Base-Catalyzed Deuterium Exchange of Several Eneammonium Salts[1,2]

M. Saunders and Elijah H. Gold

Contribution from the Department of Chemistry, Yale University, New Haven, Connecticut. Received January 21, 1966

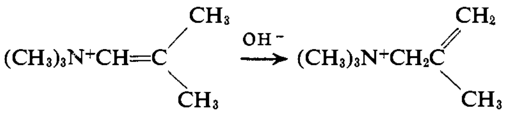
Abstract: The kinetics of aqueous base-catalyzed deuterium exchange of several eneammonium salts, including the new 1,2-dihydropyridinium and 1,2-dihydroquinolinium systems, have been investigated. Both electrostatic and resonance effects must be considered in explaining the results. The exchange of the methylene hydrogens in the 1,2-dihydropyridinium cation was faster than exchange in the tetramethylammonium cation, by a factor of 1.8×10^{10}. The deuterium exchange of all the ring hydrogens in N,N-dimethyl-1,2,5,6-tetrahydropyridinium cation III is explained by postulating the formation of a 3,5-allylic ylide. The transition states leading to allylic ylides, at least in the cases studied, are shown to be close to the intermediates on the energy surface. The allylic ylide from I or II appears to be stereospecifically formed, the evidence indicating a *cis* configuration of the negatively and positively charged atoms.

Much has been published about methods of formation, qualitative stability, and reactions of ylides.[3–7] However, few quantitative data are available concerning the factors which affect the relative energies of different ylides. We were particularly interested in the effects of unsaturation conjugated to the anionic center.

Since only the more stable ylides can be obtained preparatively, and since direct thermochemical comparison even of these would be difficult, we sought to obtain and use data on the kinetics of formation of ylides by proton removal from ammonium salts to examine effects on the relative energies in the structurally modified ylides. Of course, kinetics provides direct information only about the thermodynamic differences between the starting materials and the transition states; so it is therefore necessary to demonstrate that the transition states for the reactions considered resemble the ylides in order to draw thermodynamic conclusions. We were thus led to investigate the transition states of base-catalyzed deuterium exchange reactions of quaternary ammonium salts to see whether these were close to ylides on the energy surface. The base-catalyzed exchange of tetramethylammonium salts with D_2O had already been investigated[8] and served as a reference system for comparison with the exchange reactions of the unsaturated ammonium salts.

Preparation of Eneammonium Salts

N,N,N-Trimethyl-1-isobutenylammonium iodide (I) was prepared by alkylation of the corresponding eneamine[9] with methyl iodide.[10] The nmr spectrum demonstrated alkylation on nitrogen. Isomerization of I to N,N,N-trimethyl-2-isobutenylammonium iodide (II) was readily accomplished with base.[10] The nmr spectrum of II indicated the loss of one C-methyl and the CH adjacent to the nitrogen and the gain of the two methylene groups.



$$(CH_3)_3N^+CH{=}C(CH_3)_2 \xrightarrow{OH^-} (CH_3)_3N^+CH_2C({=}CH_2)CH_3$$

I II

N,N,N-Trimethyl-2,4-pentadienylammonium iodide (IV) was prepared from III[11] in a manner similar to that employed by Lukes and Pfliml.[12] Under the conditions used for the deuterium exchange kinetics (1 *N* NaOH in H_2O for 45 min at 100°) no change was noted in the nmr spectrum. Only the 2,4 isomer was reisolated. Addition of bromine to III was attempted unsuccessfully many times using conventional procedures. Since the ionic processes, which normally occur, were apparently inhibited by the positive charge, a radical chain process was attempted. Photobromination of III followed by dehydrobromination with methanolic KOH yielded N,N-dimethyl-1,2,-dihydropyridinium bromide (V, see Scheme I).[13] Its structure was determined on the basis of the following evidence. Its ultraviolet spectrum in ethanol shows one maximum at 247 mμ (log ϵ 3.66).[14] Its nmr spectrum shows a multiplet at τ 3.57 ((3.98 ± 0.03) area with respect to the area of the N-dimethyl peak as 6.00) due to the four olefin hydrogens, a broad doublet at 5.69 (1.97 ± 0.02) due to the methylene hydrogens, and a singlet

---

[1] This work was supported in part by a grant from the National Science Foundation and a fellowship to E. H. G. from the National Institutes of Arthritis and Metabolic Diseases of the National Institutes of Health.

[2] Part of a Ph.D. thesis submitted by E. H. G. in partial fulfillment of the requirements for the degree of Doctor of Philosophy at Yale University.

[3] G. Wittig and G. Felletschin, *Ann.*, **555**, 133 (1944).

[4] D. Lloyd and J. S. Sneezum, *Tetrahedron*, **3**, 334 (1958); E. Kosower and B. Ramsey, *J. Am. Chem. Soc.*, **81**, 856 (1959); F. Krohnke, *Ber.*, **83**, 253 (1950).

[5] H. J. Dauben, Jr., Abstracts of Papers, 126th National Meeting of the American Chemical Society, New York, N. Y., Sept 1954, p 18-O; W. W. Spooncer, *Dissertation Abstr.*, **16**, 458 (1956).

[6] Z. Arnold, *Chem. Ind.* (London), 1478 (1960).

[7] G. Wittig and M. H. Wetterling, *Ann.*, **557**, 193 (1947); G. Wittig and M. Rieber, *ibid.*, **562**, 177 (1949).

[8] W. von E. Doering and A. K. Hoffmann, *J. Am. Chem. Soc.*, **77**, 521 (1955).

[9] K. C. Brannock, A. Bell, R. D. Burpitt, and C. A. Kelly, *J. Org. Chem.*, **26**, 635 (1961).

[10] The methylation and the base-catalyzed isomerization were first carried out in these laboratories by B. Platz.

[11] R. Lukes, *Collection Czech. Chem. Commun.*, **12**, 71 (1947); J. J. Panouse, *Compt. Rend.*, **233**, 260 (1951).

[12] R. Lukes and J. Pfliml, *Collection Czech. Chem. Commun.*, **21**, 625 (1956).

[13] We are grateful to Mr. T. Record for carrying out the original synthesis of V from III.

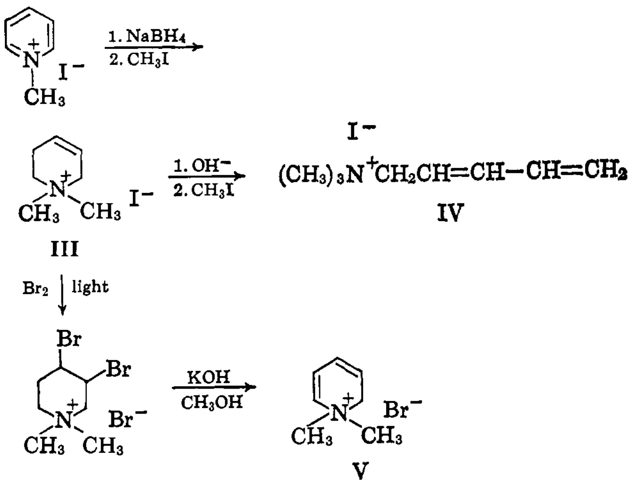
[14] Cyclohexadiene is reported by B. V. Erofeev, N. P. Emel'ianov, and S. F. Naumova, *J. Gen. Chem. USSR*, **28**, 1314 (1958), to have one maximum in ethanol at 259 mμ (log ϵ 4.01).

Table I. Kinetics of Exchange of Methylene Hydrogens Adjacent to the Quaternary Nitrogen

Compd	Temp, °C	k, l./mole sec	Calcd rel rate at 50°	ΔH^*, kcal/mole	ΔS^*, eu
$(CH_3)_4N^{+a}$	83.6	3.11×10^{-9}	1.0	32.2 ± 0.6	-8^b
	100.0	2.29×10^{-8}			
II	101.3	$3.00 \pm 0.08 \times 10^{-5}$	1400	31.2 ± 0.5	$+4 \pm 3$
	124.3	$3.40 \pm 0.05 \times 10^{-4}$			
III	101.3	$1.10 \pm 0.03 \times 10^{-4}$	5700	30.7 ± 1.0	$+5 \pm 3$
	124.3	$1.20 \pm 0.07 \times 10^{-3}$			
IV	85.0	$3.00 \pm 0.07 \times 10^{-4}$	120,000	29.4 ± 0.5	$+7 \pm 1$
	109.5	$4.22 \pm 0.08 \times 10^{-3}$			
V	35.00	0.132 ± 0.005	1.8×10^{10}	17.5 ± 1.0	-6 ± 3
	50.00	0.494 ± 0.02			
VI	37.0	$5.42 \pm 0.06 \times 10^{-3}$	8.0×10^{8}	21.0 ± 1.2	-1 ± 4
	50.00	$2.22 \pm 0.10 \times 10^{-2}$			
VII	37.0	$1.14 \pm 0.04 \times 10^{-4}$	1.9×10^{8}	22.9 ± 1.6	$+5 \pm 2$
	50.00	$5.16 \pm 0.22 \times 10^{-3}$			

[a] See ref 8. [b] Calculated from the published data (published calculation = −15).

Scheme I



at 6.59 due to the methyl hydrogens.[15] Catalytic reduction of V on platinum with 2 moles of hydrogen afforded the corresponding dimethylpiperidinium salt. No isomerization to the 1,4 isomer was noted, even under much more vigorous conditions than those used for the deuterium-exchange kinetics (0.5 M NaOH in H_2O for 45 min at 100°). No new N-methyl or olefin peaks appeared in the nmr spectrum. Only the 1,2 isomer was reisolated.

Despite unsuccessful attempts at alkylation of dihydropyridines,[16] it was found possible to allow N-methyl-1,2-dihydroquinoline[17] and N-methyl-2-phenyl-1,2-dihydroquinoline[18] to react with triethyloxonium fluoroborate to give the N-methyl-N-ethyl-1,2-dihydroquinolinium (VI) and N-methyl-N-ethyl-2-phenyl-1,2-dihydroquinolinium (VII) salts, respectively.

That the ethylation indeed took place on the nitrogen atom is clear from the observation that of the sixteen possible nmr lines for the two nonequivalent N-methylene hydrogens (*i.e.*, attached to an asymmetric nitrogen atom), eight and thirteen lines are found for VI and VII, respectively. Since the N-methyl hydrogens of VII are shifted τ 0.45 upfield from those of VI, it is reasonable to assume that the N-methyl group and the phenyl groups in VII are *cis* to each other. This assumption is also reasonable on steric grounds, since it means that the ethyl group has entered from the less hindered side. As in the case of V, under alkaline conditions used for the deuterium exchange kinetics, neither of the two dihydroquinolinium salts, VI nor VII, isomerized to the 1,4 isomer, since no new nmr peaks were found. Only the 1,2 isomers were reisolated.

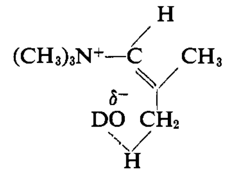
Results and Discussion

Equilibrium constants between I and II were obtained at 100 and 161°. They were 58.1 ± 1 and 41.8 ± 1, respectively, with II favored. This gives $\Delta H = 1.82 \pm 0.1$ kcal/mole and $\Delta S = 3.2 \pm 1$ eu. The kinetic data on deuterium exchange and isomerization are summarized in Tables I and II.

One way of rationalizing the preference of the double bond for being away from the positive charge is to consider the stabilization energy resulting from the polarization of the bonds to the quaternary nitrogen. In I the positive nitrogen is attempting to polarize a vinyl bond but in II a much more polarizable allylic bond is substituted.

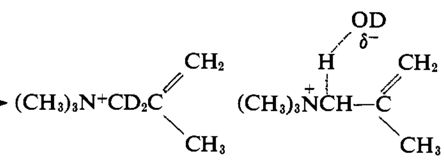
Using data on the rate of isomerization of I to II, the rates of deuterium exchange at aliphatic and olefin positions of II and the heat of isomerization obtained from the equilibrium constants for interconversion, the following enthalpies are obtained for the transition states, with the enthalpy of II taken as zero. It may

I ⟶ II



30.1 ± 0.3 kcal/mole (1)

II ⟶



31.2 ± 0.5 (2)

---

(15) The samples of V used for the spectra were prepared *via* a procedure (see the Experimental Section) differing from that used by T. Record. The sample originally prepared by T. Record (and used in the kinetic study) showed a small contamination of III, as evidenced by the integrals of the nmr spectral peaks areas.

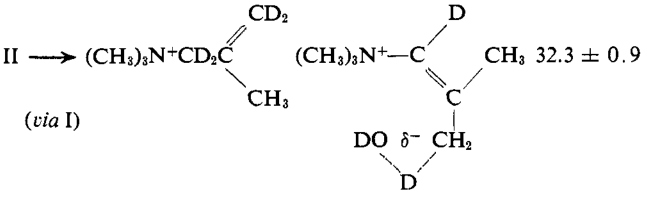
(16) M. Saunders and E. H. Gold, *J. Org. Chem.*, **27**, 1439 (1962).

(17) H. Schmid and P. Karrer, *Helv. Chim. Acta*, **32**, 960 (1949).

(18) J. Meisenheimer, E. Stotz, and K. Baver, *Ber.*, **58**, 2320 (1925).

Table II. Other Exchange and Isomerization Rates

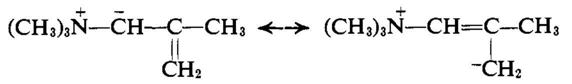
Compd	Reactive site	Temp, °C	k, l./mole sec	ΔH^*, kcal/mole	ΔS^*, eu	Calcd k, l./mole sec at 50°
I	CH_3 (*cis*)	101.3 ± 0.2	$5.82 \pm 0.07 \times 10^{-4}$	30.1 ± 0.3	$+6.5 \pm 1$	9.87×10^{-7}
		124.3 ± 0.2	$6.07 \pm 0.08 \times 10^{-3}$			
II	$=CH_2$ (*via* I)	124.3 ± 0.2	$1.90 \pm 0.10 \times 10^{-5}$	32.3 ± 0.9	-0.4 ± 3	1.61×10^{-9}
		146.8 ± 0.2	$1.68 \pm 0.10 \times 10^{-4}$			
III	H-5	101.3 ± 0.2	$4.4 \pm 0.7 \times 10^{-5}$	27.0 ± 4.5	-7 ± 12	$1 \pm 5.5 \times 10^{-7}$
		124.3 ± 0.2	$3.6 \pm 0.7 \times 10^{-4}$			
V	H-4	35.05 ± 0.03	$1.19 \pm 0.05 \times 10^{-3}$	19.6 ± 1.0	-8.5 ± 3	4.93×10^{-3}
		50.00 ± 0.03	$4.93 \pm 0.17 \times 10^{-3}$			
VI	H-4	50.00 ± 0.03	$3.43 \pm 0.14 \times 10^{-4}$	22.6 ± 1.0	-4.5 ± 3	3.43×10^{-4}
VII	H-4	50.00 ± 0.03	7×10^{-4}			7×10^{-4}
		69.0 ± 0.2	8×10^{-3}			



(3)

be seen that transition states 1 and 2, which are related to the two modes of formation or reprotonation of the ylide (coming from or going to I or II), are very similar in enthalpy, the difference being within the experimental error. At a single temperature 124°, the ratio of rates of formation of 1 and 2 may be determined with greater precision. Protonation occurs on the α carbon about three times faster than on the γ carbon. We considered two extreme models for the transition states of the reactions studied. We were concerned with whether the transition states might be more closely approximated as the ylide or as the starting ammonium salts plus an hydroxide ion. Clearly the true situation could lie somewhere between these extremes but we did not feel that the evidence justified greater precision. We concluded that, to the extent that the transition states were similar to the ammonium salts, a much larger difference in enthalpy should be expected, since approach of hydroxide ion to the α position produces a much larger gain in electrostatic energy than approach to the γ position. We therefore feel that the transition states 1 and 2 probably resemble the ylide to a much greater extent than I or II. Another point of view is that the near equivalence in rate of protonation of the ylide on the α and γ positions argues that there is a low barrier for protonation at either position. A very low barrier would make the rates diffusion controlled and therefore equal. Again, we conclude that the transition states lie close to the ylide. Similar small rate ratios between protonation rates at the α and γ positions were obtained for compounds III, V, VI, and VII. Thus similar conclusions may be drawn, and we infer that measurements of the rates of deuterium exchange in these systems are relevant toward conclusions concerning the energies of the ylides formed as intermediates in these reactions. Of course, we cannot claim to find *precise* energies for the ylides.

Referring to Table I, it may be seen that substituting a vinyl group for a hydrogen on tetramethylammonium produces a rate increase of 1400 at 50° and that the enthalpy of activation is lowered approximately 1 kcal/mole. Allylic resonance in the anion portion of the ylide from II would be expected on the basis of simple molecular orbital calculations[19] to lead to a rather large energy gain (0.8β) of approximately 15 kcal/mole. Exchange of the CH_2 adjacent to the quaternary nitrogen in IV is 120,000 times faster than exchange of tetramethylammonium at 50° and the activation energy is approximately 2.8 kcal/mole lower. Again a much larger effect would be predicted on the basis of expected resonance stabilization in this doubly allylic system. In formation of anions from simple olefins, large effects are observed as predicted.[20] Pentadiene-1,4 was found to isomerize in strong base 1.4×10^5 times faster than butene-1, for example. Therefore, some important factor must have been left out of the considerations related to the exchange in the unsaturated ammonium salts. If we consider the resonance structures for the ylide



$$(CH_3)_3\overset{+}{N}-\overset{-}{C}H-\underset{\underset{CH_2}{\|}}{C}-CH_3 \longleftrightarrow (CH_3)_3\overset{+}{N}-CH=\underset{\underset{^-CH_2}{|}}{C}-CH_3$$

VIIIA VIIIB

we see that a basic requirement for substantial lowering of the energy by resonance is not present, since the energies of these two canonical forms differ markedly in electrostatic interaction between the positive and negative charge. From a very rough calculation (see Appendix A) it was concluded that electrostatic interaction was worth about 35 kcal/mole in VIIIA, but only 8 kcal/mole in VIIIB; therefore most of the charge should remain on the α carbon and resonance stabilization should affect the energy only little. The same factors would result in a smaller than expected contribution of resonance energy in the ylide from IV. Since this effect proceeds from the interaction of positive and negative charge, it may be described as *electrostatic inhibition of resonance*. This effect, of course, is only a specific example of the inhibition of resonance occurring when resonance structures differ in energy and is widely used in explaining the unimportance of zwitterionic resonance forms in common neutral molecules.

A number of additional results of this work may be discussed satisfactorily using this concept. From the study of deuterium exchange in II, it may be deduced that only one of the two possible ylides (*cis* or *trans*) is formed, since at long reaction times the olefin CH_2

---

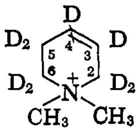
[19] A. Streitwieser, Jr., "Molecular Orbital Theory for Organic Chemists," John Wiley and Sons, Inc., New York, N. Y., 1963.

[20] A. Schreisheim, C. A. Rowe, Jr., and L. Noslund, *J. Am. Chem. Soc.*, 85, 2112 (1963).

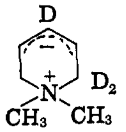
hydrogens are replaced by deuterium but the C-methyl hydrogens remain. It may be seen that if both the *cis* and *trans* ylides were formed, that I, which is an intermediate in this reaction, might lose a proton from either the *cis* or *trans* C-methyl and that this would result in introduction of deuterium into the C-methyl of II. Since this is not observed, we conclude that the reaction is stereospecific. From the fact that the exchange of CH_2 in III, which is constrained to give a *cis* ylide, goes at approximately the same rate as exchange in II, we conclude that the *cis* ylide is the favored one. This result would be predicted on the basis of greater electrostatic interaction between the positive charge and the fraction of negative charge on the α carbon in the *cis* ylide.

Since the lack of help from full allylic resonance was attributed to the lack of equivalence between the sites of negative charge in the resonance forms, it was decided to make compound V, which gives an ylide in which two of the three resonance forms have negative charge adjacent to the quaternary nitrogen. The enormous acceleration of rate of exchange (1.8×10^{10} with respect to tetramethylammonium and 10^5 over V) and the reduction of activation enthalpy (12 kcal/mole over IV) are in agreement with this conclusion. The exchange kinetics of V are complicated when carried beyond the initial period, since two different dideuterio compounds may be formed and the rate constants between the various species present include statistical factors and isotope effects. Therefore, it was necessary to employ a computer program to obtain the rate constant (see Appendix B).

Examination of recovered quaternary ammonium salt from the deuterium exchange of III showed that IX was the eventual product. This may be explained by



IX



X

applying considerations of electrostatic energy as above. Initial exchange would be expected and is observed at 2 and 4 as in II. Abstraction of the 5 hydrogen to form X would eventually yield the observed products, since reprotonation can occur on 3 or 5 and deuterium from 2 can then appear in 6. The experimental data in this case are not nearly as precise as in the other systems since a side reaction of Hoffman elimination also occurs and, while the product does not produce peaks in the spectrum, quaternary salt is thus used up. As far as can be determined, however, this two-stage mechanism is in agreement with the experimental results, the most important observation being that the *rate* of appearance of deuterium in 6 (which can be observed separately) increases with time to a maximum and then falls off. This is to be expected as exchange must occur in 2 previous to the isomerization process. From the data obtained it appears that the rate of formation of ylide X is approximately one-fourth the rate of formation of the 2,4-ylide. The explanation of this near equality in the transition-state free energies, and therefore probably also in the ylide energies, which we favor is that although the estimated electrostatic energy in the γ position is only approximately 17kcal/mole instead of 35 kcal/mole in the α position, the two α positions are equivalent and therefore the full resonance energy of the allylic system is now available. If this is about 15 kcal/mole then the energy of X would be expected to be approximately the same as that of the 2,4-ylide.

We therefore conclude that electrostatic energy in nitrogen ylides is extremely important, so much so that in order to maximize it in many cases resonance may be inhibited.

Experimental Section[21]

I. Preparation of Materials. 1. N,N,N-Trimethyl-1-isobutenylammonium Iodide (I). To a flask fitted with a reflux condenser, 21.0 g (0.21 mole) of 1-dimethylaminoisobutene-1[22] and 120 g (0.84 mole) of methyl iodide were added. The mixture was then heated at reflux for approximately 0.5 hr, after which it was heated overnight on a steam bath. The reaction mixture was filtered and washed with ether. One crystallization of the white salt from absolute ethanol yielded 43.0 g (85%) of white needles that melted at 146–148°. One further crystallization from absolute ethanol raised the melting point to 148–149°.

Anal.[10] Calcd for $C_7H_{16}NI$: C, 34.87; H, 6.69; N, 5.81; I, 52.63. Found: C, 34.70; H, 6.58; N, 5.83; I, 52.89.

2. N,N,N-Trimethyl-2-isobutenylammonium Iodide (II). In a flask fitted with a reflux condenser, 13.0 g (0.054 mole) of N,N,N-trimethyl-1-isobutenylammonium iodide was dissolved in 20 ml of 1.5 *N* sodium hydroxide solution and refluxed for 24 hr. The solution was neutralized with 47% hydriodic acid and evaporated to dryness. The remaining white solid was recrystallized twice from anhydrous ethanol, yielding 10.2 g (78.5%) of white needles that melted with decomposition at 205–206°.

Anal.[10] Calcd for $C_7H_{16}NI$: C, 34.87; H, 6.69; N, 5.81; I, 52.63. Found: C, 34.72; H, 6.65; N, 5.73; I, 52.83.

3. N,N-Dimethyl-1,2,5,6-tetrahydropyridinium Iodide (III). In a flask, fitted with a dropping funnel and a magnetic stirring bar, 10 g (0.045 mole) of N-methylpyridinium iodide, dissolved in 75 ml of water, and 50 ml of CCl_4 were added. To the stirred solution, 5.2 g (0.14 mole) of sodium borohydride dissolved in 50 ml of water containing 2 drops of 10 *M* sodium hydroxide was added dropwise over a 30-min period. The reaction mixture was stirred for 2 more hr. The layers were separated and the water layer was extracted three times with 15-ml portions of CCl_4. The water layer was discarded, and the CCl_4 layer was dried over magnesium sulfate. To the CCl_4 solution of N-methyl-1,2,5,6-tetrahydropyridine, 12.8 g (0.091 mole) of methyl iodide was added. The mixture was allowed to stand at room temperature for 24 hr, and the white salt was filtered and washed with ether, yielding 10.5 g (97%) of the desired dimethyl salt melting at 275–277°. Recrystallization from absolute ethanol afforded 6.6 g (61%) of the pure N,N-dimethyl-1,2,5,6-tetrahydropyridinium iodide that melted at 278–279° (lit.[11] mp 278°).

4. 1-Dimethylaminopentadiene-2,4. N,N-Dimethyl-1,2,5,6-tetrahydropyridinium iodide (8.0 g, 0.034 mole) was dissolved in 75 ml of 10 *N* KOH solution and refluxed under nitrogen for 2 hr. The mixture was extracted three times with 30-ml portions of ether. The combined and dried ether extract was distilled, affording 2.5 g (67%) of the desired amine that distilled at 130° (lit.[12] bp 129–129.3°).

Reaction under the Exchange Conditions for III. Into a tube, 1.5 ml of a D_2O solution, 0.3 *N* in NaI and 1.0 *N* in NaOD, and 0.06 g of 1-dimethylaminopentadiene-2,4 were added. The tube was sealed and heated to 100° for 15 hr. The amine layer was then removed and dissolved in 1 ml of carbon tetrachloride, and the

---

[21] All melting points are uncorrected. Infrared spectra were taken on a Perkin-Elmer Model 221 spectrophotometer. A Cary Model 11 was used for taking ultraviolet spectra. Nmr spectra were recorded on a Varian Associates HR-60. All the kinetic work (integration of peak intensities) was done with a Varian Associates A-60 nuclear magnetic resonance spectrometer. Analyses were performed by Schwarzkopf Microanalytical Laboratory, Woodside, N. Y.

[22] 1-Dimethylaminoisobutene-1 was supplied by B. Platz[10] and was prepared from equimolar amounts of isobutyraldehyde and dimethylamine in the presence of calcium hydride. Its physical properties corresponded to those reported by Brannock, *et al.*,[11]

resultant solution was dried over molecular sieve pellets (Linde type 4A). An infrared spectrum of this solution showed no new peaks due to C–D stretching and was identical with an infrared spectrum of the starting material.

5. N,N,N-Trimethyl-2,4-pentadienylammonium Iodide (IV). N,N-Dimethyl-1,2,5,6-tetrahydropyridinium iodide (10.0 g, 0.418 mole) was dissolved in 100 ml of 10 *N* KOH solution and refluxed under nitrogen for 2 hr. The mixture was extracted with four 40-ml portions of ether. The combined and dried ether extract was added to 100 ml of ethanol containing 7.1 g (0.050 mole) of methyl iodide. After 1 day the mixture was filtered, affording 10.5 g (99%) of N,N,N-trimethyl-2,4-pentadienylammonium iodide that melted at 165–160.5°. Two crystallizations from ethanol raised the melting point to 170–171.5° (lit.[12] mp 169°). The ultraviolet spectrum in absolute ethanol was 222 mμ (log ϵ 4.58).

6. N,N-Dimethyl-1,2-dihydropyridinium Bromide (V). a. N,-N-Dimethyl-3,4-dibromopiperidinium Bromide. N,N-Dimethyl-1,2,5,6-tetrahydropyridinium iodide (10.0 g, 0.042 mole) was added to 100 ml of 1,2-dimethoxyethane. Upon addition of 20.0 g (0.126 mole) of bromine, the salt went into solution. The water-cooled solution was irradiated by a sun lamp for 3 hr. In order to decompose the resulting perbromide, 50 ml of cyclohexene was added dropwise, and the solution was refluxed for 30 min. Two crystallizations of the precipitated salt from methanol afforded 10.0 g (68%) of N,N-dimethyl-3,4-dibromopiperidinium bromide that melted at 206.5–207.5°.

Anal.[16] Calcd for $C_7H_{14}NBr_3$: C, 23.83; H, 3.98; N, 3.98; Br, 68.19. Found: C, 23.74; H, 3.99; N, 3.98; Br, 67.91.

b. Dehydrobromination of N,N-Dimethyl-3,4-dibromopiperidinium Bromide. N,N-Dimethyl-3,4-dibromopiperidinium bromide (7.0 g, 0.0199 mole) and 2.36 g (0.042 mole) of KOH were dissolved and refluxed in 75 ml of methanol for 2 hr. The solution was acidified with hydrobromic acid, filtered to remove precipitated KBr, and evaporated to dryness. One recrystallization from ethanol–ethyl acetate afforded 2.3 g (42.3%) of N,N-dimethyl-1,2-dihydropyridinium bromide. It melted at 167–170° with decomposition. Two further crystallizations from isopropyl alcohol raised the melting point to 174–174.3° with decomposition. The sample was placed in the oil bath at 170°, and the temperature was raised 1° per minute.

Anal.[15] Calcd for $C_7H_{12}NBr$; C, 44.30; H, 6.37; N, 7.37. Found: C, 44.27; H, 6.56; N, 7.15.

In a microhydrogenation apparatus, 0.100 g of PtO_2 in 50 ml of methanol was reduced with hydrogen. To this mixture, 0.190 g (0.001 mole) of N,N-dimethyl-1,2-dihydropyridinium bromide was added. The mixture was stirred, and in 20 min 0.00206 mole of hydrogen was taken up, with no further hydrogen uptake. N,N-Dimethylpiperidinium bromide (0.110 g, 58%) that melted at 340–345° (lit.[23] mp 175–180°) was obtained. The literature melting point is apparently in error since an authentic sample of the bromide salt, prepared *via* metathesis of N,N-dimethylpiperidinium iodide with Ag_2O followed by addition of HBr, melted at 341–347° (mmp 340–346°). The infrared spectra of the authentic bromide and the hydrogenation product were identical.

The hydrogenation product was converted to the iodide salt by treatment with Ag_2O followed by addition of HI, and melted at 350–355° (lit.[24] mp 351°). A mixture melting point with an authentic iodide sample was 350–354°. The infrared spectra of the authentic iodide and the iodide obtained from the hydrogenation product were identical.

7. Triethyloxonium Fluoroborate. Triethyloxonium fluoroborate was prepared according to the method of Meerwein, *et al.*[25] It melted sharply at 92° (lit.[25] mp 92°).

8. N-Methyl-1,2-dihydroquinoline. N-Methyl-1,2-dihydroquinoline was prepared according to the method of Schmid and Karrer[17] from 19.5 g (0.072 mole) of N-methylquinolinium iodide and 125 ml of 0.7 *M* lithium aluminum hydride in ether. The nmr spectrum of the distilled yellow oil, obtained upon evaporation of the ether, was consistent with that expected for the 1,2-dihydro compound with approximately 15% of the N-methyl-1,2,3,4-tetrahydroquinoline as an impurity.

9. N-Methyl-2-phenyl-1,2-dihydroquinoline. N-Methyl-2-phenyl-1,2-dihydroquinoline was prepared in 69% yield from N-methylquinolinium iodide and phenylmagnesium bromide according to the method of Meisenheimer, *et al.*[18] The compound was recrystallized from 95% ethanol, and melted at 88–89° (lit.[18] mp 89–90°).

10. N-Methyl-N-ethyl-1,2-dihydroquinolinium Salts (VI). a. N-Methyl-N-ethyl-1,2-dihydroquinolinium Picrate. In a flask fitted with a reflux condenser, 1.4 g (0.072 mole) of triethyloxonium fluoroborate dissolved in 60 ml of methylene chloride was added to the unpurified N-methyl-1,2-dihydroquinoline all at once, resulting in a vigorous exothermic reaction. The solution was refluxed on a steam bath for 10 min and the methylene chloride was removed on a rotary evaporator, yielding the desired fluoroborate salt as a dark oil that could not be crystallized. The dark oil was redissolved in 60 ml of methylene chloride, and 16.5 g (0.072 mole) of picric acid dissolved in 40 ml of acetone was added. The solvent was removed and the resulting yellow oil was crystallized once from 25% aqueous ethanol, yielding 25.0 g (86.5%, based on N-methylquinolinium iodide) of yellow needles that melted at 148–151°. Two more recrystallizations from 25% ethanol afforded 23.0 g (79%) of N-methyl-N-ethyl-1,2-dihydroquinolinium picrate that melted at 151–152°.

Anal. Calcd for $C_{18}H_{18}N_4O_7$: C, 53.73; H, 4.51; N, 13.93. Found: C, 53.46; H, 4.74; N, 13.87.

b. N-Methyl-N-ethyl-1,2-dihydroquinolinium Chloride. Pure N-methyl-N-ethyl-1,2-dihydroquinolinium picrate (10.0 g, 0.0249 mole) dissolved in 200 ml of 50% aqueous acetone was treated with five batches of Dowex AG 3-X4 anion-exchange resin in the chloride form (35% moisture content), the first batch weighing 20 g and the subsequent four batches weighing 10 g each. The resulting colorless solution was evaporated at 40° *in vacuo*, yielding an exceedingly hygroscopic salt that could not be recrystallized. The salt was ground to a fine powder in a drybox, and the remaining traces of solvent were removed at 10^{-5} mm for 2 days. N-Methyl-N-ethyl-1,2-dihydroquinolinium chloride (4.6 g 88%) was obtained as a white powder. The chloride began to decompose at 120°, became red, and finally melted with effervesence at 125–138°.

The nmr spectrum of the chloride was exactly the same as that of the picrate salt except for the disappearance of the peak due to the two aromatic protons of the picrate anion.

11. N-Methyl-N-ethyl-2-phenyl-1,2-dihydroquinolinium Salts (VII). a. N-Methyl-N-ethyl-2-phenyl-1,2-dihydroquinolinium Fluoroborate. In a flask, fitted with a reflux condenser, 6.7 g (0.035 mole) of triethyloxonium fluoroborate was added in one portion to a solution of 5.5 g (0.025 mole) of N-methyl-2-phenyl-1,2-dihydroquinoline dissolved in 50 ml of methylene chloride. The solution was refluxed on a steam bath for 1.5 hr. The solvent was removed on a rotary evaporator and the resulting white solid was washed with ether, and melted at 110–150° with decomposition. Two crystallizations from absolute ethanol afforded 6.8 g (81%) of white needles that melted with decomposition at 176–177°.

Anal. Calcd for $C_{18}H_{20}NBF_4$; C, 64.12; H, 5.98; N, 4.16. Found: C, 63.92; H, 6.10; N, 4.37.

b. N-Methyl-N-ethyl-2-phenyl-1,2-dihydroquinolinium Picrate. To 6.8 g (0.0202 mole) of N-methyl-N-ethyl-2-phenyl-1,2-dihydroquinolinium fluoroborate dissolved in 60 ml of methylene chloride, 6.4 g (0.0280 mole) of picric acid dissolved in 20 ml of acetone was added. Evaporation of the solvent, followed by crystallization of the resulting yellow oil from a 30% aqueous ethanol solution, afforded 9.7 g (99%) of yellow needles that melted with decomposition at 144–146°. Two subsequent recrystallizations from 50% aqueous ethanol yielded 8.9 g of the pure N-methyl-N-ethyl-2-phenyl-1,2-dihydroquinolinium picrate that melted with decomposition at 145.5–146.5°.

Anal. Calcd for $C_{24}H_{22}N_4O_7$: C, 60.24; H, 4.63; N, 11.71. Found: C, 60.14; H, 4.81; N, 11.80.

c. N-Methyl-N-ethyl-2-phenyl-1,2-dihydroquinolinium Chloride. Pure N-methyl-N-ethyl-2-phenyl-1,2-dihydroquinolinium picrate (9.6 g, 0.0201 mole) dissolved in 200 ml of 50% aqueous acetone was treated with five batches of Dowex AG 3-X4 anion exchange resin in the chloride form (35% moisture content) of total weight 60 g. The colorless solution was evaporated *in vacuo*, yielding 5.2 g (91%) of white chloride salt melting over 124–127° dec. The chloride was recrystallized three times by precipitation with ether from methanol–acetone yielding white needles melting with decomposition at 133–135° (placing the melting point tube in the oil bath at 129° and raising the temperature 2° per minute).

Anal. Calcd for $C_{18}H_{20}NCl \cdot H_2O$: C, 71.15; H, 7.30; N, 4.61. Found: C, 71.35; H, 7.56; N, 4.69.

II. Base(OD⁻)-Catalyzed Deuterium Exchange Kinetics. 1. General Procedure. a. Sodium Deuterioxide Solutions. The

---

(23) J. v. Braun, *Ber.*, **33**, 2734 (1900).

(24) J. v. Braun, W. Teuffert, and K. Weiszbach, *Ann.*, **472**, 134 (1929).

(25) H. Meerwein, G. Hinz, P. Hoffmann, E. Kronig, and E. Pfeil, *J. Prakt. Chem.*, **147**, 257 (1937).

D_2O used was 99.8% pure, and was degassed and stored under nitrogen prior to preparing the solutions. The deuterioxide solutions were prepared under nitrogen, either by adding clean sodium to the D_2O or by diluting more concentrated solutions.

b. **Salt Solutions.** The salt solutions were prepared by weight. The solution densities were then determined by weighing syringed aliquots on a microbalance. The salt concentrations were then calculated to within ±1%. The solutions were prepared and stored under nitrogen in glass containers fitted with rubber septum covers.

c. **Reaction Solutions and Kinetics Runs.** All the reaction solutions were made 0.31 *M* with respect to the organic salts. In each case, exchanged starting material was recovered and compared with nondeuterated starting material using melting points and mixture melting points. Thin-walled, 5-mm (outside diameter) Pyrex tubing was used for the kinetic runs carried out at 69° and below. For the higher temperature work, standard-walled, 5-mm alkali-resistant tubing (Corning No. 7280) was employed.

All the exchange reactions were followed by observing the disappearance of the nmr peaks due to the hydrogen atoms of interest, by integrating the peak areas at successive times. Five integrated spectra were taken for each kinetic point. Titration of the solutions was carried out under nitrogen, using standardized HCl and employing a Gilmont microtitrator. Four methods were used to follow the kinetics.

a. **Method 1A.** The proper amounts of salts and base solutions to make up the desired salt and base concentrations were injected, with a syringe, into tubes that were previously flushed with nitrogen and fitted with rubber septum covers. These solutions were immediately frozen and the tubes were sealed. The reaction was followed by removing the tube at various intervals from the thermostated bath and immediately quenching the reaction by freezing the solution in Dry Ice-acetone. The solution was then warmed to room temperature and the integrated spectrum was taken, after which the solution was refrozen until it was replaced in the thermostated bath. Sample solutions were titrated at the beginning and end of the runs.

b. **Method 1B.** This method was the same as method 1A, except that a different tube was used for each time interval. If alkali-resistant tubing was used, the solutions were first syringed into the larger inner diameter thin-walled tubing before integrating the spectra.

c. **Method 2A.** The reaction solutions were prepared on a large scale under nitrogen and then syringed into the individual tubes as in method 1A. The reactions were followed as in method 1A.

d. **Method 2B.** This method was the same as method 2A, except that a different tube was used for each time interval. The same procedure as in method 1B was used with regard to alkali-resistant tubing.

e. **Errors.** The standard deviations of the results of titration were generally less than 1.5%. The largest source of error by far was in evaluating the integrals. In most cases this could be done anywhere from ±1 to ±3%. In general ±5% of the standard deviation was the greatest limit (except in the case of N,N-dimethyl-1,2,5,6-tetrahydropyridinium iodide). Generally, fairly good straight lines in first-order plots were obtained, and each slope was determined by visually fitting the best straight line to the experimental points.

Changes in the base concentration with time were not observed except in the cases of N,N-dimethyl-1,2,5,6-tetrahydropyridinium iodide, N,N,N-trimethylisobutenylammonium iodide and N-methyl-N-ethyl-2-phenyl-1,2-dihydroquinolinium chloride. In these cases correction was made for the base consumed.

f. **Equilibrium between I and II.** Integration of the relative areas of the two N-methyl peaks as well as a direct comparison of their relative peak heights (despite the fact that they were both sharp peaks and due to hydrogens of a very similar nature) proved to be quite unreliable. However, by first calibrating the HR-60 spectrometer with known mixtures of the two isomers at the same total concentration (0.31 *M*) as the equilibrium mixtures, a direct comparison of the relative heights of the two N-methyl peaks afforded results with a precision of ±2%.

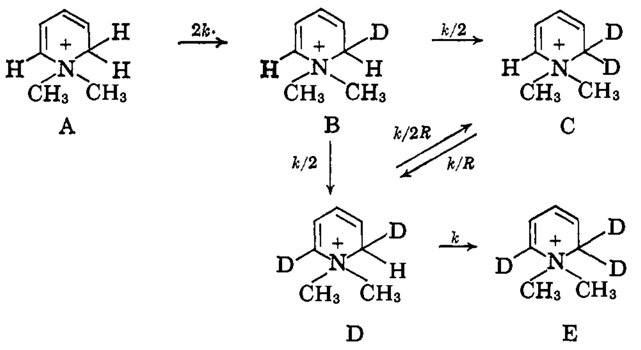
The samples at 100 and 161° were equilibrated in 1 *N* aqueous NaOH solution for 12 and 2 hr, respectively.

Appendix A

Approximate calculation of electrostatic energies of the ylides was carried out using the Kirkwood–Westheimer[26] treatment. Normal bond distances and angles were assumed, and various radii for the cavity in the high dielectric constant solvents were tried. A range of results was obtained using a range of reasonable seeming radii of cavities in the solvent. The range of results was taken as the uncertainty. The results were: for tetramethylammonium ylide 35 ± 10, for the 2, 3, and 4 ylides from dimethylpiperidinium, respectively, 36 ± 10, 13 ± 5, and 9 ± 3 kcal/mole. Using these figures an activation energy leading to the neopentyl anion of approximately 67 kcal/mole is predicted by taking away the electrostatic interaction energy in tetramethylammonium.

Appendix B

Calculation of the Rate Constant from Exchange Data of V. The rate of disappearance of CH_2 hydrogens in V does not give the rate constant for proton abstraction directly since all the steps illustrated below are involved



where *k* is the rate constant for abstraction of a proton and *R* is the isotope effect relating abstraction of protons to removal of deuterium. Exchange of the hydrogen at 4 also occurs through protonation of the intermediate ylide to give the 1,4-dihydropyridinium salt followed by rapid isomerization back to the stable 1,2-dihydro isomer. Since no appreciable concentrations of the 1,4-dihydro compound accumulates, it can be neglected.

Although solution of the set of differential equations arising from these reactions might be possible, it would be difficult and the results difficult to use. Instead, a program was written for the IBM 709 computer which numerically integrates these differential equations. During the course of integration the magnitude of quantities which would be observable is calculated. In this case the absorption under the CH_2 peak is found as 2[A] + [B] + [D]. When the observed dependence of this quantity is fit by calculation, the time equivalent to the integration step is found and from this the rate constant can be easily found.

This technique is of great help in treating data from complex reactions, since little labor and computer time are required.

---

[26] J. G. Kirkwood and F. H. Westheimer, *J. Chem. Phys.*, **6**, 506 (1938).