[CONTRIBUTION NO. 823 FROM THE DEPARTMENT OF CHEMISTRY, INDIANA UNIVERSITY]

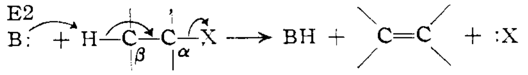
The Mechanism of the Hofmann Elimination Reaction. Deuterium Exchange and Isotope Rate Effects[1]

BY V. J. SHINER, JR., AND MORRIS L. SMITH[2]

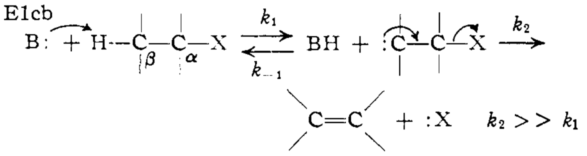
RECEIVED MARCH 6, 1958

It has been observed that, relative to their rates of elimination, *n*-butyltrimethylammonium, isopropyltrimethylammonium and *t*-butyltrimethylammonium ions exchange carbon-bound hydrogen for deuterium in basic ethylene glycol-d_2 with decreasing ease in the order listed. This exchange is predominantly if not exclusively in the α-position to the nitrogen. Ethyltrimethylammonium ion eliminates triethylamine in basic ethylene glycol solution at 137° *ca.* 4.0 times more rapidly than does its β-d_3 analog. The latter material does not exchange deuterium for solvent hydrogen under these conditions, but yields ethylene containing two deuterium atoms per molecule. These results are interpreted as indicating that neither the conjugate base (E1cb) nor the α-elimination mechanisms contribute in the simple Hofmann elimination reactions which are presumably best described by the synchronous (E2) mechanism exclusively. The magnitude of the β-deuterium isotope rate effect and the occurrence of α- exchange indicate that the nitrogen pole causes a larger degree of C–H bond rupture in the transition state for these reactions than occurs in the hydrogen halide eliminations, in accord with the suggestion of Ingold that the "Hofmann rule" of elimination orientation is due to the presence of this pole.

The second order, base-promoted elimination reactions of both quaternary ammonium ions and alkyl halides are thought to proceed by a single-step mechanism involving simultaneous attack by base at a β-hydrogen atom, formation of the double bond and loss of the electronegative eliminant. This mechanism has been designated E2 by Ingold.[3]

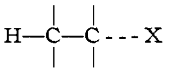


Another mechanism, designated E1cb by Ingold,[3] which involves two steps with base attack and proton loss preceding the loss of the electronegative eliminant, would also explain the second-order nature of the reaction.

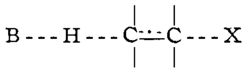


This mechanism is believed not to obtain in the alkyl halide reactions because of Skell and Hauser's[4] observation that β-phenylethyl bromide does not exchange hydrogen for deuterium when allowed to react with sodium ethoxide in ethanol-*d*. The argument is that if the carbanion were formed as an intermediate it should reform the starting material by reversal of the first step and that this would lead, in the presence of ethanol-*d*, to hydrogen–deuterium exchange. This conclusion is also valid for the reaction of isopropyl bromide with sodium ethoxide because of the observation that isopropyl-β-d_6 bromide undergoes a smooth second order elimination reaction under these conditions at about one-seventh of the rate of the corresponding reaction of the protium analog.[5] The E1cb mechanism also does not conveniently explain the accelerating influence of β-alkyl substituents on the rate of the base-promoted elimination of hydrogen halide from alkyl halides (Saytzeff rule), or the strong preference that certain representative examples show for *trans* elimination.[6,7]

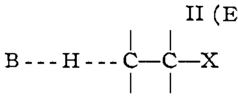
If one visualizes an E1cb reaction in which the lifetime of the intermediate ion can be reduced continuously, it is obvious that in the limit this mechanism would merge into the E2 mechanism in which the two eliminants are lost simultaneously and the electron shifts occur synchronously. However, as the lifetime of the carbanion intermediate is reduced the various criteria indicative of the E1cb mechanism will be lost at different stages. One of the first characteristics to be lost would be the ability of the carbanion to react with solvent and show the exchange reaction. At some stage of carbanion life still shorter the elimination will begin to show a *trans* stereochemical preference. At this point the reaction might more accurately be described as an E2 process in which transition state the C–H bond breaking had occurred to a relatively large extent and double bond formation and loss of the electronegative eliminant had proceeded to a small extent. Saunders and Williams[8] have described this situation and the possible variations on it in terms of varying contributions of structures I, II and III to the transition state. An E2 reaction with considerable carbanion character might still show electronic characteristics similar to those expected for the E1cb reactions, such as a fairly high ρ value when *m* and *p* substituted phenyl rings are attached to the β-carbon atom[8] and rate retardation by β-alkyl substituents.



I (E1)



II (E2)



III (E1cb)

---

[1] This research was supported in part by a grant from The Petroleum Research Fund administered by the American Chemical Society. Grateful acknowledgment is hereby made to the donors of this fund.

[2] (a) Abstracted in part from a thesis submitted by Morris L. Smith to the Graduate School of Indiana University in partial fulfillment of the requirements for the Ph.D. degree; (b) presented in part before the Division of Organic Chemistry at the 133rd National Meeting of the American Chemical Society, San Francisco, Calif., April 14, 1958.

[3] For a general discussion of olefin-forming elimination reactions and further references to the original literature see C. K. Ingold, "Structure and Mechanism in Organic Chemistry," Cornell University Press, Ithaca, N. Y., 1953, Ch. VIII.

[4] P. S. Skell and C. R. Hauser, THIS JOURNAL, **67**, 1661 (1945).

[5] V. J. Shiner, Jr., *ibid.*, **74**, 5285 (1952).

[6] W. Hückel, W. Tappe and G. Legutke, *Ann.*, **543**, 191 (1940).

[7] S. J. Cristol, THIS JOURNAL, **69**, 338 (1947).

[8] W. H. Saunders, Jr., and Richard A. Williams, *ibid.*, **79**, 3712 (1957).

The elimination reactions of quaternary ammonium compounds show retardation of rate by β-alkyl substituents (Hofmann rule), and also apparently show a preference for *trans* elimination[6] although the evidence for this last point is not so extensive. Doering and Meislich[9] have presented evidence that optically active trimethyl-α-phenylethyl- and trimethyl-β-phenylisopropylammonium ions did not racemize under conditions which produced elimination with the latter compound and pointed out that under certain reasonable assumptions this made the E1cb mechanism seem unlikely for these reactions. This example might, however, represent a special case of the Hofmann elimination, due to the presence of the phenyl group which makes the elimination much more facile.

Doering and Hoffmann[10] observed the exchange of hydrogen of tetramethylammonium iodide for deuterium in basic deuterium oxide solutions at 100°, indicating that the formation of α-carbanions by hydroxide attack on quaternary ammonium compounds is possible under these conditions. Since many of the simple Hofmann eliminations require much more drastic conditions than this there seemed some possibility of β-carbanion formation being a step in these reactions. Therefore it was decided that deuterium exchange experiments on simple quaternary ammonium bases, analogous to the experiments of Skell and Hauser on β-phenylethyl bromide, would be worthwhile. In addition, since the magnitude of the deuterium isotope rate effect is dependent on the extent of C–H or C–D bond breaking in the transition state, it was thought that a comparison of this effect in the quaternary ammonium eliminations with the one already reported[5] for the alkyl halide elimination would be of interest. Consequently *n*-butyltrimethylammonium, isopropyltrimethylammonium and *t*-butyltrimethylammonium hydroxides were synthesized and caused to react in ethylene glycol-*d* under conditions such that the elimination reaction would proceed to about fifty or more per cent. The quaternary ammonium compound was recovered as the iodide in the first example, the trimethylamine formed in each case was recovered as the hydrochloride and the olefins from the last two members of the series were recovered as the dibromides. All of these compounds and the ethylene glycol-*d* were analyzed for deuterium content. The results are given in Table I.

TABLE I

EXCHANGE OF QUATERNARY BASES IN ETHYLENE GLYCOL-*d*

R of $\overset{+}{R}NMe_3$	Temp., °C.	Atoms of D per molecule in recovered compounds			
		Quat. iodide	Me_3N	Olefin	Glycol-*d*
n-Butyl	165	1.04	0.61	...	1.05
Isopropyl	130	..	0.068	0.016	1.22
t-Butyl	110	..	0.009	0.001	1.20

The first horizontal entry in Table I shows that the primary alkyl trimethylammonium material underwent considerable exchange. However, since the recovered trimethylamine, which must have been in the reaction mixture on the average roughly one-half as long as the unreacted starting material, contained roughly one-half as much deuterium it appears that the exchange was occurring principally in the positions alpha to the nitrogen. The second horizontal entry shows that the trimethylamine from the isopropyltrimethylammonium ion had exchanged much less than in the first example, presumably because the temperature of the reaction was lower. Although a small amount of deuterium showed up in the propylene, comparison of this figure with that for trimethylamine suggests that this was probably mainly if not exclusively in the α-position of the isopropyl group. The last entry in Table I shows that still much less if any exchange occurred in the reaction of *t*-butyltrimethylammonium ion, presumably again because the temperature of this reaction was considerably lower. Assuming the possibility of an E1cb mechanism for these reactions the deuterium exchange experiments would detect it only if $k_2/k_{-1} <\sim 10^2$. If the carbanion mechanism were operative it is obvious that alkyl substituents at C_α and probably also at C_β, because of their stabilizing effects on the olefin formed in the last step, would increase the ratio k_2/k_{-1}. Such substitution might conceivably operate to change the mechanism to the synchronous type. It therefore appeared that the most favorable example for the operation of the E1cb mechanism in the alkyl quaternary ammonium series would be the ethyltrimethylammonium ion.[11] However it was obvious that this material would undergo considerable exchange of the α-hydrogen atoms and that this would tend to obscure any small amount of β-exchange occurring with ethylene glycol-*d*. Therefore, ethyl-β-d_3-trimethylammonium iodide was synthesized and its exchange in ethylene glycol studied under conditions which allowed some elimination to proceed. The starting material, the recovered unreacted quaternary compound, the isolated products ethylene (as the dibromide) and trimethylamine (as the hydrochloride) were found to contain, respectively, 2.95 ± 0.03, 2.93 ± 0.03, 1.95 ± 0.02 and 0.00 average atoms of deuterium per molecule.

The exchange experiments show that even though in some cases considerable α-hydrogen exchange may accompany the Hofmann elimination, β-exchange is insignificantly small in the examples studied. It seems a reasonably safe generalization that none of the Hofmann reactions of fairly simple (monofunctional, etc.) compounds would involve any reversible β-hydrogen abstraction. As far as this criterion is applicable, the E1cb, two-step elimination mechanism for these reactions is ruled out. Also, the results on the reaction of β-trideuterioethyltrimethylammonium ion rule out the possibility of the operation of any significant amount of an α-elimination mechanism[12] because the recovered ethylene contained within experimental error exactly one less deuterium atom per molecule than the starting material. This seems

---

[9] W. von E. Doering and Herbert Meislich, THIS JOURNAL, **74**, 2099 (1952).

[10] W. von E. Doering and A. Kentaro Hoffmann, *ibid.*, **77**, 531 1955).

[11] The recent work of Saunders and Williams[8] indicates that β-phenyl substituents might promote this mechanism.

[12] Douglas G. Hill, William A. Judge, Philip S. Skell, Simon W. Kantor and Charles R. Hauser, THIS JOURNAL, **74**, 5599 (1952).

somewhat surprising in view of the observations of Hauser and co-workers[12] that some small amount of α-elimination occurred in the reaction of n-octyl bromide with potassium amide even though the octyl bromide underwent no α-exchange. The present example almost certainly undergoes α-hydrogen exchange and presumably α-carbanion formation under the conditions of the reaction, but gives no evidence for α-elimination.

The occurrence of α-exchange in the quaternary ammonium compounds which is not observed with the alkyl halides certainly indicates that the electronic effect of the nitrogen pole, to which Ingold[3] attributes the cause of the Hofmann rule, is operating in the predicted way although this does not prove its exclusive or major control of the situation.

TABLE II

COMPETITIVE REACTIONS OF $CD_3CH_2N^+Me_3$ AND $CH_3CH_2N^+Me_3$ IN BASIC ETHYLENE GLYCOL AT 137°

	Run 1	Run 2
Mole D compound taken	0.0216	0.0148
Mole of H compound taken	.0260	.0114
Mole of mixt. recvd.	.0189	.0141
Atoms % D in mixt. taken	9.54	11.86
Atoms % D in mixt. recvd.	15.85	16.39
Atoms % D in pure D cpd.	21.43	21.43
Calcd. mole of D cpd. recvd.	0.0140	0.0108
Calcd. mole of H cpd. recvd.	.0049	.0033
Calculated k_H/k_D	3.87 ± 0.5	3.94 ± 0.5

In Table II are shown the results of two experiments in which mixtures of ethyltrimethylammonium hydroxide and its β-trideuterio analog were allowed to react with base to a limited extent. The recovered material was analyzed for deuterium and from the isotopic enrichment the rate ratio of H to D elimination was calculated to be 3.9 ± 0.5 at 137°. Recently the isotope rate effect in the bimolecular elimination of hydrogen bromide from 2-phenyl-1-bromopropane-2-d has been measured at a number of different temperatures.[13] This allows a comparison of deuterium isotope rate effects in elimination reactions among three different compounds as follows: (1) at 25°: k_H/k_D for β-hexadeuterioisopropyl bromide, 6.7; for 2-phenyl-1-bromopropane-2-d, 7.5; (2) at 137°: for 2-phenyl-1-bromopropane-2-d, 2.8 (calcd.); for ethyl-β-d_3-trimethylammonium hydroxide, 3.9. The first three examples refer to proton abstraction by ethoxide ion while the last one refers to abstraction by ethylene glycolate ion. The base strengths are comparable and the effect of changing base on the isotope rate effect should be small. Therefore the isotope rate effect and presumably the degree of β-C–H bond breaking in the transition state increases in the order isopropyl bromide, 2-phenyl-1-bromopropane, ethyltrimethylammonium ion. This is in the order expected if the Hofmann type reactions have more carbanion character. Saunders and Williams[8] have reported that β-phenylethyl bromide showed a surprisingly large transition state carbanion character as judged from the effect of substituents in the phenyl ring on the rate. It is interesting that Shiner and Smith[13] have observed that 2-phenyl-1-bromopropane reacts in the elimination reaction more slowly than β-phenylethyl bromide. Thus the β-methyl substituent slows the reaction. This is characteristic of Hofmann-type eliminations as exemplified by the onium compounds but differs from Saytzeff-type eliminations as exemplified by the simple alkyl halides.

Experimental

Deuterium Exchange with Ethylene Glycol-d_2 and n-Butyltrimethylammonium Iodide.—A sample of 5 ml. of deuterium oxide was mixed with 5 ml. of ethylene glycol and the mixture was allowed to equilibrate for 15 minutes. The deuterium oxide–water was distilled off at reduced pressure. Then 10 g. of n-butyltrimethylammonium iodide and 1.2 g. of sodium hydroxide were added to the ethylene glycol. The mixture was heated to 165° in a flask connected to two traps. The first contained aqueous hydrochloric acid to remove any trimethylamine and the second contained bromine in chloroform to remove any olefin. The reaction was interrupted after one hour and cooled. The evaporation of the hydrochloric acid solution gave, after recrystallization from absolute ethanol, 0.5 g. of trimethylamine hydrochloride. No success was experienced in the attempt to isolate butylene dibromide from the chloroform. Ethylene glycol was removed from the reaction vessel by distillation at reduced pressure. The quaternary iodide residue, after recrystallization from n-propyl alcohol, weighed 7 g. The substances were analyzed for deuterium with the following results: glycol, 1.05; quaternary iodide, 1.04; trimethylamine, 0.61 average atoms of D per molecule.

Deuterium Exchange between Ethylene Glycol-d_2 and Isopropyltrimethylammonium Hydroxide.—A sample of 15 g. of isopropyltrimethylammonium iodide was treated with an aqueous suspension of a slight excess of silver oxide. After shaking, the precipitate was removed and washed by centrifugation and the aqueous phase was evaporated under reduced pressure. The viscous liquid residue was added to 15 ml. of ethylene glycol and any remaining water was removed by slight warming at reduced pressure. Then 5 g. of deuterium oxide was added and after standing for a while removed under reduced pressure. This was repeated with a second 5-g. portion of deuterium oxide. The remaining mixture was heated for four hours at 130° when all evidence of reaction ceased. The trimethylamine formed was trapped out in aqueous hydrochloric acid and the propylene formed was trapped with bromine in chloroform. The ethylene glycol was recovered from the reaction vessel by distillation at reduced pressure. The trimethylamine hydrochloride was recovered from the aqueous acid solution by evaporation and recrystallized from absolute ethanol. The propylene dibromide was recovered from the chloroform by distillation. These compounds on analysis showed the following amounts of deuterium, respectively: 1.22, 0.0684, 0.016 average atoms of D per molecule.

Deuterium Exchange between Ethylene Glycol-d_2 and t-Butyltrimethylammonium Hydroxide.—The procedure was closely analogous to that described above for the isopropyl derivative except that complete decomposition occurred in about one hour at 100–126°. The deuterium analyses were as follows: isobutylene dibromide, 0.001; trimethylamine hydrochloride, 0.009; ethylene glycol, 1.20 average atoms of D per molecule.

Preparation of Acetic-d_3.—Malonic acid, 0.2 mole, was mixed with 10 ml. of 99.5% deuterium oxide and 40 ml. of dioxane. After stirring at room temperature for 48 hours the solvent was removed using a freeze-drying technique. Heating at this point was avoided because of the relatively low temperature of the malonic acid decarboxylation reaction. The exchange was continued successively with fresh deuterium oxide samples. Combustion analyses after the fifth, sixth and seventh exchanges showed the acid to contain 3.62, 3.59 and 3.61 atoms of deuterium per molecule instead of the 3.96 to 4.00 desired. It is believed that the exchange was actually complete and that the analyses were low because of the presence of impurities. The exchanged malonic acid was heated and decarboxylated. The crude acetic-d_3 acid product was used directly in the next step.

Preparation of Ethanol-β-d_3.—The acetic-d_3 acid of the previous preparation was dissolved in 50 ml. of ether and

---

(13) V. J. Shiner, Jr., and Morris L. Smith, unpublished results.

added to a slurry of 7.6 g. (0.2 mole) of lithium aluminum hydride over a period of one hour. The reaction mixture was decomposed with 200 ml. of 25% sulfuric acid. The combined ether and water layers were distilled together and after the ether was removed the ethanol-β-d_3 was collected as the water azeotrope. This material contained 0.175 mole of ethanol-β-d_3; yield 87.5%.

Ethyl-β-d_3 Iodide.—The ethanol-β-d_3–water azeotrope was treated with 60 ml. of 47% hydroiodic acid and the mixture refluxed. Every two or three hours the mixture was cooled and the ethyl-β-d_3 iodide layer was withdrawn with a capillary pipet. After drying with calcium chloride the yield was 19.82 g. (0.13 mole) or 74% of theoretical.

Ethyl-β-d_3-trimethylammonium Iodide.—Into a refluxing solution of 19.8 g. (0.13 mole) of ethyl-β-d_3 iodide in 20 ml. of absolute methanol was slowly bubbled anhydrous trimethylamine. After two hours the reaction was complete and upon cooling the product crystallized in long, white needles. After standing overnight, the product was filtered and recrystallized from methanol and dried in the 110° oven. The dry crystals weighed 16 g. (0.075 mole) or 58% of the theoretical amount. A second crop, obtained from the mother liquor, weighed 6.2 g. A dithiourea adduct,[14] recrystallized four times from absolute ethanol, melted at 139.5–141° as compared with the reported value of 141°.

Deuterium analysis of the ethyl-β-d_3-trimethylammonium iodide, showed that it contained 2.95 ± 0.03 average atoms of deuterium per molecule.

Elimination Reaction of Ethyl-β-d_3-trimethylammonium Hydroxide.—Silver nitrate (16 g., 0.1 mole) and sodium hydroxide (4 g., 0.1 mole) were dissolved in water and slowly mixed together with agitation. The resulting precipitate was filtered on a fine sintered glass funnel and washed several times with distilled water. The 10 g. (0.046 mole) of ethyl-β-d_3-trimethylammonium iodide was added slowly to a rapidly stirred slurry of the freshly prepared silver oxide and the stirring continued for 15 minutes. The resulting precipitate was filtered on the sintered glass funnel and washed thoroughly with four portions of water of 25 ml. each. The mother liquor was then centrifuged and decanted into a flask and the water removed with an aspirator. The last traces of water were removed by heating at low pressure. Upon cooling, the ethyl-β-d_3-trimethylammonium hydroxide solidified as a white wax-like solid. It was then treated with 10 ml. of ethylene glycol and the resulting solution heated in a flask to a temperature of 130°. The flask was connected to two traps, the first containing dilute hydrochloric acid and the second containing bromine in chloroform at 0°. After the reaction had proceeded approximately one-half toward completion (as indicated by the disappearance of the bromine color), it was halted and the unchanged quaternary salt isolated as the iodide by titration of the contents of the reaction flask with hydriodic acid and subsequent evaporation of the solvent with an aspirator. After drying in the 110° oven, the recovered ethyl-β-d_3-trimethylammonium iodide was analyzed for deuterium and found to contain 2.93 ± 0.03 atoms of deuterium per molecule. Evaporation of the dilute hydrochloric acid solution contained in one of the traps yielded the trimethylamine hydrochloride which upon recrystallization from ethanol and deuterium analysis was found to contain 0.0025 atom of deuterium per molecule. Distillation of the chloroform solution contained in the second trap yielded 4 ml. of ethylene dibromide boiling at 130.5°, which, by combustion analysis, was shown to contain 1.95 atoms of deuterium per molecule.

Competitive Kinetics for the Hofmann Elimination of Ethyl-β-d_3-trimethylammonium Hydroxide and its Protium Analog.—Known amounts of both the deuterated and protonated quaternary iodides were weighed out and converted to their hydroxides in the manner described above. Then a known amount of ethylene glycol was added and the reaction conducted as before. After interruption of the reaction at the midway point, the products were recovered in the usual manner, except that the unchanged mixture of hydroxides was diluted to 100 ml. and several 5-ml. aliquots titrated with standard acid. Then the remaining solution was titrated with hydroiodic acid and the quaternary iodides isolated, dried and analyzed for deuterium content.

	Kinetic run 1	Kinetic run 2
Mole D cpd.	0.0216	0.148
Mole H cpd.	0.0260	0.0114
Glycol, g.	10.2103	8.3172
Mole recovd. quat. hydroxide	0.0189	0.0141
Deuterium, %	15.85	16.39
Reaction temp., °C.	137 ± 2	137 ± 2
Reaction time, min.	105	90

The reaction of basic ethylene glycol with the glass reaction flask was shown to be negligible. After heating in the flask for four hours at 140° the loss of base was only 1.04%.

The reaction of silver oxide with the quaternary iodide to yield the quaternary hydroxide was shown to be quantitative by preparation of the hydroxide from a known amount of iodide and titration of the resulting solution with standard acid; 2.944 meq. of iodide yielded, after treatment with silver oxide, 2.939 meq. of hydroxide.

Calculation of the Isotope Rate Effects.—The concentrations of hydrogen compound, H, and deuterium compound, D, at time, t, of the interruption of the reaction can be calculated from the deuterium analysis of the recovered mixture of isotopic molecules. If H_0 and D_0 represent the concentrations of these materials at the beginning of the reaction then, by an analysis similar to that given by Bigeleisen[15] it is easily shown that $\log (H_0/H)/\log(D_0/D) = k_H/k_D$.

Deuterium Analyses.—Combustion analyses for deuterium using the gradient density tube method were done as described in an earlier paper.[5] The analyses are generally reproducible to within ±2% or ±0.01 atom of D per molecule, whichever is greater.

BLOOMINGTON, IND.

---

[14] W. R. G. Atkins and E. A. Werner, *J. Chem. Soc.*, 1990 (1912).

[15] J. Bigeleisen, *Science*, **110**, 14 (1949).