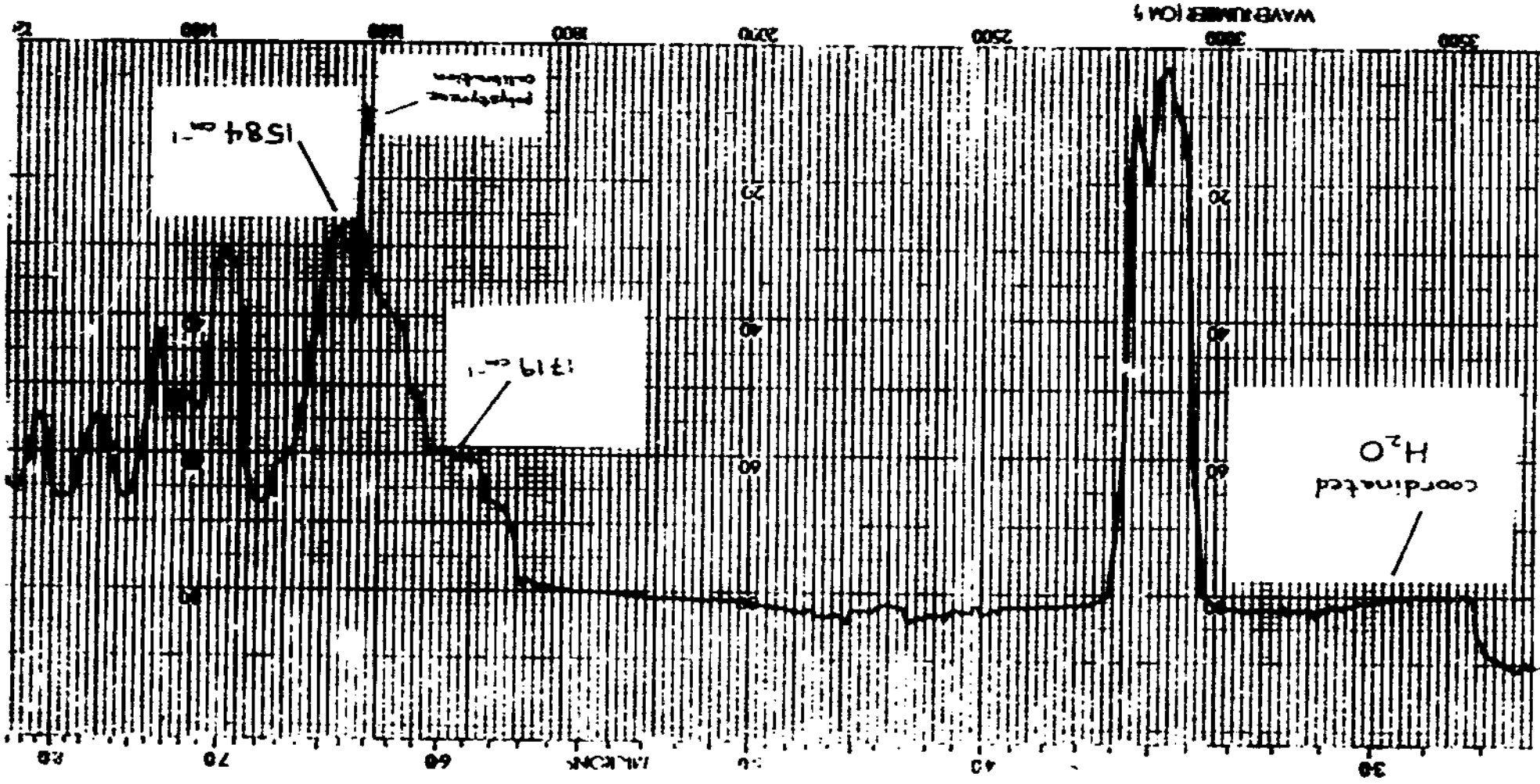
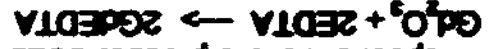


Figure 13
IR spectrum of the product GdEDTA obtained from the following reaction:



The complexed carboxyl groups exhibit absorption at 1584cm⁻¹, and the uncomplexed carboxyl groups show a much weaker absorption at 1719cm⁻¹. Note the presence of coordinated water (See Figs. 2, 3).

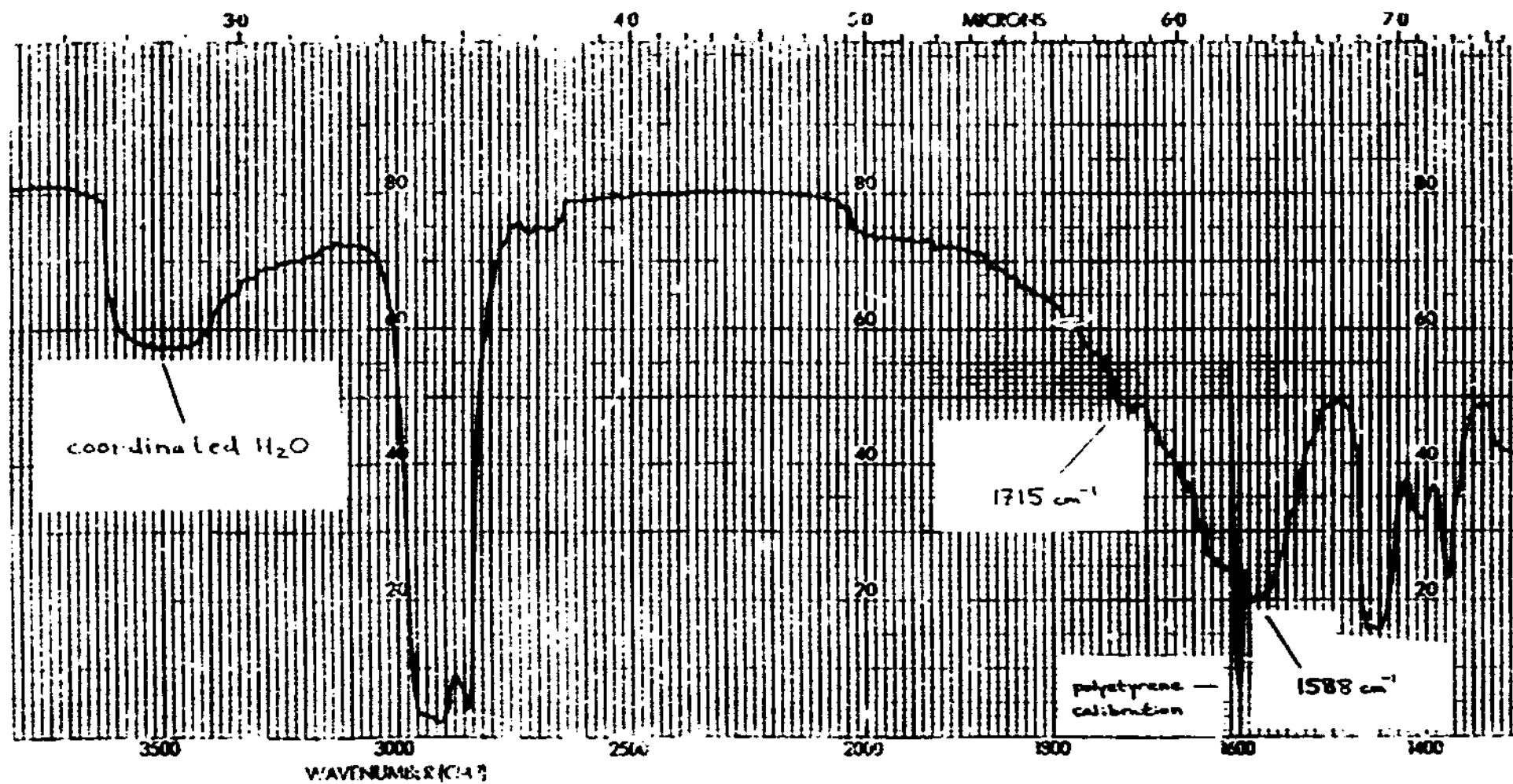


Figure 14

IR spectrum of the product GdEDTA obtained from the following reaction:



The complexed carboxyl groups exhibit absorption at 1588cm^{-1} , and the uncomplexed carboxyl groups show a much weaker absorption at 1715cm^{-1} . Note the presence of coordinated water (see Figs. 2, 3).

C-14

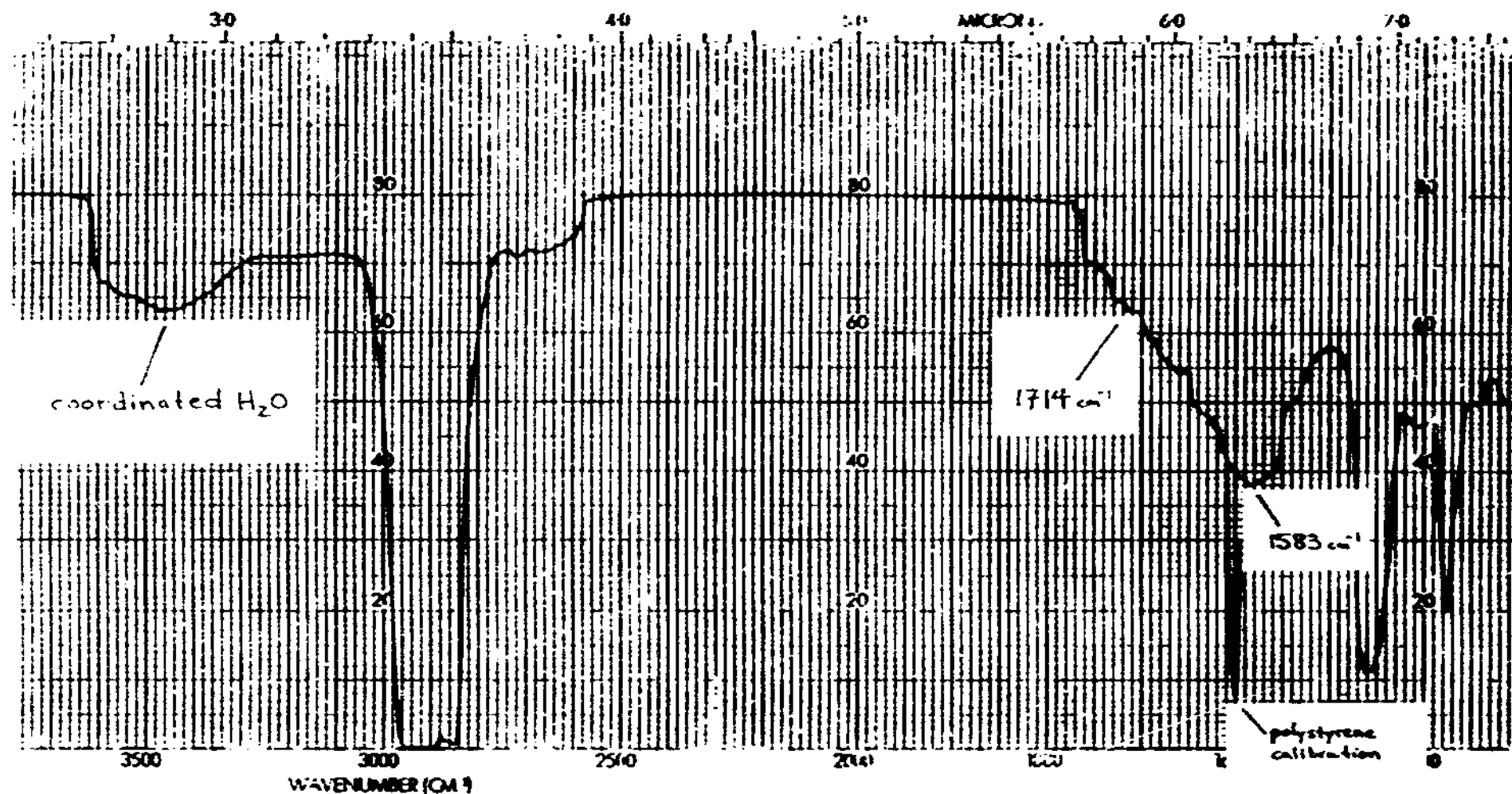


Figure 15

IR spectrum of the product GdEDTA obtained from the following reaction:



The complexed carboxyl groups exhibit absorption at 1583cm^{-1} , and the uncomplexed carboxyl groups show a much weaker absorption at 1714cm^{-1} . Note the presence of coordinated water (see Figs. 2, 3).

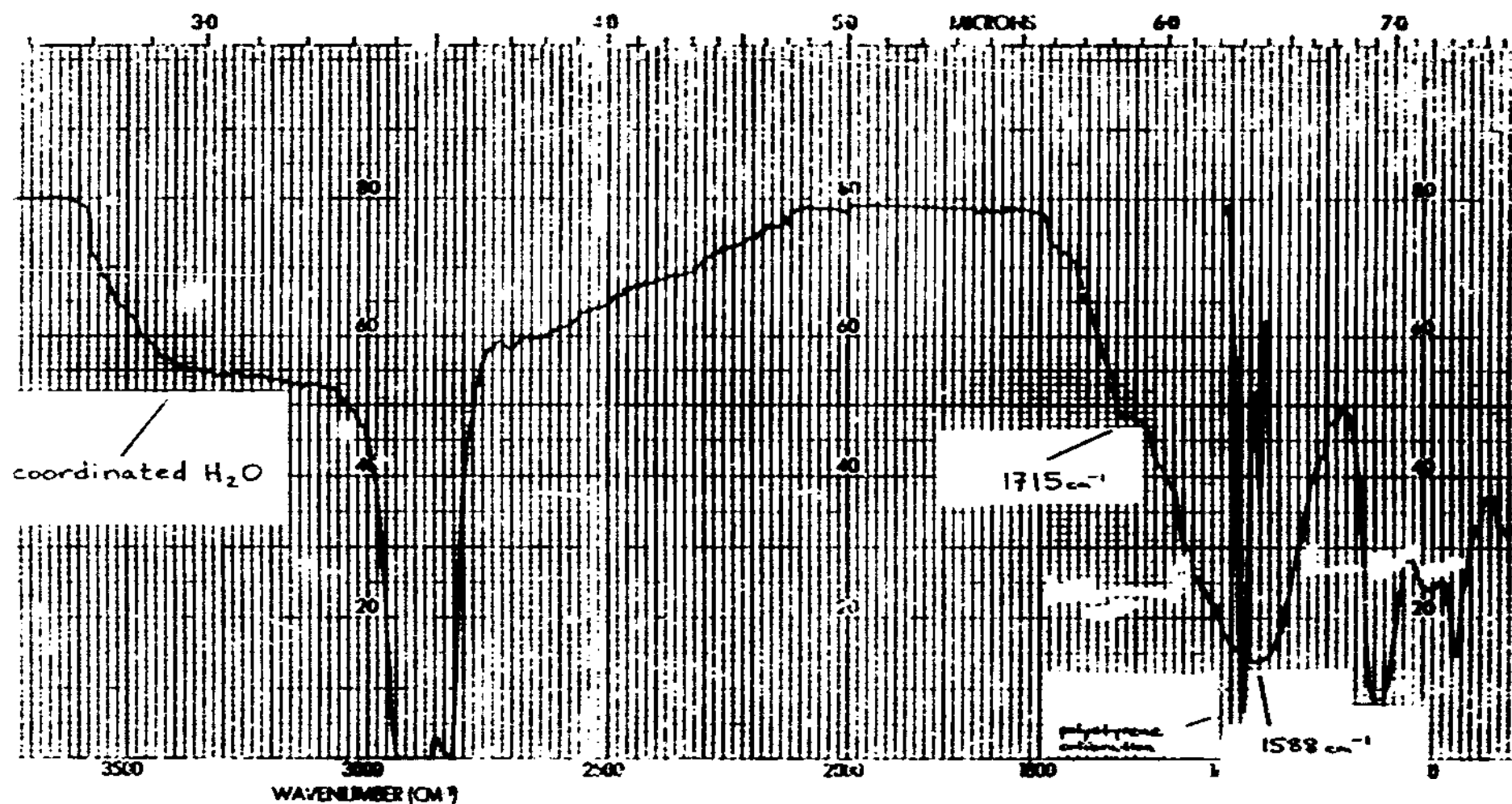


Figure 16

IR spectrum of the product GdDTPA obtained from the following reaction:



The complexed carboxyl groups exhibit absorption at 1588cm^{-1} , and the uncomplexed carboxyl groups show a much weaker absorption at 1715cm^{-1} . Note the presence of coordinated water (see Figs. 5).

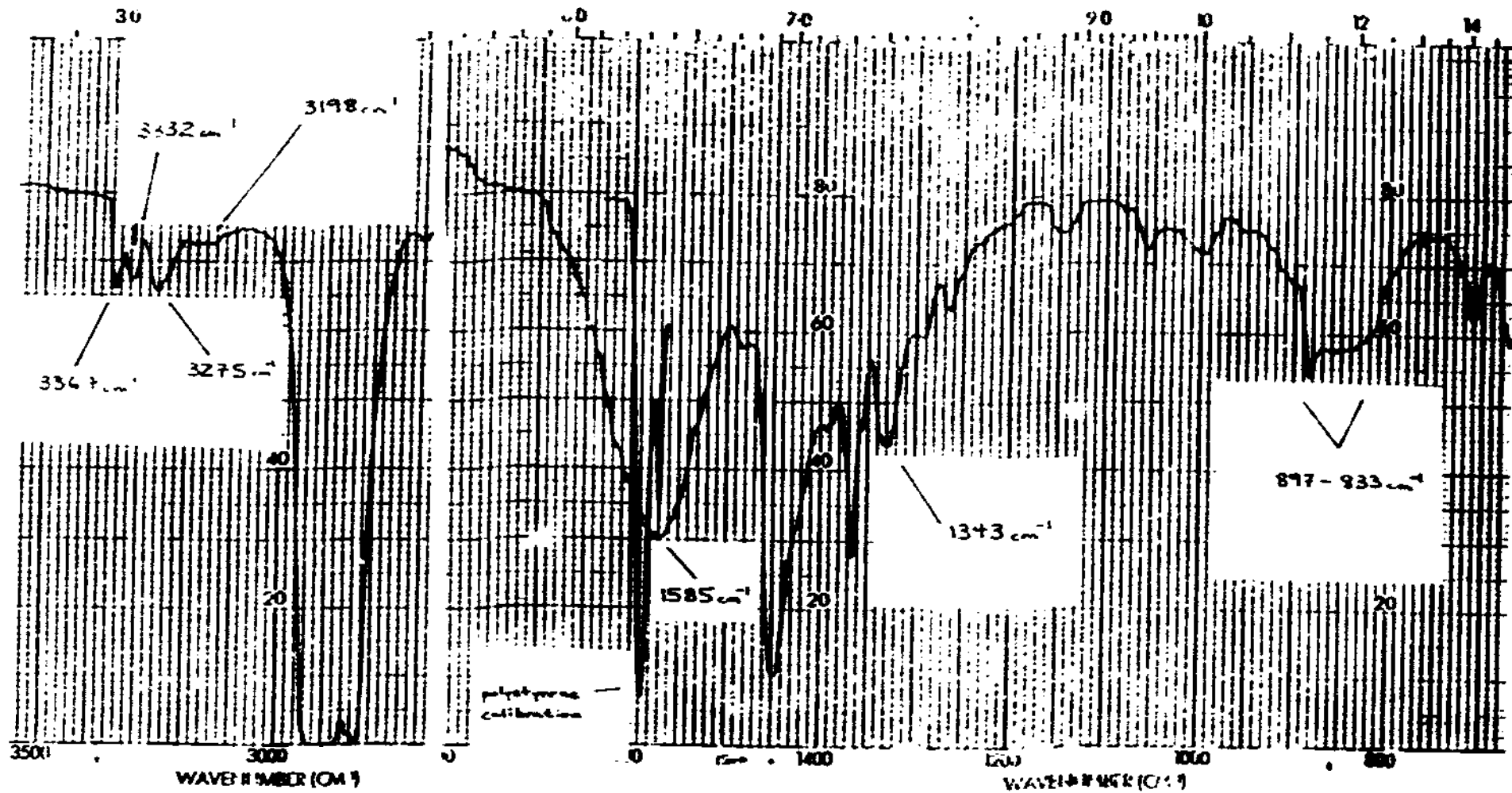


Figure 17

IR spectrum of the product Na₄EDTA obtained from the following reaction:



The carboxyl groups show a strong absorption at 1585 cm⁻¹, N-H stretch (an impurity) shows its characteristic broad band from 897-933 cm⁻¹. Note the presence of coordinated water (see Table 4 for a complete analysis of this spectrum).

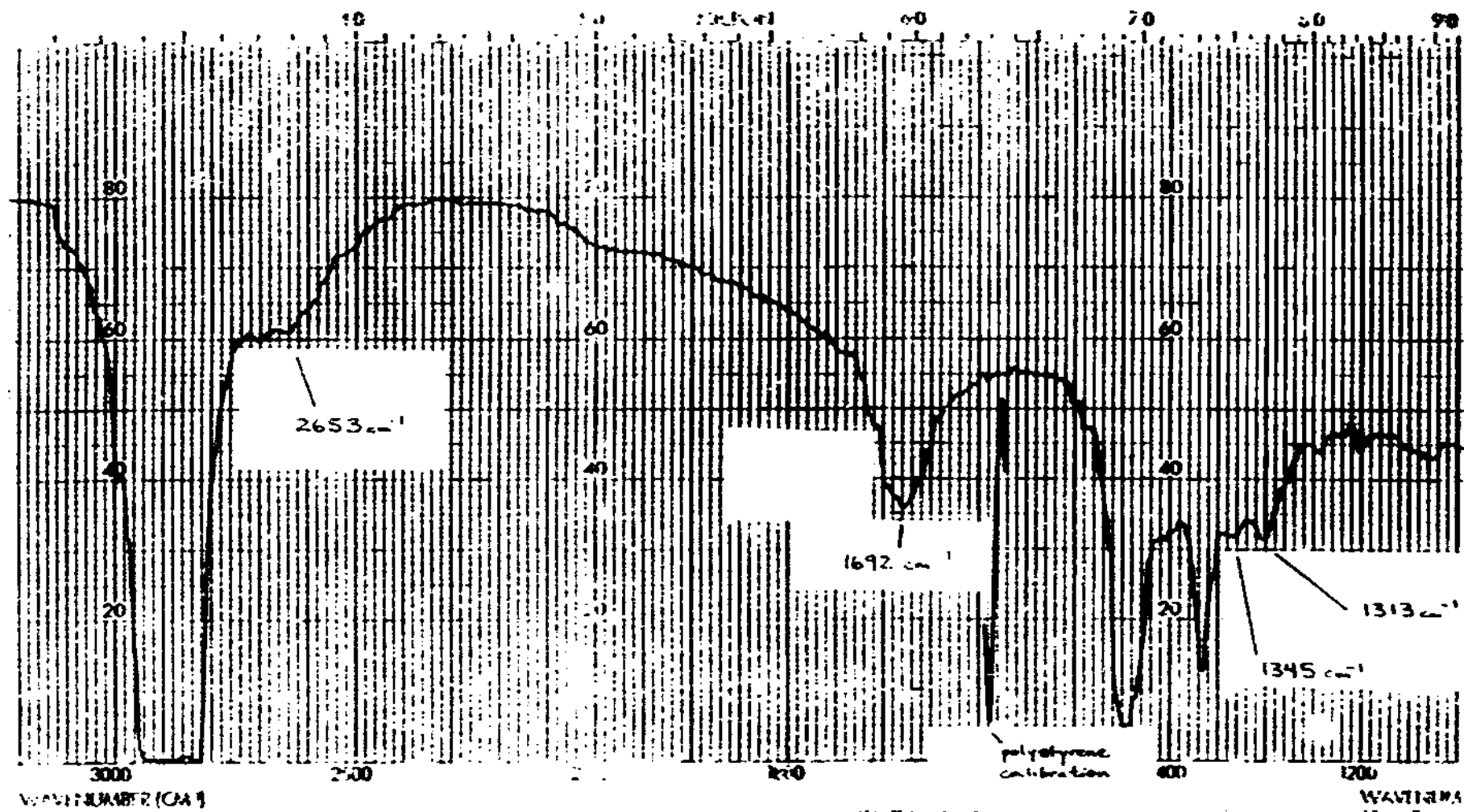


Figure 18
 IR spectrum of EDTA after purification. Associated OH exhibits absorption at 2653 cm^{-1} , Type A carboxyl groups exhibit absorption at 1692 cm^{-1} , and CO_2H exhibits weak absorption at 1345 cm^{-1} and 1313 cm^{-1} (see Figure 20).

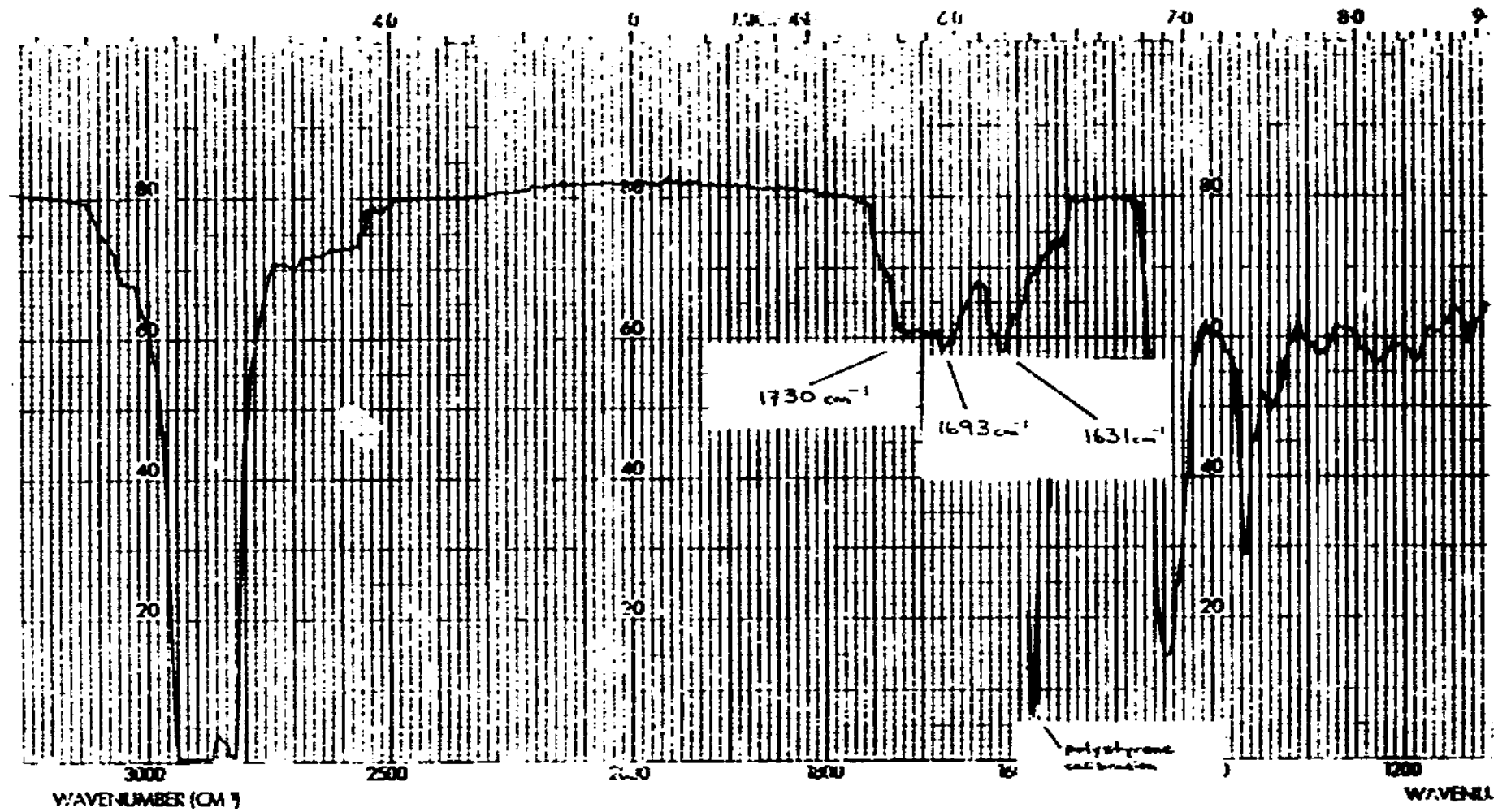


Figure 19

IR spectrum of DTPA after purification.

Type A carboxyl groups exhibit absorption at 1730 cm⁻¹ and 1693 cm⁻¹, Type B carboxyl groups exhibit absorption at 1631 cm⁻¹ (see Fig. 21).

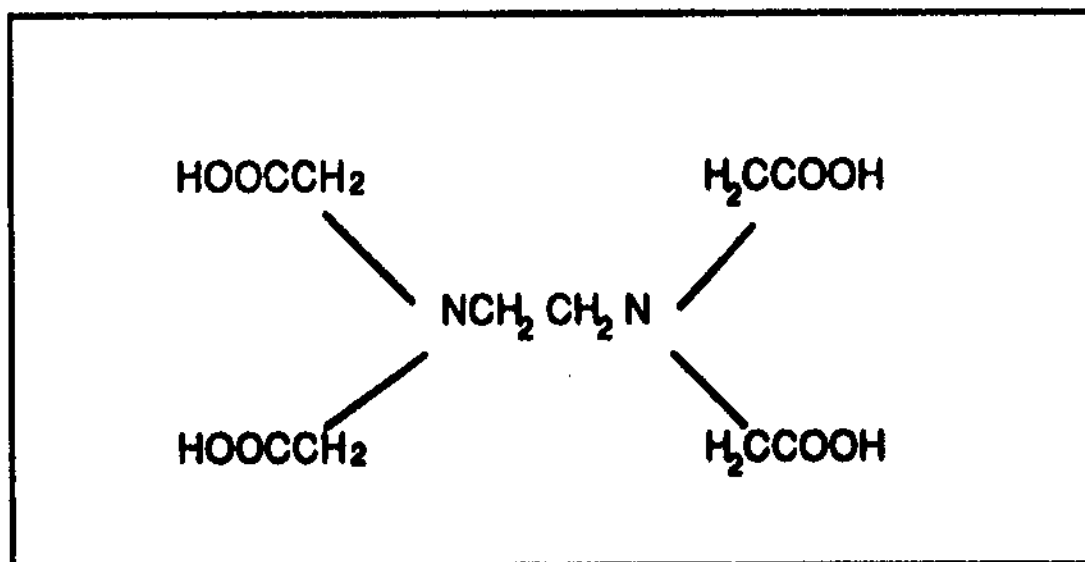


Figure 20
The ethylenediaminetetraacetic acid ligand, having only Type A carboxyl groups (ref. 54).

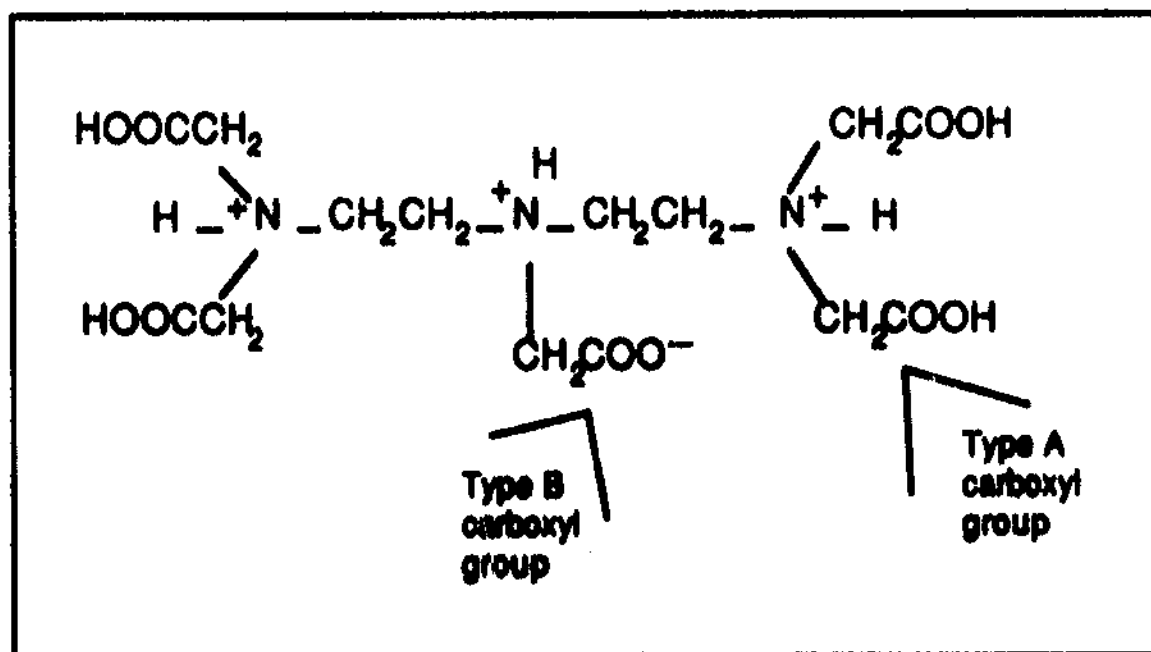


Figure 21
The diethylenetriaminepentaacetic acid ligand. Examples of Type A and Type B carboxyl groups are shown (ref. 54).

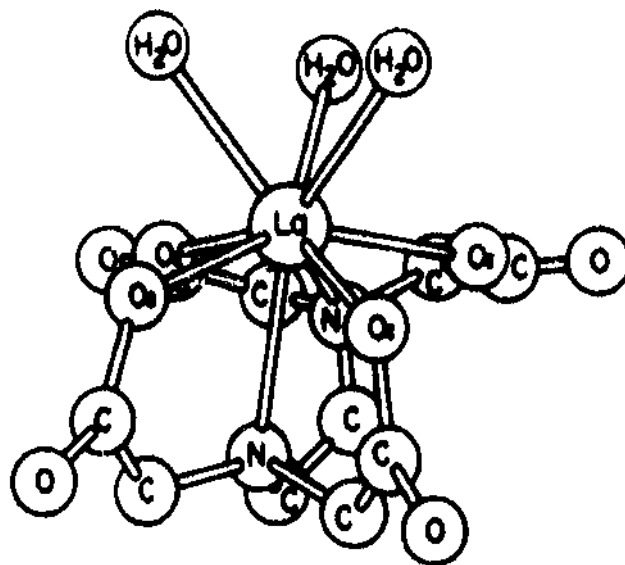


Figure 22

Scaled model of the $\text{La}(\text{OH}_2)_3\text{EDTA}^-$ ion seen in perspective. The ligand occupies roughly one hemisphere of the ion; leaving the other side relatively open for coordination by labilizing ligands or oxo-bridged dimer formation (ref. 41).

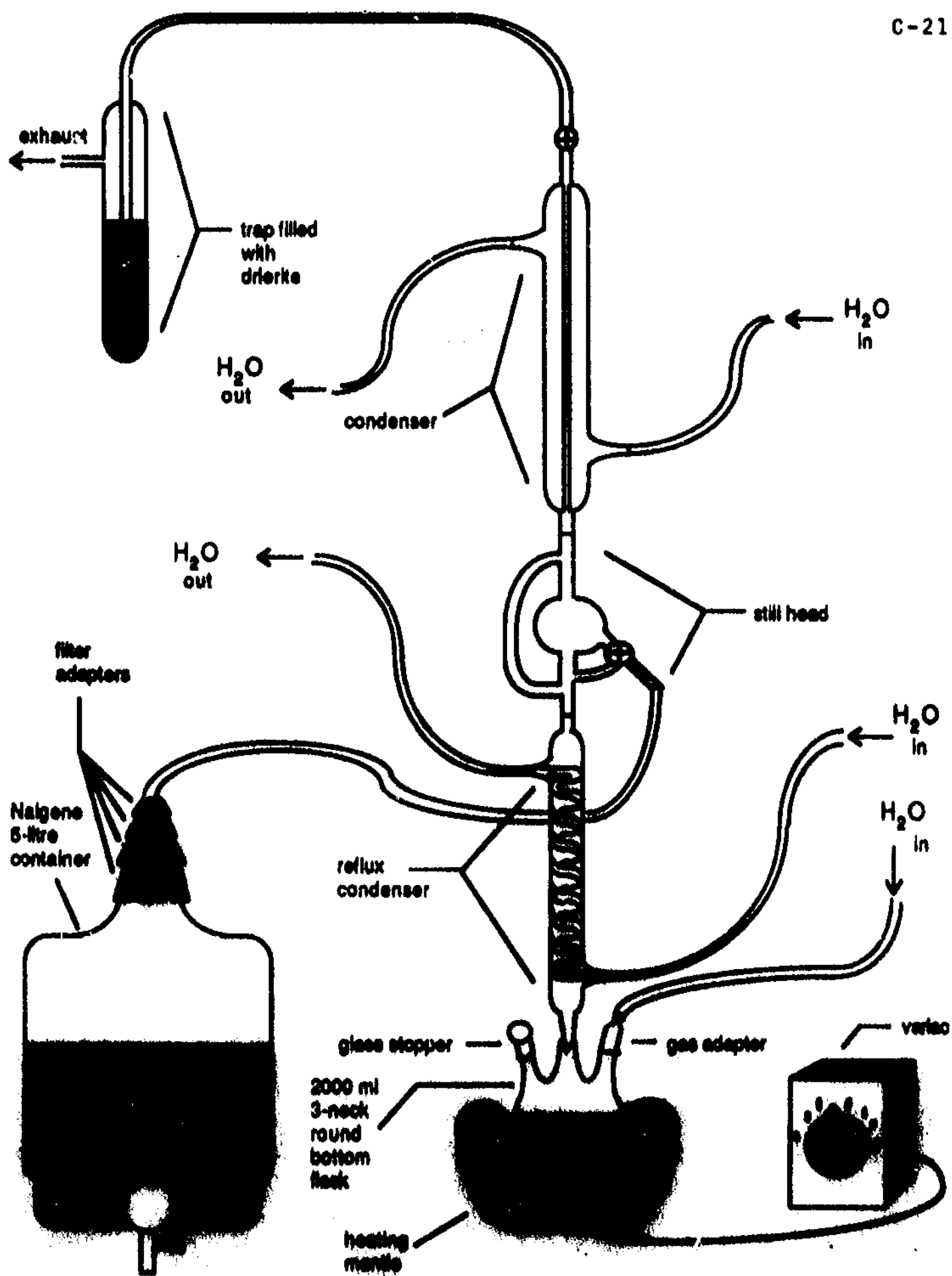


Figure 23
Distillation apparatus.

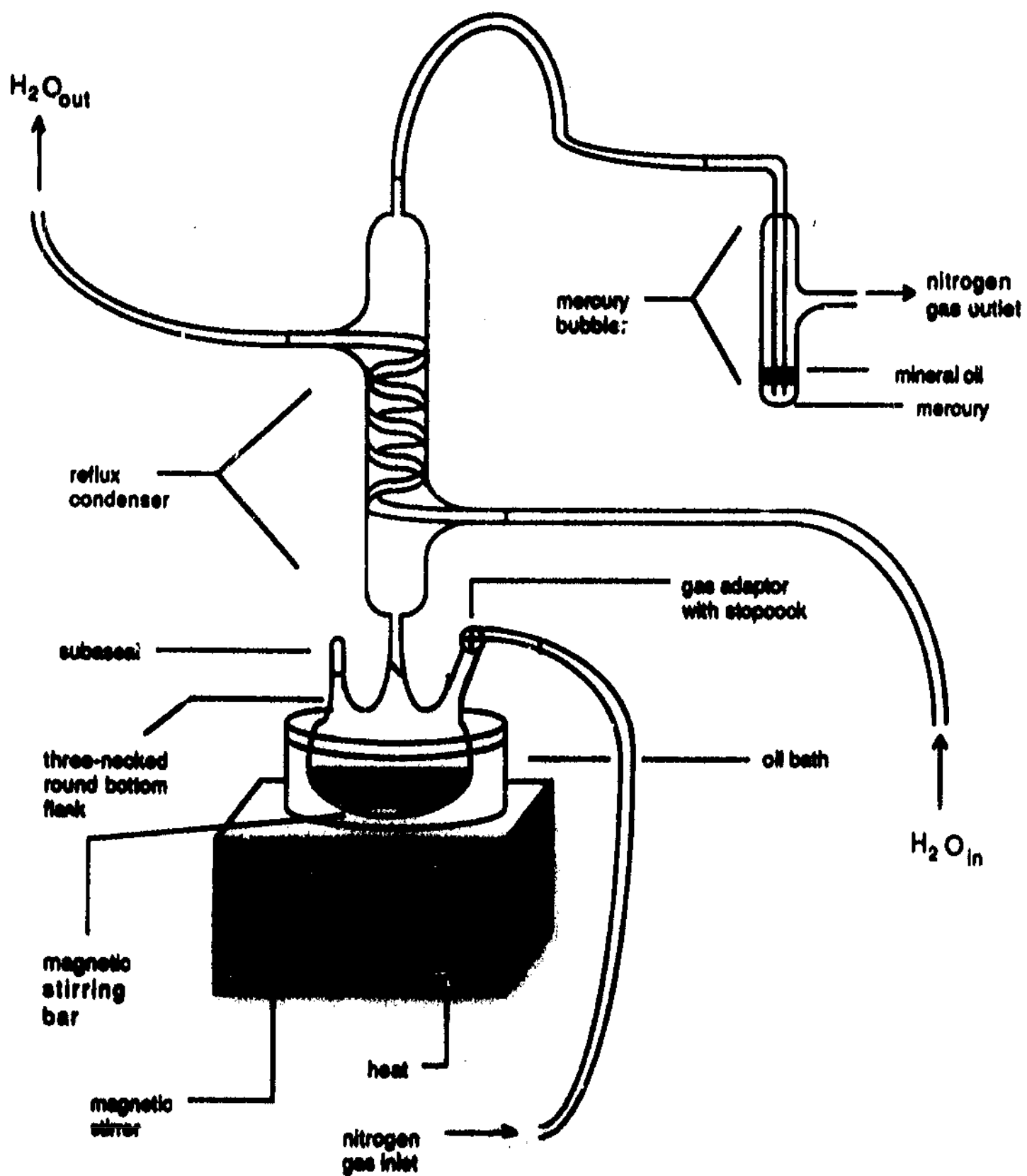


Figure 24
Apparatus for synthesis of air-sensitive compounds

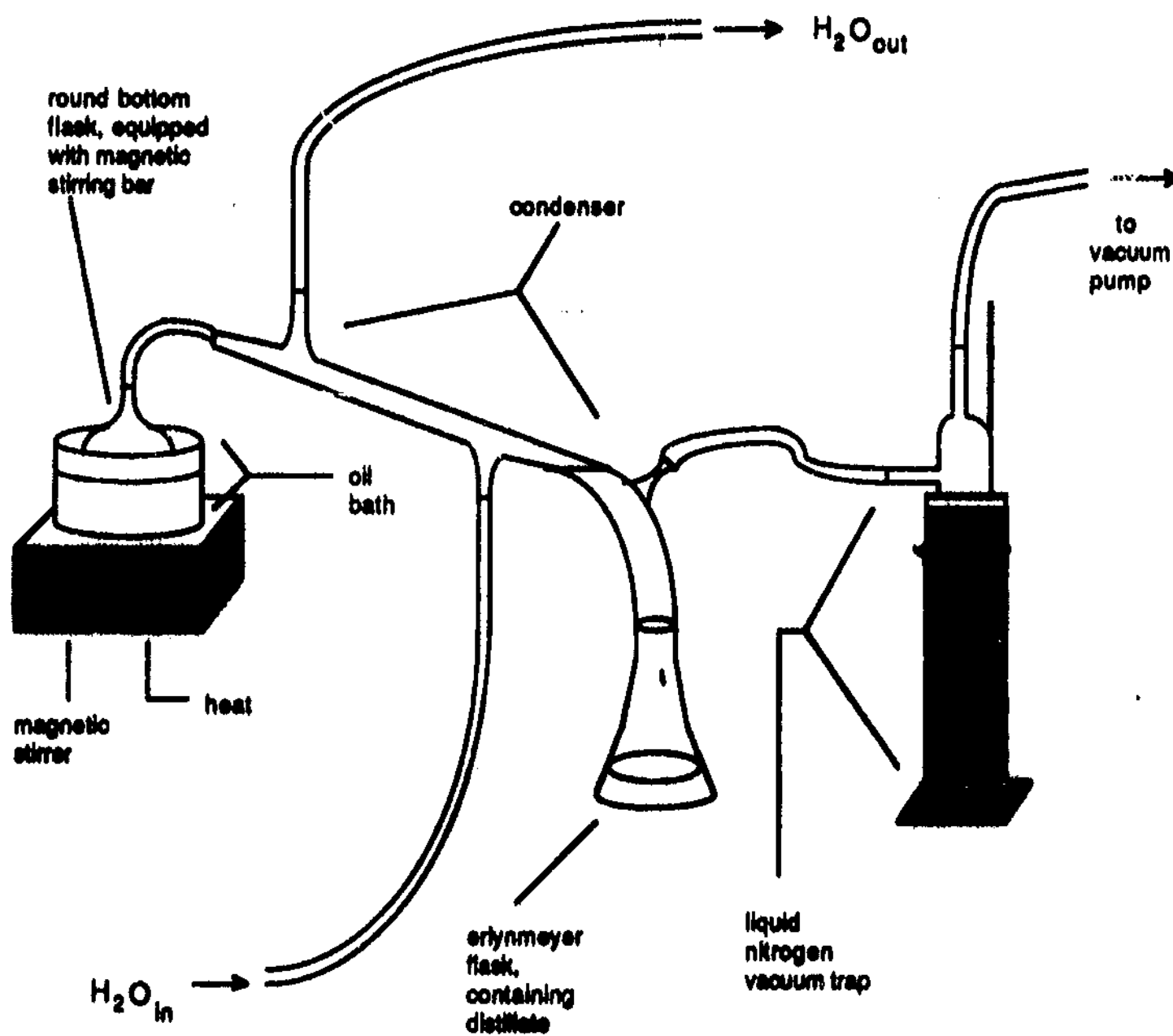


Figure 25
Vacuum distillation apparatus.

Appendix D
Historical Summary of LnEDTA Literature

In the early 1950s, Wheelwright, Spedding and Schwarzenbach¹⁵ proposed, from their study of the formation constants of rare earth-EDTA chelates, that the rare earth chelates of La through Gd were hexadentate, and those of the heavier Tb through Lu were pentadentate. This was concluded from what they termed the "gadolinium break," or complete change in the slope of their plot of the log of La-EDTA (La = Lanthanum) formation constants versus the atomic numbers of the lanthanide series. It was concluded that the smaller atomic radii, according to the lanthanide contraction (Table 1), could not accommodate all four, but instead only three of the bulky carboxylate groups of the EDTA ligand (Figs. 2, 3). However, models of the Fisher-Hirschfelder type strongly suggested that a hexadentate structure would be considerably sterically strained.⁴

In that same time period, Moeller, Moss and Marshall²² published infrared studies of rare earth-EDTA chelates showing the presence of two varieties of carboxyl group. They postulated the presence of one uncoordinated, and three coordinated carboxyl groups; and predicted that the sixth coordination position was occupied by a water molecule (Fig. 2). Pecsok published polarographic studies of metal-EDTA chelates that also favored the tetradentate structure.³

Some six years later, Betts and Dahlinger⁴⁴ published a thermodynamic study that exhibited the same gadolinium break for enthalpies and entropies of formation for rare earth-EDTA chelates. They interpreted their data as indicating that the rare earths La-Gd form pentadentate complexes (Fig. 2) and Tb-Lu form tetradentate complexes (Fig. 3) with the EDTA chelate - essentially separating the rare earths into the same two series that

Wheelwright, Spedding, and Scharzenbach did. Prik explained the gadolinium break that was also evidenced in his thermodynamic data²⁰ by stating that the ligand field for complexes of elements with incomplete f-shells, such as Nd and Sm (see Table 1), would make them more exothermic. However, the crystal field splittings for 4f levels are of the order of 100 cm^{-1} , which would correspond to a contribution later determined to be negligible.⁵⁶

Although Betts' and Dahlinger's method introduced very large cumulative errors into their data and calculations, Mackey, Powell, and Spedding's later,⁵⁶ more accurate study showed the exact same trends and gadolinium break. However, Mackey, Powell, and Spedding gave no hypothesized reason for the rare earths falling into two apparent series in their thermodynamic study, and furthermore, extensively refuted the idea that the two series are evidence of a change in the number of coordination sites of the EDTA ligand. Moeller and Ferrus concurred,⁴⁵ and stated that variations in enthalpy and entropy of formation are better correlated with a gradual weakening of the bond between the metal ion and a donor carboxyl group as cation radius decreases, than with a complete rupture of such a bond in a particular place in the rare earth series.

Kolat's and Powell's data⁵⁷ on the acid dissociation constants of rare earth chelates also indicate no change in the number of coordinated positions occupied by the ligand.