The Deuteration of Some N-Methyl-4-pyridones

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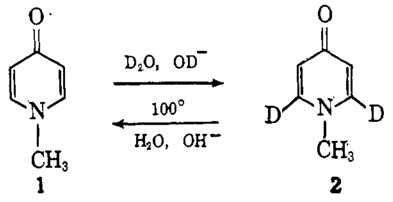
In contrast to other α,β-unsaturated carbonyl systems N-methyl-4-pyridone (**1**), *3,5-dimethyl-N-methyl-4-pyridone* (**3**), *and 3,5-dibromo-N-methyl-4-pyridone* (**9**) *substitute deuterium for protium at the β-(2 and 6)-position in basic deuterium oxide at 100°. A mechanistic proposal, supported by kinetic data, is given for these substitutions.*

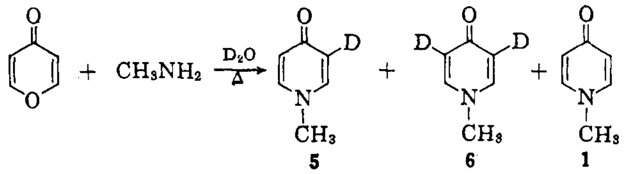
The base-catalyzed protium–deuterium exchange of the hydrogen located on the α-carbon atom has been reported for a number of α,β-unsaturated carbonyl compounds.[2-5] In marked contrast to this, the base-catalyzed deuterium exchange of N-methyl-4-pyridone (**1**) leads to substitution at the β-(2 and 6) position of the unsaturated system.[6,7] The present paper details the evidence, provides additional examples, and proposes a mechanism for this reaction.

Results

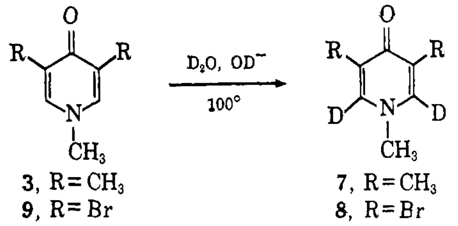
Deuterations. Treatment of N-methyl-4-pyridone (**1**) with 0.5 *N* sodium deuteroxide at 100° for 12 hr. yielded a product which was shown by infrared, ultraviolet, n.m.r. (*vide infra*), and mass spectroscopic criteria to be 92% N-methyl-4-pyridone-2,6-d_2 (**2**) and 8% N-methyl-4-pyridone-2-*d* in 39% isolated yield. A preparative experiment yielded 58% of **2**. These yields apparently reflect the difficulty of isolation and purification since ultraviolet, n.m.r., and mass spectral analyses of subsequent kinetic runs indicated that **2** is the major product of the reaction. N-Methyl-4-pyridone-2,6-d_2 could be reconverted to the unlabeled compound **1** in 56% isolated yield by heating at 95–98° with 1.0 *N* aqueous sodium hydroxide for 9 hr. Similar treatment of **1** at pD 8.5 or with strong acid in deuterium oxide did not lead to measurable (>5%) deuterium incorporation.[8]



Structural Assignments. The positional assignment of the deuterium atoms in **2** is based on a comparison of the chemical shifts of the ring protons of 3,5-dimethyl-N-methyl-4-pyridone (**3**) (H-2 and H-6 at $\delta = 8.13$ p.p.m.), 2,6-dimethyl-N-methyl-4-pyridone (**4**) (H-3 and H-5 at $\delta = 6.88$ p.p.m.), and N-methyl-4-pyridone (**1**) (H-2 and H-6 at $\delta = 8.28$ p.p.m., H-3 and H-5 at $\delta = 7.01$ p.p.m.)[9] with the chemical shift observed for the ring protons in N-methyl-4-pyridone-2,6-d_2 (**2**) (H-3 and H-5 at $\delta = 7.05$ p.p.m.). Confirmation of the critical chemical shift assignments comes from the n.m.r. spectrum of a mixture of N-methyl-4-pyridone-3-*d* (**5**, 50%) and N-methyl-4-pyridone-3,5-d_2 (**6**, 41%) prepared by treatment of 4-pyrone with methylamine in deuterium oxide. In the spectrum of the product mixture the resonance at $\delta = 7.01$ p.p.m. (H-3 and H-5) is *ca.* one-third of the area of the signal at $\delta = 8.28$ p.p.m. (H-2 and H-6), in agreement with the mass spectral data used above to determine the relative amounts of monodeuterated and dideuterated compounds. The formation of **5** and **6** can readily be accounted for by an imine–enamine or keto–enol tautomerism of the ring-opened intermediates usually formulated to rationalize the course of this reaction.[10]



Additional support for the assigned course of the base-catalyzed deuteration of **1** is found in the fact that 3,5-dimethyl-N-methyl-4-pyridone-2,6-d_2 (**7**) and 3,5-



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(1) Standard Oil of California Fellow, 1964–1965.

(2) P. Yates and L. L. Williams, *J. Am. Chem. Soc.*, **80**, 5896 (1958).

(3) M. F. Zinn, T. M. Harris, D. G. Hill, and C. R. Hauser, *ibid.*, **85**, 71 (1963); B. W. Rockett, T. M. Harris, and C. R. Hauser, *ibid.*, **85**, 3491 (1963).

(4) R. H. Shapiro, J. M. Wilson, and C. Djerassi, *Steroids*, **1**, 1 (1963).

(5) J. Warkentin and L. K. M. Lam, *Can. J. Chem.*, **42**, 1676 (1964).

(6) A cyanide-catalyzed deuterium exchange at the 4-position of the nicotinamide pyridinium ring of DPN has been reported by A. San Pietro, *J. Biol. Chem.*, **217**, 579 (1955). In this case the activation required for proton removal is presumably provided in the usual manner by the cyanide group in the cyanide–DPN adduct.

(7) A preliminary report of this reaction has appeared; P. Beak and J. Bonham, *Tetrahedron Letters*, 3083 (1964).

(8) This result is different from the case of 4-pyridone which is reported to substitute deuterium for protium at the 3- and 5-positions in strong acid: P. J. Van Der Haak and Th. J. DeBoer, *Rec. trav. chim.*, **83**, 186 (1964).

(9) The chemical shifts in δ, p.p.m., are extrapolated to infinite dilution relative to external tetramethylsilane for deuterium oxide solutions. (a) These relative chemical shifts are in agreement with those of R. A. Y. Jones, A. R. Katritzky, and J. M. Lagowski, *Chem. Ind.* (London), 870 (1960). (b) The chemical shifts refer to the centers of each multiplet. Analysis of the n.m.r. spectrum of **1** in deuteriochloroform solution as an A_2B_2 system provides a fit of the calculated and observed spectrum within experimental error with $J_{23} = J_{56} = 7.96$ c.p.s., $J_{25} = J_{36} = 0.01$ c.p.s., $J_{35} = J_{26} = 2.78$ c.p.s., and $\delta\nu_{AB} = 66.23$ c.p.s. We are grateful to Dr. J. Jonáš for advice during the course of this analysis and for the use of a computer program; J. Jonáš, W. Derbyshire, and H. S. Gutowsky, *J. Phys. Chem.*, **69**, 1 (1965), give a relevant discussion of this type of system.

(10) H. Meislich, "Pyridine and Its Derivatives," Part III, E. Klingsberg, Ed., John Wiley and Sons, Inc., New York, N. Y., 1962, pp. 552–560.

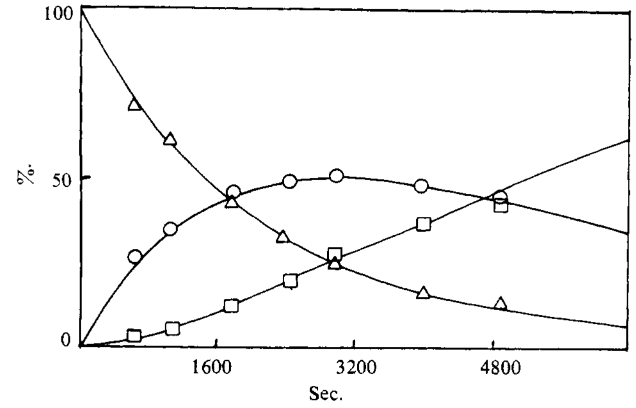
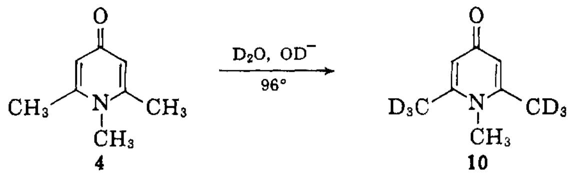


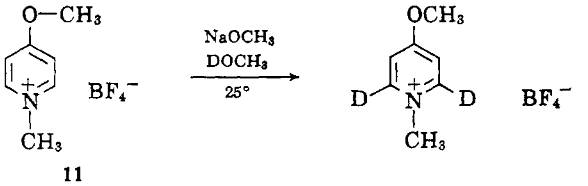
Figure 1. The amounts of N-methyl-4-pyridone (△), N-methyl-4-pyridone-2-d (○), and N-methyl-4-pyridone-2,6-d_2 (□) as a function of time in 0.471 M NaOD in deuterium oxide at 100°. The lines were drawn with the aid of an analog computer programmed for two consecutive first-order reactions.

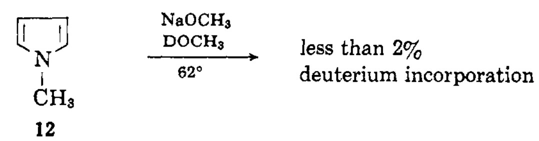
dibromo-N-methyl-4-pyridone-2,6-d_2 (**8**) can be prepared in 77 and 91% yields, respectively, by heating the corresponding unlabeled pyridones, **3** and **9**, in basic deuterium oxide. 3,5-Dibromo-N-methyl-4-pyridone (**9**) was regenerated from **8** in 64% yield by heating in strong aqueous base.

In contrast to the deuteration of **3** treatment of 2,6-dimethyl-N-methyl-4-pyridone (**4**) with 0.5 N base at 96° overnight led to deuterium incorporation at the C-methyl groups to produce **10**.



In a comparison of the base-catalyzed deuterations of molecules formally similar to **1** it was found that treatment of 4-methoxy-N-methylpyridinium fluoborate (**11**) with 0.85 N sodium methoxide in deuteriomethanol led to essentially complete selective substitution of deuterium at the ring carbon atoms adjacent to nitrogen within 15 min. at room temperature. On the other hand, N-methylpyrrole (**12**), pyridine, and 4-methoxypyridine gave less than 5% exchange on heating at 62° for 66 hr. in the same medium.[11] Under the latter conditions N-methyl-4-pyridone substituted 85% deuterium for protium at the ring atoms adjacent to nitrogen.





Kinetics. The rate of the over-all conversion of **1** to **2** as followed by n.m.r. was found to be first order in base and first order in N-methyl-4-pyridone over a concentration range of 0.5 to 1.5 N for both species. As summarized in Table I the kinetic data gave a second-order rate constant of 4.26 ± 0.21 × 10^{-4} l. mole^{-1} sec.$^{-1}$ as an average of ten runs. Titrations throughout the run established that base was constant to 95 ± 5% of the initial base concentration during the reaction, and ultraviolet analysis showed that the chromophore of N-methyl-4-pyridone was essentially invariant throughout the reaction. The rate of the formation of **2** in deuterium oxide with deuteroxide catalysis at 100° (k_H) was compared with the rate of formation of **1** from **2** in water with hydroxide catalysis at 100° (k_D) (Table II) and a k_H/k_D ratio of 1.23 ± 0.16 obtained.

Table I. Rates of Formation of N-Methyl-4-pyridone-2,6-d_2 (**2**) in Deuterium Oxide at 100°

NaOD, M	**1**, M	$k_{obsd} \times 10^4$, sec.$^{-1a}$	$k_{sp} \times 10^4$, l. mole^{-1} sec.$^{-1b}$	$k_{sp,av} \times 10^4$
0.471	0.499	1.91 ± 0.09	4.05	
0.471	0.521	1.94 ± 0.06	4.12	
0.471	0.980	2.05 ± 0.06	4.35	
0.471	1.04	1.81 ± 0.04	3.84	
0.471	1.38	2.09 ± 0.07	4.44	
0.471	1.48	2.05 ± 0.04	4.35	4.26 ± 0.21
0.945	0.535	3.97 ± 0.14	4.20	
0.945	0.45	3.81 ± 0.06	4.03	
1.530	0.5	7.15 ± 0.17	4.67	
1.530	0.5	6.89 ± 0.19	4.50	

[a] The first-order rates were calculated using a weighted, least-squares program. [b] The base concentration used in calculating k_{sp} was not corrected for a small carbonate error.

Table II. Rates of Formation of N-Methyl-4-pyridone in Water at 100°

NaOH, M	**2**, M	$k_{obsd} \times 10^4$, sec.$^{-1a}$	$k_{sp} \times 10^4$, l. mole^{-1} sec.$^{-1b}$	$k_{sp,av} \times 10^4$
1.00	0.56	3.07 ± 0.09	3.07	3.47 ± 0.27
1.00	0.56	3.81 ± 0.06	3.81	
1.00	0.56	3.53 ± 0.12	3.53	

[a] The first-order rates were calculated using a weighted, least-squares program. [b] The base concentration used in calculating k_{sp} was not corrected for a small carbonate error.

Further consideration of the reaction suggests that it proceeds in two steps with the rate of formation of the monodeuterio compound **13** being twice the rate of formation of **2** on a statistical basis. This sequence was tested by isolation of the organic material at seven points of one kinetic run and determination of the amounts of **1**, **2**, and **13** by mass spectrometry. The values obtained are shown in Figure 1. The data were fitted with the aid of an analog computer programmed for a two-step, consecutive, first-order sequence of reactions and the resultant rate constants obtained were

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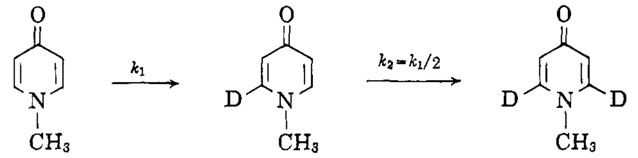
(11) (a) N-Methylpyrrole is reported to metallate at the 2-position: K. Hess and F. Wissing, *Ber.*, **47**, 1416 (1914); D. A. Shirley, B. H. Gross, and P. A. Rousell, *J. Org. Chem.*, **20**, 225 (1955); (b) Pyridine has been reported to undergo deuterium exchange at the 2- and 6-positions on heating in strongly basic deuterium oxide at 220° for 10 hr.: Y. Kawazoe, M. Ohnishi, and Y. Yoshioka, *Chem. Pharm. Bull.* (Tokyo), **12**, 1386 (1964).

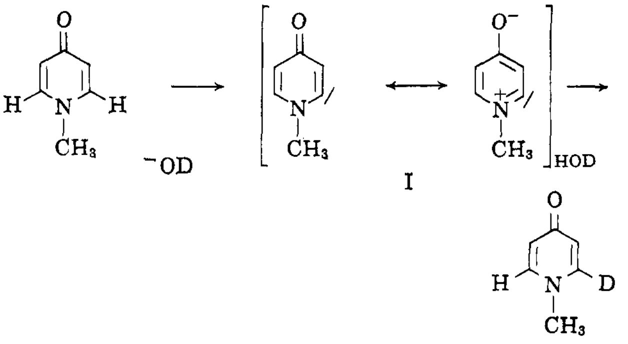


1 **13** **2**

$k_1 = 4.63 \times 10^{-4}$ sec.$^{-1}$ and $k_2 = 2.18 \times 10^{-4}$ sec.$^{-1}$ in accord with the proposed scheme. The analog computer used this data to synthesize the rate of disappearance of **1** plus one-half of **13**, the rate observed by the n.m.r. analysis.[12] The calculated rate of 2.25 $\times$ 10^{-4} sec.$^{-1}$ fits well with the observed rate of 2.05 $\times$ 10^{-4} sec.$^{-1}$ for this particular run.

Discussion

The base-catalyzed substitutions of deuterium at the 2- and 6-positions in N-methyl-4-pyridone may proceed by the pathway shown below. The direct removal of a proton from the ring-carbon atom adjacent to nitrogen would be facilitated by the s-character of the carbon hydrogen bond being broken and by inductive stabilization of the developing negative charge by the contingent mesomerically positive nitrogen atom. A concerted protonation of the oxygen atom of the carbonyl group[9a,13] could be invoked to strengthen the analogy to the relatively facile exchange of 4-methoxy-N-methylpyridinium fluoborate (**11**).



The observed isotope effect k_H/k_D of 1.2 at 100° includes a solvent–base effect as well as a primary kinetic isotope effect. If allowance is made for the temperature difference, this value is comparable to the measured values of 1.7–2.0 obtained for the rate of the deuterium exchange reactions of haloforms and related compounds *via* carbanion intermediates in deuterium oxide at 0°.[14] In the case of 3,5-dibromo-N-methyl-4-pyridone (**9**) the ylide intermediate could conceivably give an aryne[15,16] by loss of bromide ion. The recovery of unrearranged **9** in reasonable yield from treatment of the deuterated compound **8** with aqueous base is suggestive evidence against such an intermediate under the present conditions.

Inductive support for pathway I is found in the ylide intermediates which have been proposed or can be formulated to rationalize the base-catalyzed deuterium substitution at the carbon atoms adjacent to nitrogen in the ammonium[17] and pyridinium[11b,18] ions, and pyridine N-oxides.[11b] Similar intermediates have been proposed to explain the facile decarboxylations of N-methylpicolinic acid,[19] picolinic acid,[19,20] and its analogs.[21] In the Hammick reaction the ylide produced by decarboxylation is trapped by reaction with a carbonyl group[22] or other electrophile[23] to give the expected adduct.

Similar processes have been proposed for the base-catalyzed deuterium exchange of a protium located on a formally sp^2 carbon atom adjacent to two heteroatoms in a cationic five-membered ring.[24–27] Exchanges which may be analogous to these have also been observed in formally neutral systems with the same structural features.[28–31] In the case of the C-5 proton exchange in the isothiazoles and 1,2,3-thiadiazoles[31] the position of exchange as in the present case is adjacent to a single heteroatom.

The course of the deuteration of N-methyl-4-pyridone in basic media is considerably different than that observed with 4-pyrone in neutral or acidic media.[32,33] The present work suggests the working hypothesis that reactive ylide intermediates may be readily produced by the direct attack of base on a proton bonded to a formally sp^2 carbon atom which is adjacent to a heteroatom formally conjugated with an electron-withdrawing group. The scope, synthetic possibilities, and theoretical implications of this enhanced acidity are of further interest.[34]

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[12] It follows directly from the usual kinetic treatment of consecutive first-order reactions, $A \xrightarrow{k_1} B \xrightarrow{k_2} C$, that if $k_2 = k_1/_2$ then $A + B/2 = A_0$ (exptl.) $-k_1t/2$: A. A. Frost and R. G. Pearson, "Kinetics and Mechanism," 2nd Ed., John Wiley and Sons, Inc., New York, N. Y., 1961, p. 166.

[13] A. R. Katritzky and R. A. Y. Jones, *Proc. Chem. Soc.*, 313 (1960); C. C. Bell, J. Shoffner, and L. Bauer, *Chem. Ind.* (London), 1435 (1963); D. Cook, *Can. J. Chem.*, **41**, 2575 (1963).

[14] J. Hine, R. Weisboeck, and R. G. Ghiradelli, *J. Am. Chem. Soc.*, **83**, 1219 (1961); J. Hine, N. W. Burke, M. Hine, and P. B. Langford, *ibid.*, **79**, 1406 (1957); J. Hine and N. W. Burke, *ibid.*, **78**, 3337 (1956).

[15] G. Wittig, *Pure Appl. Chem.*, **7**, 173 (1963).

[16] T. Kaufmann, A. Risberg, J. Schulz, and R. Weber, *Tetrahedron Letters*, 3563 (1964).

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

[18] H. E. Dubb, M. Saunders, and J. H. Wang, *ibid.*, **80**, 1767 (1958); A. San Dietro, *J. Biol. Chem.*, **217**, 589 (1955).

[19] P. Haake and J. Mantecon, *J. Am. Chem. Soc.*, **86**, 5230 (1964).

[20] N. H. Cantwell and E. V. Brown, *ibid.*, **74**, 5967 (1952); *ibid.*, **75**, 4466 (1953).

[21] B. R. Brown and D. L. Hammick, *J. Chem. Soc.*, 659 (1949).

[22] P. Dyson and D. C. Hammick, *ibid.*, 1724 (1937); M. R. F. Ashworth, R. P. Daffern, and D. L. Hammick, *ibid.*, 809 (1939); B. R. Brown, *ibid.*, 2577 (1949); N. H. Cantwell and E. V. Brown, *J. Am. Chem. Soc.*, **75**, 1489 (1953).

[23] B. R. Brown and D. L. Hammick, *J. Chem. Soc.*, 173 (1949).

[24] R. Breslow, *J. Am. Chem. Soc.*, **79**, 1762 (1957). For a review see R. Breslow, *Ann. N. Y. Acad. Sci.*, **98**, 445 (1962).

[25] P. Haake and W. B. Miller, *J. Am. Chem. Soc.*, **85**, 4044 (1963).

[26] W. Hafferl, R. Lundin, and L. L. Ingraham, *Biochemistry*, **2**, 1298 (1963).

[27] R. A. Olofson, W. R. Thompson, and J. S. Michelman, *J. Am. Chem. Soc.*, **86**, 1865 (1964).

[28] H. Stabb, M. Th. Wu, A. Mannschreck, and G. Schwalbach, *Tetrahedron Letters*, 845 (1964).

[29] M. P. Schweizer, S. I. Chan, G. K. Helmkamp, and P. O. Tso, *J. Am. Chem. Soc.*, **86**, 696 (1964).

[30] F. Bullock and O. Jardetzky, *J. Org. Chem.*, **29**, 1988 (1964).

[31] R. A. Olofson, private communication.

[32] P. Beak and G. Carls, *J. Org. Chem.*, **29**, 2678 (1964).

[33] D. W. Mayo, P. J. Sapienza, R. L. Lord, and W. D. Phillips, *ibid.*, **29**, 2682 (1964).

[34] N-Methyl-2-pyridone and 1-thia-4-pyrone undergo a similar base-catalyzed deuterium exchange. The latter reaction has a half-life of about 18 min. at 25° in deuterium oxide with 0.5 *N* base: E. McLeister, unpublished results.

Experimental[35]

N-Methyl-4-pyridone (**1**), m.p. 92–93° (lit.[36] m.p. 92°), was prepared in 83.5% yield by heating 0.15 g. of methyl iodide and 1.33 g. of 4-methoxypyridine[6,37,38] at 130° in a sealed tube for 14 hr. Following chromatography on alumina with chloroform elution, distillation in a microsublimator heated at 130–140° (0.5 mm.) reproducibly provided purest product. The infrared,[39] ultraviolet,[40] and n.m.r.[9a] spectra were consistent with the established structure.

3,5-Dimethyl-N-methyl-4-pyridone (**3**) was prepared by refluxing 0.450 g. of 3,5-dimethyl-4-pyrone[32] in 25 ml. of ethanol with 10 ml. of a 40% methylamine solution[41] for 24 hr. After evaporation of the solvent and extraction of the resulting residue with methylene chloride, the extracts were dried and concentrated. Chromatography of this material on 10 g. of alumina provided 0.443 g. of white crystals upon elution with methylene chloride. Recrystallization from methylene chloride–petroleum ether (b.p. 40–46°) gave 0.350 g. (74%) of 3,5-dimethyl-N-methyl-4-pyridone, m.p. 131–133°.

Anal. Calcd. for $C_8H_{11}NO$: C, 70.04; H, 8.08; N, 10.21 Found: C, 70.24; H, 8.17; N, 10.08.

The infrared spectrum had adsorptions at 1685, 1460, 1355, 1260, and 1163 cm.$^{-1}$. The ultraviolet spectrum had a maximum at 275 mμ (ϵ 16,740). The n.m.r. spectrum consisted of a singlet at δ = 2.02 p.p.m. (relative area 6) CCH_3, a singlet at δ = 3.62 p.p.m. (relative area 3) NCH_3, and a singlet at δ = 7.22 p.p.m. (relative area 2) H-2 and H-6.

Upon exposure to the atmosphere, the melting point of the compound decreased to 72–74°, presumably due to hydration. Reheating of the lower melting material or dissolution of the material in methylene chloride followed by treatment with a drying agent and evaporation regenerated the higher melting form.

The 1-isopropoxy-1-ene-2-methyl-3-pentanone previously reported in impure form[32] was obtained as a stable liquid, b.p. 50–55° (0.2 mm.).

Anal. Calcd. for $C_9H_{16}O_{12}$: C, 69.19; H, 10.32. Found: C, 69.16; H, 10.33.

The infrared spectrum had adsorptions at 1455, 1378, 1045, 1219, 1112, and 935 cm.$^{-1}$. The ultraviolet spectrum of a sample which was *ca.* 98% pure had a maximum at 255 mμ (ϵ 18,500). The n.m.r. spectrum of a 30% solution in chloroform-*d* consisted of a triplet at δ = 1.10 p.p.m. (J = 7.5 c.p.s., relative area 3) CH_3-CH_2, a doublet at δ = 1.33 p.p.m. (J = 6.0 c.p.s., relative area 6) $(CH_3)_2CH_3$, a doublet at δ = 1.71 p.p.m. (J = 1.0 c.p.s., relative area 3) CCH_3, a quartet at δ = 2.56 p.p.m. (J = 7.5 c.p.s., relative area 2) CH_3CH_2, a septet at δ = 4.22 p.p.m. (J = 6.0 c.p.s., relative area 1) $-CH(CH_3)_2$, and a quartet at δ = 7.43 p.p.m. (J = 1.0 c.p.s., relative area 1) $=CH$.

2,6-Dimethyl-N-methyl-4-pyridone (**4**) was prepared according to Garratt,[42] m.p. 248–250° (lit.[41] m.p. 247–248°). The infrared,[43] ultraviolet[44] (λ_{max} 261 mμ (ϵ 16,800), and n.m.r. spectral data (in deuterium oxide singlets at δ = 2.88 p.p.m. (relative area 6) CCH_3, δ = 4.10 p.p.m. (relative area 3) NCH_3, and δ = 6.88 p.p.m. (relative area 2) H-3 and H-5 were in accord with the established structure.

3,5-Dibromo-N-methyl-4-pyridone (**9**) was prepared by a modification of the procedure of Elkaschef and Nosseir.[41] After dropwise addition of 1.25 g. of bromine in 7 ml. of glacial acetic acid to a stirred solution of 0.419 g. of N-methyl-4-pyridone in 10 ml. of glacial acetic acid, the mixture was kept at room temperature for 12 hr. and then evaporated. To the red-orange residue was added 1.0 ml. of water, followed by solid potassium carbonate until carbon dioxide evolution ceased. Recrystallization of the solid material from water provided, after drying, 0.340 g. (30%) of 3,5-dibromo-N-methyl-4-pyridone, m.p. 193–194° (lit.[45] 193–194°).

Anal. Calcd. for $C_6H_5Br_2NO$: C, 26.99; H, 1.89; N, 5.24. Found: C, 27.25; H, 1.88; N, 4.97.

The infrared spectrum had two strong overlapping absorptions at 1633 and 1601 and a weaker absorption at 890 cm.$^{-1}$. The ultraviolet spectrum had a maximum at 280 mμ (ϵ 10,930). The n.m.r. spectrum consisted of two singlets at δ = 3.76 p.p.m. (relative area 3) NCH_3 and δ = 7.73 p.p.m. (relative area 2) H-2 and H-6.

4-Methoxy-N-methylpyridinium Fluoborate (**11**). To a solution of 0.980 g. of N-methyl-4-pyridone in 50 ml. of ethylene chloride was added 1.76 g. of silver fluoborate and 6.0 ml. of methyl iodide. After standing overnight, the precipitate was collected by filtration and washed several times with methanol. Ether was added to the combined filtrate and washings, and the cloudy solution was concentrated. The resulting white solid was washed twice with cold absolute ethanol and then with cold anhydrous ether to give 1.15 g. (60%) of 4-methoxy-N-methylpyridinium fluoborate, m.p. 56–58°. Recrystallization was carried out using absolute ethanol containing sufficient methanol to effect solution. The same compound was also obtained by alkylation of 4-methoxypyridine in a similar manner.

Anal. Calcd. for $C_7H_{10}BF_4NO$: C, 39.86; H, 4.74; N, 6.65. Found: C, 39.82; H, 4.86; N, 6.64.

The infrared spectrum (Nujol) had strong absorptions at 3090, 1640, 1575, 1305, 1050 (very broad), and 850 cm.$^{-1}$. The ultraviolet spectrum had a maximum at 245 mμ (ϵ 13,940). The n.m.r. spectrum of a 30% solution in acetone-d_6 consisted of two singlets at δ = 4.17 p.p.m., OCH_3, and δ = 4.31 p.p.m., NCH_3, and a

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(35) The melting points were determined with a Thomas–Hoover capillary apparatus and are corrected. The infrared spectra were determined on a Perkin-Elmer Model 521 infrared spectrometer using 10% chloroform solutions, unless otherwise noted. The ultraviolet spectra were measured on a Cary Model 14m spectrophotometer using methanol solutions. The proton magnetic resonance spectra were obtained on a Varian Associates A-60 spectrometer using 10% chloroform-*d* solutions containing tetramethylsilane as an internal standard, unless otherwise noted. The molecular weight mass spectra were determined on an Atlas CH4 mass spectrometer using in most cases *ca.* 15 e.v. as the ionizing potential. The microanalyses and deuterium analyses were performed by Mr. Joseph Nemeth and associates. The deuterium oxide used for the preparation of any stock solutions and in the reactions was in all cases at least 99.5% pure.

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pair of A_2B_2 multiplets centered at δ = 7.55 p.p.m. H-3 and H-5 and δ = 8.70 p.p.m. H-2 and H-6.

N-Methyl-4-pyridone-2,6-d_2 (**2**). A solution containing 0.800 g. of N-methyl-4-pyridone in 1.5 ml. of *ca.* 0.5 *N* sodium deuteroxide was heated for 12 hr. at 100 ± 2°. The basic solution was concentrated almost to dryness at room temperature under reduced pressure (0.5 mm.) to give a semisolid material, which was washed several times with methylene chloride. Anhydrous magnesium sulfate was added to the residue and the washings were again repeated, combined, dried, filtered, and concentrated to give 0.314 g. (39%) of a deliquescent solid. An n.m.r. spectrum indicated the product contained 95 ± 5% deuterium at the 2- and 6-positions. Further purification of 0.200 g. of this material by sublimation gave 0.153 g. of an analytical sample of N-methyl-4-pyridone-2,6-d_2, m.p. 91–93°.

Anal. Calcd. for $C_6H_5D_2NO$: C, 64.86; H, 6.35; N, 12.61; atom % D, 28.5. Found: C, 64.50; H, 6.62; N, 12.74; atom % D, 27.4.

Deuterium analysis by the falling-drop method showed the product to be 96 ± 1% deuterium substituted based on an incorporation of two. In the mass spectrum of this material the peak heights at *m/e* 109, 110, 111, and 112 were in a ratio of 0, 7.8, 85.0, 7.2 (indicative of the presence of less than 1% C_6H_7NO, 8 ± 1% C_6H_6DNO, and 92 ± 1% $C_6H_5D_2NO$). Similar analyses were used in subsequent cases. The infrared spectrum had absorption bands at 1620, 1510, 1490, and 1350 cm.$^{-1}$. The ultraviolet spectrum had a maximum at 262 mμ (ϵ 16,150). The n.m.r. spectrum consisted of a sharp singlet at δ = 7.05 p.p.m. (relative area 1.9) H-3 and H-5.

A solution containing 0.054 g. of N-methyl-4-pyridone in 0.5 ml. of 0.85 *N* sodium methoxide in 98% methanol-*d* was heated for 66 hr. at 62°. The n.m.r. spectrum indicated that 86 ± 5% deuterium had been incorporated at positions 2 and 6.

In a preparative run a solution of 1.63 g. of N-methyl-4-pyridone in *ca.* 8.0 ml. of 0.5 *N* sodium deuteroxide was heated for 36 hr. at 90–110°. A continuous extraction of the reaction mixture for 5 days with methylene chloride provided 1.20 g. (73%) of crude N-methyl-4-pyridone-2,6-d_2. Sublimation produced 0.950 g. (58%) of crystalline N-methyl-4-pyridone-2,6-d_2, m.p. 91–93°. A n.m.r. spectrum of this material indicated at least 95% deuterium substitution at positions 2 and 6.

Analysis of an n.m.r. spectrum of N-methyl-4-pyridone in deuterium oxide (pD 8.5) after being heated for 6 hr. at 100° indicated less than 5% deuterium incorporation. Solutions of N-methyl-4-pyridone in 1 *N* solutions of deuterium chloride and 5 *N* deuteriosulfuric acid were heated overnight at 98°. The n.m.r. spectra indicated less than 5% deuterium substitution.

To 0.75 ml. of 1.0 *N* sodium hydroxide was added 0.045 g. of N-methyl-4-pyridone-2,6-d_2 and the resulting solution was heated for 9 hr. at 95–98°. N.m.r. analysis of the solution indicated that N-methyl-4-pyridone had been regenerated by this treatment. Isolation of the product by the procedures employed above gave 0.026 g. of N-methyl-4-pyridone identified by infrared spectroscopy.

3,5-Dimethyl-N-methyl-4-pyridone-2,6-d_2 (**7**). A solution containing 0.112 g. of 3,5-dimethyl-N-methyl-4-pyridone in 0.75 ml. of 0.5 *N* sodium deuteroxide was heated at 100 ± 2° for 48 hr. Material isolated by a procedure identical with that for **2** was only 50% deuterated and was subjected to a similar reaction for another 16 hr. An 88% recovery of material which was *ca.* 70% deuterated at positions 2 and 6 was obtained. When 0.081 g. of this material was heated at 100° in a 1.4 *N* sodium deuteroxide solution for 14 hr., isolation gave 0.078 g. (over-all 77%) of 3,5-dimethyl-N-methyl-4-pyridone-2,6-d_2, m.p. 132–133°. The n.m.r. spectrum indicated the product to be 95 ± 5% deuterium substituted at position 2 and 6. The deuterium analysis by the falling-drop method showed the product to be 89 ± 4% deuterium incorporated based on an incorporation of two. Mass spectral analysis indicated the presence of 2.5 ± 1% $C_8H_{11}NO$, 12.5 ± 1% $C_8H_{10}DNO$, and 85 ± 1% $C_8H_9D_2NO$.

Anal. Calcd. for $C_8H_{10}D_2NO$: C, 69.06; H, 8.08; N, 10.07; atom % D, 18.18. Found: C, 68.84; H, 8.44; N, 9.99; atom % D, 16.80.

The n.m.r. spectrum consisted of two singlets at δ = 2.48 p.p.m. (relative area 6) CCH_3 and δ = 4.22 p.p.m. (relative area 3) NCH_3. The infrared spectrum had adsorptions at 1629, 1550 (b), 1432, 1382, 1319, 1280, and 920 cm.$^{-1}$. The ultraviolet spectrum had a maximum at 275 mμ (ϵ 17,870).

3,5-Dibromo-N-methyl-4-pyridone-2,6-d_2 (**8**). A heterogeneous reaction mixture of 0.100 g. of 3,5-dibromo-N-methyl-4-pyridone in 1.0 ml. of 0.5 *N* sodium deuteroxide was heated for 24 hr. at 100 ± 5°. After cooling in ice water, the white precipitate was separated by centrifugation and dried to give 0.091 g. of 3,5-dibromo-N-methyl-4-pyridone-2,6-d_2, m.p. 193–194°. The n.m.r. spectrum indicated the product to be at least 95% deuterium substituted in the 2- and 6-positions. A recrystallization of 60 mg. of the above material from water gave 50 mg. of an analytical sample, m.p. 193–194°. The deuterium analysis by the falling-drop method showed the product to be 94 ± 2% deuterated based on an incorporation of two. Mass spectral analysis indicated the presence of less than 1.0% $C_6H_5Br_2NO$, 3 ± 1% $C_6H_4DBr_2NO$, and 97 ± 1% $C_6H_3D_2Br_2NO$.

Anal. Calcd. for $C_6H_3Br_2D_2NO$: C, 26.72; H, 1.89; N, 5.21; atom % D, 40.00. Found: C, 27.17; H, 2.00; N, 5.01; atom % D, 37.57.

The n.m.r. spectrum consisted of a singlet at δ = 3.75 p.p.m., NCH_3. The infrared spectrum had a single, sharp peak at 1606 and absorptions at 1290 and 1130 cm.$^{-1}$. The ultraviolet spectrum had a maximum at 280 mμ (ϵ 12,100) as well as end absorption.

A solution containing 0.014 g. of 3,5-dibromo-N-methyl-4-pyridone-2,6-d_2 in 0.2 ml. of 0.5 *N* sodium hydroxide was heated for 12 hr. at 100 ± 5°. Isolation provided 0.009 g. (64%) of N-methyl-3,5-dibromo-4-pyridone, m.p. 193–195°. A mixture melting point with an authentic sample of N-methyl-3,5-dibromo-4-pyridone gave no depression. The infrared spectrum was also identical with that of an authentic sample.

Deuterium Substitution in 4-Methoxy-N-methylpyridinium Fluoborate (**11**). When 0.035 g. of the pyridinium salt was heated for 60 hr. at 62° in 98% methanol-*d*, no exchange was noted.[46] Two symmetrical multiplets of equal area at 250 c.p.s. (H-3 and H-5) and 317 c.p.s. (H-2 and H-6) downfield from the methyl proton resonance of the solvent were present before and after heating. When 0.049 g. of the pyridinium salt was dissolved in 0.5 ml. of 0.85 *N* sodium methoxide in methanol-*d*, exchange of the protons in the 2- and 6-positions occurred in less than 15 min. The downfield multiplet which appeared at 317 c.p.s. from the solvent protons had almost disappeared, and the proton resonance (H-3 and H-5) at 250 c.p.s. downfield was now a singlet.

Attempted Deuterium Substitution in N-Methylpyrrole, Pyridine, and 4-Methoxypyridine. The n.m.r. spectrum of 0.047 g. of N-methylpyrrole in 0.5 ml. of 0.85 *N* sodium methoxide in methanol-*d* remained unchanged after heating at 62° for 66 hr. Isolation and mass spectral examination of the product indicated less than 2% deuterium incorporation. Similar treatment of pyridine and 4-methoxypyridine gave material which showed less than 5% deuterium incorporation as determined by n.m.r.

N-Methyl-4-pyridone-3-d (**5**) *and N-Methyl-4-pyridone-3,5-d_2* (**6**). To a solution which was *ca.* 20% by weight of methylamine in 4 ml. of deuterium oxide was added 0.345 g. of 4-pyrone. Heating at 100° for 60 hr. followed by the usual isolation procedure provided 0.298 g. of an oil which solidified upon cooling. Chromatography of this solid on 15 g. of neutral alumina gave 0.215 g. (54%) of product, m.p. 92–94°, in the chloroform eluates. An n.m.r. analysis indicated the product to be 72 ± 5% deuterium substituted in the 3- and 5-positions. The deuterium analysis by the falling-drop method showed the product to be 68.5 ± 2% deuterium substituted based on an incorporation of two. A mass spectral analysis indicated the presence of 9 ± 2% C_6H_7NO, 50 ± 2% C_6H_6DNO, and 41 ± 2% $C_6H_5D_2NO$.

The n.m.r. spectrum consisted of a sharp singlet at δ = 4.31 p.p.m. (relative area 3) NCH_3, a broad singlet at δ = 8.29 p.p.m. (relative area 2) H-2 and H-6, and a multiplet at δ = 7.01 p.p.m. (relative area 0.56) H-3 and H-5. The ultraviolet spectrum had a maximum at 262 mμ (ϵ 16,600). The infrared spectrum of the mixture had adsorptions at 1670, 1550, 1391, 1356, 1190, and 930 cm.$^{-1}$.

N-Methyl-4-pyridone-2,6-dimethyl-7,8-d_6 (**10**). A solution of 0.183 g. of 2,6-dimethyl-N-methyl-4-pyridone in 1.5 ml. of 0.5 *N* sodium deuteroxide was heated overnight at 98 ± 2°. The white solid, which precipitated upon cooling the reaction mixture in ice water, was collected and dried to give 0.113 g. (59%) of N-methyl-4-pyridone-2,6-dimethyl-7,8-d_6, m.p. 247–249°. The n.m.r. spectrum indicated almost complete deuterium incorporation at the 2- and 6-methyl groups. Mass spectral analysis showed that the material was 2 ± 1% $C_8H_7D_4NO$, 19 ± 1% $C_8H_6D_5NO$, and 79 ± 1% $C_8H_5D_6NO$. The deuterium analysis by the falling-drop method indicated 96 ± 1% deuterium substitution based on an incorporation of six.

Anal. Calcd. for $D_8H_5D_6NO$: C, 64.86; H, 6.35; N, 12.61; atom % D, 28.5. Found: C, 64.50; H, 6.62; N, 12.79; atom % D, 27.4.

The ultraviolet spectrum had a maximum at 261 mμ (ϵ 18,550) and end absorption. The n.m.r. spectrum in deuterium oxide consisted of a singlet at δ = 4.09 p.p.m. (relative area 3) and a singlet at δ = 6.88 p.p.m. (relative area 1.8). The infrared spectrum (Nujol) had absorption bands at 1625, 1545, 1510, 1455, 1370, 1225, and 1200 cm.$^{-1}$.

Kinetics. Appropriate aliquots of stock solutions, prepared by the careful addition of sodium metal to 99.5% deuterium oxide, were diluted to give reagents of desired concentration. Subsequent standardizations using hydrochloric acid as the titrant and a phenolphthalein indicator provided exact concentrations. A typical kinetic experiment involved addition of a known amount of the standardized base to a known amount of N-methyl-4-pyridone to give solutions of known pyridone concentration which were sealed into n.m.r. tubes. No special precautions were taken to exclude carbon dioxide at this point and this introduced small errors into the rate constants. The reaction mixture was placed in a constant temperature bath at 100 ± 0.05°. A tube was removed at the appropriate time (0, 10, 20, 30, 40, 45, 50, 55, 60, and 70% of the total reaction) and the reaction quenched by cooling in ice water. The amount of deuterium incorporation at positions 2 and 6 relative to the two protons at positions 3 and 5 was determined from the n.m.r. spectrum. Normally, the average height of three to five integration traces per peak was used in this calculation. A weighted, least-squares program for the calculation of first-order rate constants was used to calculate the observed rate constants.[47] To obtain the specific rate constant, the observed rate constant was divided by the initial base concentration.

Ultraviolet analysis of a reaction mixture, which was 0.471 *N* in sodium deuteroxide and 1.04 *M* in N-methyl-4-pyridone, at 17, 40, and 60% of total reaction indicated that at least 96% of the theoretical amount of N-methyl-4-pyridone as such or isotopically substituted was present at these times. The base concentration was shown to be constant to 95 ± 5% of the initial concentration during a run by titration of initial, intermediate, and final reaction mixtures. Titrations of appropriate controls indicated a carbonate error of *ca.* 5–10% was introduced in the sealing of the n.m.r. tubes. The average value of k_H was $4.26 \pm 0.21 \times 10^{-4}$ l. mole^{-1} sec.$^{-1}$.

The kinetics of the reverse reaction was performed in a similar manner using N-methyl-4-pyridone-2,6-d_2 which was at least 95% deuterium incorporated and 1.00 *N* aqueous sodium hydroxide. The average value of k_D and its average deviation was $3.47 \pm 0.27 \times 10^{-4}$ l. mole^{-1} sec.$^{-1}$.

The observed isotope effect k_H/k_D, calculated from the above values was 1.23 ± 0.16.

Mass Spectral Analysis of a Kinetic Run. The partially deuterated N-methyl-4-pyridone was isolated from samples obtained during a kinetic run which had a base concentration of 0.471 *N* and a pyridone concentration of 1.48 *M*. A mass spectral analysis of

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(46) A similar lack of exchange of N-methylpyridinium iodide has been noted by Hafferl, Lundin, and Ingraham[26] presumably under neutral or weakly basic conditions.

(47) We are grateful to Dr. John Petrovich and Dr. S. G. Smith for furnishing this computer program.

these samples gave the percentages of undeuterated, monodeuterated, and dideuterated material as a function of time. A scan of the mass spectra from m/e 30 to 150 at 15 e.v. showed that there was less than 2% of other volatile material. The results are plotted in Figure 1. Using an Electronic Associates, Inc., TR 20 analog computer programmed for two consecutive, first-order reactions, the curves were fitted to the data (Figure 1) and the rate constants $k_1 = 4.63 \pm 0.05 \times 10^{-4}$ and $k_2 = 2.18 \pm 0.05 \times 10^{-4}$ were compiled. The computer was used to synthesize the rate of disappearance of the protons at the 2- and 6-positions which is the rate observed by n.m.r. The k_{calcd} of 2.25×10^{-4} sec.$^{-1}$ agrees reasonably well with the k_{obsd} of 2.05×10^{-4} sec.$^{-1}$.

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Liquid-Phase and Vapor-Phase Reactions of Ethylene with Carbon Tetrachloride[1]

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The telomerization of ethylene and carbon tetrachloride, initiated by t-Bu_2O_2*, has been studied at 140° in the liquid phase in carbon tetrachloride, n-octane, and methanol as solvents, and in the vapor phase at total pressures of 0.3–28 atm. The objective was to determine the effects of solvent change and phase change on the variation with n of the transfer constants of the radicals* $Cl_3C(C_2H_4)_n\cdot$*. In the liquid phase, kinetic chain lengths are in the thousands and normal telomers are nearly the sole products. In the vapor phase, chain lengths fall between about 10 and 200. Unexpectedly, intramolecular chain-transfer reactions of hydrogen and chlorine atoms in the 5-positions in the radicals become dominant at low pressures, leading to so much of numerous isomers of normal telomers and of 1-hexene that normal telomers become minor products. Rate constants for these rearrangements have been evaluated in terms of the rate constants for normal chain propagation and intermolecular chain transfer and then applied to chain branching in polyethylene. Except for the intrusion of intramolecular reactions of free radicals at low concentrations, there are no important differences between liquid-phase and vapor-phase telomerizations, and the effects of polar solvents are small. Comparison of these liquid-phase results at 140° with literature data at 70° shows that the activation energies for chain transfer with carbon tetrachloride and for chain propagation with ethylene are about the same for each of the radicals involved.*

Introduction

This research originally had two objectives. One was to further some general comparisons of vapor-phase and liquid-phase reactions of free radicals. A more specific objective was to determine the effects of solvent and phase change on the transfer constants in the telomerization of ethylene with carbon tetrachloride. When we carried out our first vapor-phase experiments, a wholly unexpected problem arose: how to identify and account for the large number of new products and isomers formed.

In the polymerization of a vinyl monomer, E (here ethylene), the transfer constant of a solvent (here carbon tetrachloride) is the ratio of the rate constants for chain transfer and chain propagation as shown in eq. 4 (eq. 1 to 3 are in Chart I).

When n is large, C is constant and is a convenient measure of the reactivity of a solvent in chain transfer. However, when n is small and the solvent is carbon tetrachloride, C_n is sensitive to chain length with ethylene,[3,4] higher alkenes,[5] or styrene.[6] C_1 is usually much smaller than C_2, which means that the 1:1 telomer is hard to obtain in good yield (except in short-chain reactions in a large excess of carbon tetrachloride), but that the 2:1 product is easier to obtain, and so on. In the instances cited, the transfer constant increases regularly from C_1 up to about C_3 and thereafter remains nearly independent of chain length. More recently Robb and co-workers[7,8] have examined the reactions of styrene and methyl methacrylate with bromotrichloromethane. They found that the transfer constant goes through a maximum when n is 3 or 4 and that high telomers are therefore obtained only at very low $BrCCl_3$ concentrations. With alkenes or styrene and carbon tetrachloride, the effect of chain length on C_n has been ascribed to polar effects[5]: a nearby Cl_3C– group retards reaction of the free radical with carbon

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