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ISOTOPIC STUDIES ON THE RADIATION DECOMPOSITION OF CRYSTALLINE CHOLINE CHLORIDE[1,2]

Richard M. Lemmon and Margaret A. Smith

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(2) Presented before the 141st National Meeting of the American Chemical Society, Washington, D. C., March 1962.

Abstract

Carbon-14- and deuterium-labeled choline chlorides were used to study the mechanism of the radiolysis of crystalline choline chloride. These studies demonstrate that, during the highly-sensitive radiation decomposition, (1) the carbinol group of the ethanol moiety becomes the aldehyde group of the resultant acetaldehyde, (2) no hydrogens are transferred to or from the trimethylamino group, (3) the hydrogens of the ethanol moiety are highly mobile, and (4) intermolecular hydrogen transfers take place.

This paper is part of a continuing study of the extraordinary radiation sensitivity of crystalline choline chloride, $[(CH_3)_3NCH_2CH_2OH]^+Cl^-$, a compound that decomposes with G values as high as 55,000.[3,4,5]

Earlier work had indicated the possibility of a symmetrical intermediate between choline chloride and one of its principal radiolysis products, acetaldehyde. Such a structure was based on the electron spin resonance spectra obtained from selectively deuterated, irradiated choline chloride. To test this possibility, in the present work $[(CH_3)_3NCH_2C^{14}H_2OH]^+Cl^-$ was prepared and decomposed by electron irradiation. The distribution of radioactivity was then determined in the resultant acetaldehyde.

The movements of hydrogen atoms during the radiation decomposition process were determined through experiments on the following deuterated cholines: $[(CD_3)_3NCH_2CH_2OH]^+Cl^-$, $[(CH_3)_3NCD_2CH_2OH]^+Cl^-$, $[(CH_3)_3NCH_2CD_2OH]^+Cl^-$, $[(CH_3)_3NCH_2CH_2OD]^+Cl^-$, and $[(CH_3)_3NCH_2CD_2OD]^+Cl^-$. The resultant principal products, trimethylamine and acetaldehyde, were purified by gas chromatography and their deuterium contents determined by mass spectroscopy.

Experimental

Preparation of Labeled Compounds.--The method for the preparation of $[(CH_3)_3NCH_2C^{14}H_2OH]^+Cl^-$ was the condensation of ethyl bromoacetate-1-C^{14}

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(3) R. O. Lindblom, R. M. Lemmon, and M. Calvin, J. Am. Chem. Soc. 83, 2484 (1961).

(4) R. M. Lemmon, P. K. Gordon, M. A. Parsons, and F. Mazzetti, ibid. 80, 2730 (1958).

(5) R. M. Lemmon, M. A. Parsons, and D. M. Chin, ibid. 77, 4139 (1955).

with dimethylamine to give the ethyl ester of N,N-dimethylglycine, $LiAlH_4$ reduction of the latter compound to N,N-dimethylaminoethanol, and quaternization with methyl iodide. The resultant choline iodide was then converted to the chloride. Details of this preparation have been given previously.[5] The final product was recrystallized from ethanol-ether; its specific activity was 0.28 μc/mmole. The elemental analysis was: C, 43.45% (calculated 43.01); H, 9.77% (calculated 10.11); Cl, 25.07% (calculated 25.41).

The $[(CD_3)_3NCH_2CH_2OH]^+Cl^-$ and $[(CH_3)_3NCD_2CH_2OH]^+Cl^-$ used were samples of the compounds whose preparations and properties were previously reported.[3,7]

The $[(CH_3)_3NCH_2CD_2OH]^+Cl^-$ was prepared following the same procedure outlined above for the C^{14}-labeled compound. In this case, no C^{14} was involved, and $LiAlD_4$ (from Metal Hydrides, Inc., Beverly, Mass.) was used in place of $LiAlH_4$. The NMR spectrum obtained on the product was identical to that previously reported for deuterated choline chloride in which the O-methylene proton contribution was missing and the N-methylene peak was sharpened by the elimination of hyperfine interactions.[3] The identity of the compound was also determined through satisfactory elemental analyses.

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(5) M. A. Smith and R. M. Lemmon, University of California Radiation Laboratory Report No. UCRL-9208, June 1960, p. 27.

(7) R. O. Lindblom, University of California Radiation Laboratory Report No. UCRL-8910, October 19, 1959.

$[(CH_3)_3NCH_2CH_2OD]^+Cl^-$ and $[(CH_3)_3NCH_2CD_2OD]^+Cl^-$ were prepared by dissolving undeuterated (or O-methylene deuterated) choline chloride in a large excess of 99% D_2O. The solution was evaporated to dryness and the deuterated compound was recrystallized from N,N-dimethylformamide. Before using this solvent for recrystallization, we established by NMR spectroscopy that the carbonyl-bound hydrogen atom of the solvent would not exchange with D_2O. The identities of the deuterated choline chlorides were established by C and H analysis. It was not possible to obtain a check of the purities by NMR spectroscopy since no suitable aprotic solvent could be found.

Irradiations.--The C^{14}-labeled crystalline choline chloride was irradiated with the electron beam of a 3-5 Mev linear accelerator. The deuterium-labeled cholines were irradiated with Co^{60} λ rays; the irradiation techniques have been described previously.[4] There is little difference between the effects of electron beams and λ rays in the radiolysis of choline chloride. The choice of the radiation is merely one of convenience. In all experiments the radiation dose given ($2-6 \times 10^6$ rads) was sufficient to cause approximately 10% decomposition. Direct determinations of the amounts of decomposition were not made.

Acetaldehyde-C^{14} Degradations.--After an irradiation the sealed tube containing the choline chloride was opened and the contents dissolved in water at 0°. Inactive acetaldehyde was added as carrier, and the resultant solution was refluxed for two hours while a stream of helium passed through it, carrying the acetaldehyde into a liquid nitrogen-cooled trap. The trap and contents were then placed in an ice bath and cold, dilute, basic $KMnO_4$ was added. After the solution was stirred for an hour, excess $KMnO_4$ was decomposed with $FeSO_4$, and the mixture was acidified with H_2SO_4 and steam distilled. The distillate was titrated to neutrality with standard NaOH (thus giving the yield of acetic acid) and evaporated to dryness.

The resultant sodium acetate was decomposed into CO_2 and methylamine with NaN_3 and H_2SO_4 (Schmidt reaction--details given previously[6]). The evolved CO_2 was swept by helium into a trap cooled by liquid oxygen. The CO_2 was transferred to a vacuum line where it was dried (passage through a trap at -80°), determined manometrically, and transferred to an ionization chamber for radioactivity measurement. This determination was made by using a vibrating-reed electrometer and the "rate of charge" method.

The methylamine was recovered by making the solution (from which the CO_2 had been generated) basic and codistilling water and methylamine into a cold trap. The phenylmethylthiourea of the methylamine was then prepared by allowing the latter compound to diffuse into a flask containing an aqueous solution of phenyl isothiocyanate.[8] The crystals of phenylmethylurea (identity established by melting point and elemental analysis) were washed with hexane, dried, and their specific activity determined by liquid scintillation counting.

Purification of the Evolved Acetaldehyde and Trimethylamine.--The irradiated choline chloride sample tube was cooled in liquid nitrogen and opened. It was then attached to a vacuum line and volatile components vacuum-distilled into a trap suitable for introducing the sample into a

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(8) R. L. Shriner and R. C. Fuson, "Identification of Organic Compounds", John Wiley and Sons, New York, N. Y., 1945, p. 148.

gas chromatograph (Wilkens, Model A-350, 10' by 1/4" dimethylsulfolane on firebrick column). Using helium as the carrier gas, with a flow rate of 90 cc per minute, at room temperature, the acetaldehyde is cleanly separated (retention time: 11 minutes) from all other volatile materials (very small amounts of methyl chloride and ethyl ether).

Trimethylamine was recovered, after the acetaldehyde was removed, by making alkaline the solution of the irradiated choline. The volatile trimethylamine was also swept over into a cold (-196°) trap from which it was introduced into a gas chromatograph. Using the same chromatographic conditions as described above for acetaldehyde (with the exception only of a flow rate of 60 cc per minute) the trimethylamine is also cleanly separated (retention time: 3.5 minutes) from other volatile compounds (traces of dimethylamine and acetaldehyde).

Deuterium Contents of Evolved Acetaldehyde and Trimethylamine.-- The amounts of deuterium in the chromatographically-purified gases were determined by observations of the enhancements, or lack of it, of such mass peaks as 46 (CH_2DCDO), 45 (CH_2DCHO), and 30 (CDO) for acetaldehyde. Appearance of deuterium in trimethylamine would result in enhancement of mass peak 59 (58 is the major peak for ordinary trimethylamine). An additional check of the deuterium in the methyl group of acetaldehyde was made by photolyzing part of the acetaldehyde, in the presence of iodine vapor, following the procedure of Blacet and Heldman.[9] The resultant methyl iodide contains the methyl group of the acetaldehyde and the presence of deuterium is reflected in the appearance of peaks

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(9) F. E. Blacet and J. D. Heldman, J. Am. Chem. Soc. 64, 889 (1942).

at mass 143 and above. The methyl iodide was also purified by gas chromatography (on dimethylsulfolane and Apiezon columns).

The mass spectroscopy was done on a Consolidated Electrodynamics Corporation Model 21-130 mass spectrometer.

Results

Distribution of Activity in Acetaldehyde from $[(CH_3)_3NCH_2C^{14}H_2OH]^+Cl^-$.-- Two samples of irradiated choline chloride were analyzed. The results of the acetaldehyde degradations are presented in Table I.

Table I

Degradations of Acetaldehyde from Irradiated $[(CH_3)_3NCH_2C^{14}H_2OH]^+Cl^-$

	Activity per mmole CO_2	Activity per mmole $C_6H_5NHCSNHCH_3$	Activity in C-1 of CH_3CHO (%)
Sample 1	4.07×10^{-2} μc	7.1×10^{-5} μc	99.8
Sample 2	0.92×10^{-2} μc	4.8×10^{-5} μc	99.5

The results given in Table I demonstrate that there is no symmetrical two-carbon species in the mechanism yielding acetaldehyde from irradiated crystalline choline chloride. The carbinol carbon atom of choline chloride is the aldehydic carbon in the acetaldehyde.

Acetaldehyde from $[(CD_3)_3NCH_2CH_2OH]^+Cl^-$.--The mass spectral data are presented in Table II.

Table II

Mass Spectral Data* for CH_3CHO (A.P.I. Catalog and our Data) and for Acetaldehyde from $[(CD_3)_3NCH_2CH_2OH]^+Cl^-$

Mass	CH_3CHO		Deuterated Acetaldehyde		
(m/e)	A.P.I.	Ours**	Expt. 1	Expt. 2	Expt. 3
29	100.0	100.0	100.0	100.0	100.0
30	1.1	1.1	1.4	1.4	1.4
43	26.7	30.1	28.3	28.0	27.8
44	45.7	54.0	50.2	49.7	49.5
45	1.2	1.3	2.8	2.4	2.5
46	0.1	0.1	v. small	v. small	v. small

*Relative peak heights

**Reagent grade, after GLC purification on dimethylsulfolane

The data of Table II clearly indicate that there is little, if any, involvement of the methyl protons in the radiolysis of crystalline choline chloride. The mass spectrum of the acetaldehyde is almost identical to that of the acetaldehyde from ordinary choline. There is a slight enhancement of the mass 45 peak, but this increase is so small as to be of dubious significance.

Acetaldehyde from $[(CH_3)_3NCD_2CH_2OH]^+Cl^-$.--The mass spectral data are presented in Table III.

Table III

Mass Spectral Data* for CH_3CHO (A.P.I. Catalog) and for Acetaldehyde from $[(CH_3)_3NCD_2CH_2OH]^+Cl^-$

Mass		Deuterated Acetaldehyde		
(m/e)	CH_3CHO	Expt. 1	Expt. 2	Expt. 3
29	100.0	100.0	100.0	100.0
30	1.1	4.8	4.8	5.7
43	26.7	11.6	11.9	9.4
44	45.7	28.4	28.5	22.9
45	1.2	30.2	29.9	32.4
46	0.1	14.8	14.4	23.9
47	--	2.8	2.5	2.2

*Relative peak heights

The data of Table III show: (1) There is a small fraction at mass 30; thus some CDO is formed. (2) The major peak is at mass 45, not 46. Therefore, there is more CH_2DCHO than CHD_2CHO formed (by a factor of nearly 2). (3) The appearance of a small peak at mass 47 indicates the formation of acetaldehyde with three deuterium atoms. This is evidence of intermolecular hydrogen transfers during the radiolysis.

Acetaldehyde from $[(CH_3)_3NCH_2CD_2OH]^+Cl^-$.--Consistent mass spectral data on the acetaldehyde from the O-methylene deuterated choline chloride proved difficult to obtain. The acetaldehyde mass spectrum was taken after thirteen different radiolysis experiments, including those from three different preparations of the deuterated compound. Mass 30 was always the largest peak; however, the mass 45/mass 46 ratio varied all the way from 2.75 to 0.40; the average was 0.99. That this was not due to varying amounts of water present in the crystals was shown by our obtaining similar mass spectra regardless of whether the crystals were handled with rigorous exclusion of water or in the presence of atmospheric moisture.

The major products, occurring in about equal amounts, appear to be CH_3CDO and CH_2DCDO. The mass 47 peak is no greater than is the mass 45 peak for ordinary acetaldehyde; therefore, there is no evidence of CD_3CHO or CD_2HCDO.

Typical mass spectral data follow:

Table IV

Mass Spectral Data* for CH_3CHO (A.P.I. Catalog) and for Acetaldehyde from $[(CH_3)_3NCH_2CD_2OH]^+Cl^-$

Mass (m/e)	CH_3CHO	Deuterated Acetaldehyde** Expt. 1	Expt. 2	Expt. 3
29	100.0	11.6	9.6	9.3
30	1.1	100.0	100.0	100.0
43	26.7	14.7	8.5	9.6
44	45.7	10.9	15.4	13.6
45	1.2	33.8	16.4	19.9
46	0.1	16.8	33.9	30.8
47	---	---	1.5	1.4

*Relative peak heights

**Representative data from a total of 13 experiments

Acetaldehyde from $[(CH_3)_3NCH_2CH_2OD]^+Cl^-$.--The mass spectral data are presented in Table V.

Table V

Mass Spectral Data* for CH_3CHO (A.P.I. Catalog) and for Acetaldehyde from $[(CH_3)_3NCH_2CH_2OD]^+Cl^-$

Mass (m/e)	CH_3CHO	Deuterated Acetaldehyde Expt. 1	Expt. 2	Expt. 3
29	100.0	100.0	100.0	100.0
30	1.1	2.5	3.5	3.4
43	26.7	22.3	25.0	18.7
44	45.7	43.0	49.4	40.4
45	1.2	20.7	23.8	26.6
46	0.1	3.3	5.8	7.1

*Relative peak heights

There are three conclusions to be drawn from the data of Table V: (1) There is a small, but definite, fraction of deuterium appearing in the aldehyde group (mass 30)--that is, a small amount of CDO is formed; (2) a considerably greater fraction appears in the methyl group (mass 45 =

CH_2DCHO); and (3) the increase of mass 46 (= CHD_2CHO) shows that intermolecular hydrogen transfer occurs during the radiolysis.

Acetaldehyde from $[(CH_3)_3NCH_2CD_2OD]^+Cl^-$.--The mass spectral data for the acetaldehyde from this triply-deuterated choline is presented below.

Table VI

Mass Spectral Data* for CH_3CHO (A.P.I. Catalog) and for Acetaldehyde from $[(CH_3)_3NCH_2CD_2OD]^+Cl^-$

Mass (m/e)	CH_3CHO	Deuterated Acetaldehyde
29	100.0	7.1
30	1.1	100.0
43	26.7	6.2
44	45.7	10.5
45	1.2	17.1
46	0.1	24.5
47	--	15.5
48	--	4.9

*Relative peak heights

The peak at mass 48 shows that some perdeutero-acetaldehyde is formed. This is further evidence (added to that presented in Tables III and V) that intermolecular hydrogen transfers take place during the radiation decomposition process.

Trimethylamine from Deuterated Cholines.--The data of Table VII establish the failure of hydrogens to transfer from the ethanol moiety to the trimethylamine during the radiolysis.

Table VII

Mass Spectral Data* for $(CH_3)_3N$ (A.P.I. Catalog and Our Data)
and for Trimethylamine from Deuterated Choline Chloride

Mass (m/e)	$(CH_3)_3N$ A.P.I.	$(CH_3)_3N$ Ours**	Trimethylamine from Deuterated Choline Chlorides*** $\geq NCD_2CH_2OH$	$\geq NCH_2CD_2OH$	$\geq NCH_2CH_2OD$
14	6.3	5.4	6.8	4.9	5.4
15	33.7	45.5	43.0	37.1	35.0
16	0.5	0.6	1.1	0.6	0.7
57	7.4	8.5	7.5	7.5	6.5
58	100.0	100.0	100.0	100.0	100.0
59	38.7	44.3	43.7	46.9	45.0
60	1.3	1.5	1.6	1.8	1.3

*Relative peak heights

**Trimethylamine, from the radiolysis of ordinary choline chloride, after GLC purification on dimethylsulfolane

***Representative data only--either two or three experiments were done on each deuterated choline. For each compound, the separate determinations of trimethylamine mass spectra were in good agreement.

Deuterium Contents of CH_3I from CH_3CHO.--The deuterium contents in the methyl group of acetaldehyde products were checked by measurements of the mass spectra of the CH_3I obtained from aliquots of the different acetaldehydes. This was done in seven different experiments and, in all cases, the deuterium found in the CH_3I (ratios of masses 142:143:144:145) followed closely that found in CH_3CHO (ratios of masses 44:45:46:47). The finding of significant mass 145 (= CD_3I) from the acetaldehyde from N-methylene deuterated choline is further substantiation of our conclusion that intermolecular hydrogen transfer is occurring.

Summary and Conclusions

The results presented in this paper have increased our understanding of the mechanism of the unique radiation decomposition of crystalline choline chloride. Unfortunately, however, we still have no understanding of why choline chloride is so sensitive to ionizing radiation. What we now further know about the mechanism, as a result of the present work, is the following:

(1) The carbon atoms of the ethanol moiety maintain their identities during the mechanism leading to the production of acetaldehyde--i.e., the oxygen atom remains attached to the same carbon, and there is no symmetrical intermediate.

(2) None of the hydrogen atoms of the three methyl groups of choline chloride appear in the radiolytically-produced acetaldehyde.

(3) The five hydrogen atoms of the ethanol moiety show considerable mobility during the radiolysis. It is difficult to give quantitative values for these hydrogen transfers, but the following intramolecular processes do occur:

(a) Unexpectedly, protons are often lost from the N-methylene group during its transition to the methyl group of the acetaldehyde. Sometimes N-CH_2 hydrogens appear in the CHO group of the acetaldehyde. More often, a detached N-CH_2 hydrogen is simply eliminated (to appear as HCl).

(b) O-methylene hydrogens appear to have about equal probabilities of elimination and of appearance in the acetaldehyde methyl group.

(c) Hydroxyl hydrogens usually are eliminated, but their elimination probability is only about twice that of their appearance in the acetaldehyde methyl group. This latter appearance is, in turn, about ten times as probable as appearance in the acetaldehyde CHO group.

(4) Although they are only minor processes, intermolecular hydrogen transfers do take place. Transfers to another molecule occur in the cases of the N-methylene and hydroxyl hydrogens, but do not involve O-methylene hydrogens.