

THE SYNTHESIS AND INFRA-RED SPECTRUM OF CARBON-DEUTERATED ETHYLENEDIAMINE DIHYDROBROMIDE

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Abstract—Ethylenediamine-C-d₄ · 2HBr is produced in 80–90 per cent yield by the reaction of anhydrous NH₃ with 1,2-dibromoethane-d₄ in a sealed tube at 55°. An estimation of the level of C–H impurity is made from a comparison of the Infrared Spectra of normal and carbon-deuterated ethylenediamine dihydrobromide and verified by the Nuclear Magnetic Resonance Spectra of the free amines. Little or no hydrogen exchange on the carbon atoms occurs during the reaction and subsequent purification. On the basis of simplicity, high yield, relative freedom from side reactions, and lack of isotopic exchange, this method is suggested for the preparation of carbon and hydrogen isotopically substituted ethylenediamine.

ETHYLENEDIAMINE is used extensively in both organic and inorganic (co-ordination) chemistry. It is expected therefore that the need for isotopically substituted ethylenediamines will increase in the future. Methods for the preparation of carbon-14^(1,2) and nitrogen-deuterated⁽³⁾ ethylenediamine have been reported but we have been unable to find a preparation of ethylenediamine-C-d₄. A need for carbon-deuterated ethylenediamine for studies on secondary isotopic effects in coordinated compounds prompted the present research. The problem has these major aspects: a high yield is desirable because of the expense of the starting deuterium compounds; by-products must be easily separated from the main product; and, H-D exchange must not occur during the process of formation nor in the subsequent purification.

A survey of the literature indicated at least two methods might be suitable for the preparation of en-C-d₄ · 2HBr*: ammonolysis of alkyl halides⁽⁴⁾ and the GABRIEL synthesis.⁽⁵⁾ Both methods start with 1,2-dibromoethane-d₄ which may be obtained commercially (e.g. Volk Radiochemical Co.) or prepared by the action of light on a mixture of deuterioacetylene (from D₂O and CaC₂) and deuterium bromide.⁽⁶⁾ One of the methods of preparation of en · 2HCl, ammonolysis of alkyl chlorides was used by Clöez in 1853 for the first recorded preparation.⁽⁴⁾ Since that time, a great many patents for the ammonolysis of 1,2-dichloroethane and other aliphatic halides (with aqueous and anhydrous ammonia) have been issued. As indicated in the review by

* The abbreviation en is used to signify ethylenediamine (1,2-diaminoethane).

⁽¹⁾ K. KIGOSHI and S. OKAMOTO, *Bull. Chem. Soc. Japan* **29**, 438 (1956).

⁽²⁾ D. S. POPPLEWELL and R. G. WILKINS, *J. Chem. Soc.* 2521 (1955).

⁽³⁾ D. B. POWELL, *Spectrochim. Acta* **16**, 241 (1960).

⁽⁴⁾ See P. GALEWSKY, *Ber. Dtsch. Chem. Ger.* **23**, 1066 (1890).

⁽⁵⁾ S. GABRIEL, *Ber. Dtsch. Chem. Ger.* **20**, 2224 (1887).

⁽⁶⁾ A. MURRAY (III) and D. L. WILLIAMS, *Organic Synthesis with Isotopes*, Part II, p. 1475, Interscience, New York (1958).

GROGGINS and STIRTON in 1937, most of the work reported in the literature concerns aqueous ammonolysis.⁽⁷⁾ Conditions usually employed resulted in considerable polymer-amine formation and only moderate yields of $\text{en} \cdot 2\text{HCl}$. Not until the systematic study by KRISHNA MURTHY in 1958 were yields of the order of 90 per cent shown to be possible.⁽⁸⁾ These were obtained in 4–12 M ammonium hydroxide where the mole ratio was at least 19 ($\text{NH}_3:\text{ClCH}_2\text{CH}_2\text{Cl}$) and the temperature held at 110–150° for about 1 hr. Anhydrous NH_3 gave poorer yields. A maximum of 40 per cent was obtained at 60° (3 hr). It was anticipated that a higher mole ratio and a longer reaction time would give a nearly quantitative yield. This method has been used for the preparation of $\text{en-}^{14}\text{C} \cdot 2\text{HBr}$.⁽¹⁾ The second method, as proposed by GABRIEL, requires the formation, purification, and subsequent decomposition of 1,2-ethyldipthalimide.⁽⁵⁾ An improved version of this method was used by POPPLEWELL and WILKINS to make $\text{en-}^{14}\text{C} \cdot 2\text{HBr}$ in about 73 per cent yield.⁽²⁾

Since the deuterated carbon atom was the reaction site during amine formation, the possibility of hydrogen-deuterium exchange had to be considered and the extent of this exchange determined. Neither method had been investigated from this standpoint.

The recent advent of the "re-usable" (screw cap) Carius Tube⁽⁹⁾ has made the single step ammonolysis process considerable easier to handle than previously and more appealing than the two step Gabriel synthesis. Preliminary small scale preparations with ND_3 as well as with NH_3 indicated the absence of hydrogen exchange on the carbon atoms so this method was chosen for the larger scale preparations.

This paper reports the preparation of isotopically pure ethylenediamine- $\text{C-d}_4 \cdot 2\text{HBr}$ by the reaction of 1,2-dibromoethane- d_4 with liquid NH_3 . Under the conditions studied, no isotopic H-D exchange was found and yields of 80–90 per cent were obtained. The infrared spectra of the C-hydrogen and C-deuterium compounds are presented to substantiate the isotopic purity.

EXPERIMENTAL

Reagents. NH_3 -commercial anhydrous refrigeration grade; anhydrous ND_3 was prepared from Mg_3N_2 (A. D. Mackay Inc., New York) and D_2O (Norsk Hydro-Elektrisk Kvaelfabrikationselskab, Norway, 99.75 = % D_2O , density 1.10514 20/4 g/cm³); normal 1,2-dibromoethane was Eastman Practical Grade (used only for preliminary experiments), while 1,2-dibromoethane- d_4 was obtained from Volk Radiochemical Co., Skokie, Illinois. (Their analysis gave 98 per cent completely deuterated, 2 per cent (maximum) partially deuterated (100 per cent dibromoethane); all other chemicals were reagent grade.

Preparation of ethylenediamine- $\text{C-d}_4 \cdot 2\text{HBr}$. One to five millilitres of the dibromoethane was added, by vacuum techniques, to a "re-usable" Carius Tube (0.5 in. inside diameter and 18 in. long). The Carius Tube was cooled in a dry-ice-acetone bath and enough anhydrous NH_3 (to give at least a 20:1 mole ratio of NH_3 to $\text{BrCD}_2\text{CD}_2\text{Br}$) was condensed inside the tube. The Carius Tube was tightly capped by hand and allowed to warm to room temperature. The contents were mixed until homogeneous by tilting the tube and after one hour at room temperature the contents were checked for homogeneity. With great care (since the tube is now at about 10 atm NH_3 pressure), the cap of the Carius Tube was re-tightened (to avoid an NH_3 leak at higher pressures). Next, the tube was placed in a vertical tube furnace; the whole being shielded to protect against explosion. A temperature of $55 \pm 5^\circ$ was maintained for at least 48 hr after which the tube was cooled to room temperature and then to -78° with a mixture of acetone and

⁽⁷⁾ P. H. GROGGINS and A. J. STIRTON, *Industr. Engng. Chem.* **29**, 1353 (1937).

⁽⁸⁾ V. A. KRISHNA MURTHY, *J. Sci. Industr. Research (India)* **17** A, 276 (1958).

⁽⁹⁾ P. Z. ANTHONY, *J. Chem. Educ.* **36**, 489 (1959).

dry ice. The NH_3 was then *slowly* vented into the atmosphere by opening the cap and allowing the system to come to room temperature, leaving the crude $\text{en} \cdot 2\text{HBr}$ as a white semicrystalline residue. (The product must be purified soon afterward to prevent decomposition apparently catalyzed by impurities.) A minimum of warm water was added to dissolve the crude product and, after transfer from the tube to an evaporation dish, the solution was evaporated to dryness at room temperature. This evaporation removed essentially all of the residual NH_3 . The product was recrystallized from a minimum of hot 3 M HBr by the careful addition of an equal volume of absolute ethanol. The flaky white crystals were removed on a filter, washed with a small amount of chilled ethanol, and then vacuum dried at room temperature.

In order to establish the reliability of the ammonolysis method, a sample of normal $\text{en} \cdot 2\text{HBr}$ was prepared as described above. After recrystallization from a water-ethanol solution it gave an infra-red spectrum identical with that from purified commercial en .

The extent of hydrogen exchange during ammonolysis was determined by preparing a small amount of $\text{en-d}_8 \cdot 2\text{DBr}$ with ND_3 . This compound was normalized to $\text{en-C-d}_4 \cdot 2\text{HBr}$ by repeatedly evaporating solutions of it in H_2O containing some HBr . The normalized $\text{en-d}_4 \cdot 2\text{HBr}$ had an infra-red spectrum identical in every respect to $\text{en-d}_4 \cdot 2\text{HBr}$ prepared with normal NH_3 in the region studied, 2.5–16 μ . Since the hydrogens attached to the carbon atoms in ethylenediamine do not exchange with water even at elevated temperatures, the above result establishes that hydrogen exchange on the carbons does not occur during the formation of en under the reaction conditions employed.

Ten grams of 1,2-dibromoethane- d_4 were reacted in four runs of approximately 2.5g each. Mole ratios of ammonia to 1,2-dibromoethane- d_4 from 54:1 to 66:1 and reaction times at 55° of 68–157 hr were used. The net yield of recrystallized ethylenediamine- C-d_4 dihydrobromide was 84 per cent of theory.

The effect of traces of moisture on the reaction was found to be small. When the reaction was conducted with 4% H_2O , 96% NH_3 (70 hr, 55°, $\text{NH}_3:\text{BrCH}_2\text{CH}_2\text{Br}$ 63/1) a yield of 88 per cent was obtained and the infra-red spectrum of the product indicated no appreciable alcohol or polymer formation.

When the reaction was carried out under rigorously anhydrous conditions with ND_3 instead of NH_3 , slightly longer reaction times were necessary.

"Free", anhydrous ethylenediamine-C-d₄. The free amine was prepared from the hydrobromide salt by a careful treatment with an excess of saturated aqueous sodium hydroxide. The reaction was carefully cooled to prevent decomposition from overheating. The solution was resaturated with crushed sodium hydroxide pellets and centrifuged to effect the separation of the amine (upper) phase. The amine layer was transferred to a vacuum line and carefully treated with sodium metal to remove the residual water. The purified ethylenediamine- C-d_4 was vacuum transferred to a sample tube and stored in a refrigerator until needed. Due to the need for absolutely anhydrous en-C-d_4 the yield of free amine was only 29 per cent of theory.

Analytical. For analysis, the free en-C-d_4 was converted to the dihydrochloride in water and recrystallized from a solution of 3M HCl and ethanol. After drying under vacuum it was analyzed (Galbraith Labs, Knoxville, Tennessee). (Found: C, 17.91; H, 7.79(*); N, 20.27. Required for $\text{C}_2\text{H}_6\text{D}_4\text{N}_2\text{Cl}_2$: C, 17.53; H, 7.68*; N, 20.45%). The precision is essentially the same as that obtained on a sample of normal $\text{en} \cdot 2\text{HCl}$. This analysis is used solely to demonstrate that the compound is the dihydrochloride of ethylenediamine since this type of analysis is not very sensitive to deuterium content.

Samples of anhydrous en and en-C-d_4 were transferred to (by vacuum techniques) and sealed in 5 mm diameter glass sample tubes and their n.m.r. spectra obtained on a Varian A-60 Nuclear Magnetic Resonance Spectrometer. The ratio of C-H to C-D in en-C-d_4 was found to be less than 0.01. In the determination, the areas of the C-H absorption for en and en-C-d_4 were compared using the relative areas of the N-H absorption to correct for differences in bulk susceptibility and density. The C-H contamination of less than 1 per cent indicated by the n.m.r. data correlates well with the analysis of the starting dibromoethane- d_4 if we consider the 2 per cent "partially" deuterated dibromoethane to be chiefly $\text{BrCD}_2\text{CHDBr}$ (i.e.: % C-H contamination $\cong 1/4 \times 2$ per cent).

* Oxidation of the deuterated compound gives a mixture of D_2O , HDO and H_2O . The weight of this water, both actual and theoretical, is converted to % H as though it were due only to H_2O .

Spectra. For the spectrum in Fig. 1, $\text{en-C-d}_4 \cdot 2\text{HBr}$ from a large scale preparation was twice recrystallized from hot 3M HBr, filtered, washed with chilled 95 per cent ethanol, and dried in vacuum at 56° for 2 hr. A sample of normal ethylenediamine dihydrobromide was similarly purified. The spectra of the two samples, as nujol and fluorolube oil mulls, were obtained on a Beckman IR-7 Infra-red Spectrophotometer with NaCl optics. The use of fluorolube oil made it possible to subtract the Nujol absorption maxima from the spectra.

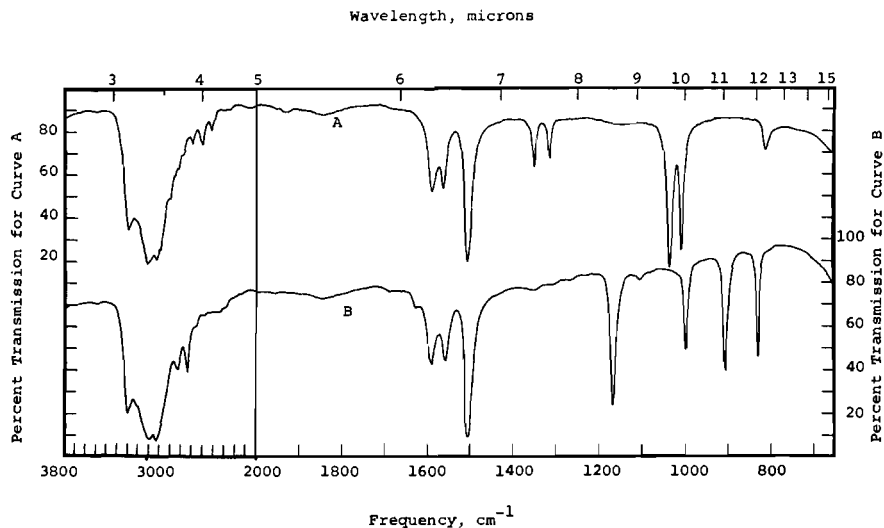


FIG. 1.—Infra-red spectra of $\text{en} \cdot 2\text{HBr}$ (curve A) and $\text{en-C-d}_4 \cdot 2\text{HBr}$ (curve B) obtained from Nujol mulls on a Beckman IR-7 Infra-red Spectrophotometer. The Nujol absorptions have been subtracted with the help of spectra obtained from fluorolube oil mulls.

RESULTS AND DISCUSSION

It has been shown that $\text{en} \cdot 2\text{HBr}$, and hence en , can be produced in yields of 80–90 per cent in a state of high purity by the action of anhydrous NH_3 on 1,2-dibromoethane. The boundary conditions for successful reaction have not been investigated, but at 55°C in a sealed pressure tube (about 23 atm pressure) with mole ratios of 20–60 (NH_3 : $\text{BrCH}_2\text{CH}_2\text{Br}$) and reaction times of 70–160 hr, the above range of yields is obtained.

Traces of water (up to at least 4 per cent) do not affect the purity of the product nor the yield. Thus, great care to exclude atmospheric moisture is unnecessary when condensing the ammonia in the Carius Tube.

The method is an excellent one for the preparation of en-C-d_4 since essentially no hydrogen exchange occurs between NH_3 and 1,2-dibromoethane- d_4 or ethylenediamine- C-d_4 . Since it is a one step reaction giving high yields of a pure product it is also well suited for the preparation of ^{14}C labelled ethylenediamine.

Slow decomposition of the 1,2-dibromoethane- d_4 was noted when the compound was stored for prolonged periods of time. The small increase in gas pressure over the sealed 1,2-dibromoethane- d_4 was probably due to the formation of vinyl bromide or ethylene, as the analogues of these have been reported as by-products in reactions of 1,2-dichloroethane⁽¹⁰⁾ and 1,3-dichloropropane.⁽¹¹⁾ These gases were pumped off

⁽¹⁰⁾ S. W. DYLEWSKI, H. G. DULUDE and G. W. WARREN, U.S. Pat. 2769841 (1956).

⁽¹¹⁾ G. DARZENS, *C.R. Acad. Sci., Paris* **208**, 1503 (1939).

prior to the transfer of the 1,2-dibromoethane- d_4 to prevent them from contributing to higher polyamine formation.

The infra-red spectrum of ethylenediamine- d_4 dihydrobromide is compared with normal ethylenediamine dihydrobromide in Fig. 1. It can be shown that the deuterated salt ($en-C-d_4 \cdot 2HBr$) is virtually uncontaminated by the C-H frequencies at 1342 and 1359 cm^{-1} and by the large absorption at 1030 cm^{-1} in $en \cdot 2HCl$. From a careful inspection of the original spectra we estimate that less than 2% C-H is present in the molecule which is about that present in the starting material, 1,2-dibromoethane- d_4 . Nuclear Magnetic Resonance spectra showed the C-H contamination to be actually less than 1 per cent. We are somewhat concerned over the apparent absence of expected C-D absorption frequencies in the $en-C-d_4 \cdot 2HBr$. However, the normal isotopic shift for the C-H stretching absorption is observed with the free amine ($\approx 2800 \rightarrow 2100\text{ }cm^{-1}$). Apparently the simple C-H and C-D frequencies in the amine salts are lost in skeletal vibrations. It should be noted that the absorption maxima at 1083 and 2042 cm^{-1} for normal $en \cdot 2HCl$ as reported by POWELL⁽³⁾ and confirmed in our laboratory, do not appear in the dihydrobromide spectrum. This is considered to be strictly an anion effect as opposed to the interpretation of POWELL. A more rigorous assignment of absorption frequencies is to be done in a later paper, where the spectra of all non-mixed H, D forms of ethylenediamine will be compared. (i.e.: en , $en-C-d_4$, $en-N-d_4$ and $en-d_8$.)

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