Secondary Isotope Effects in the Reactions of Methyl-d_3-pyridines with Alkyl Iodides. Evidence for a Smaller Steric Requirement of the Methyl-d_3 over the Methyl-d_0 Group[1,2]

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Abstract: The presence of methyl-d_3 substituents in the 3 or 4 position of the pyridine nucleus results in insignificant effects on the rates of reaction with methyl iodide over the corresponding 3- and 4-methylpyridines. However, the presence of methyl-d_3 substituents in the 2 position results in enhanced reactivity of the pyridine bases with methyl, ethyl, and isopropyl iodide. The failure to observe any significant difference in the rates of reaction of the 3- and 4-methyl-d_3-pyridines compared to the corresponding methyl-d_0 derivatives indicates that the electronic effects of the methyl-d_3 substituent are not significantly different from those of the methyl substituent. On the other hand, the observation that the presence of the methyl-d_3 group in the 2 position brings about a significant increase in the rate of reaction with the alkyl iodides is consistent with the postulated smaller steric requirements of deuterium compared to hydrogen.

Numerous examples of secondary isotope effects which have been observed in organic reactions have been interpreted variously in terms of the classical effects which have long been attributed to the more usual substituents.[5]

The rate retarding effect produced by β-deuterium substitution in compounds undergoing reaction through a carbonium ion intermediate has been interpreted in terms of a hyperconjugation isotope effect.[6] Thus the normal isotope effect, $k_H/k_D = 2.33$, observed in the solvolysis of *t*-butyl-d_9 chloride[6i] has been attributed to hyperconjugative weakening of the carbon–deuterium bonds in the transition state leading to the carbonium ion.

On the other hand, an inductive isotope effect[7] has been proposed to account for the decrease in the acidities of weak organic acids which accompanies deuterium labeling. The pK_a of acetic acid-d_3 has been reported to be greater than that of the normal acid by 0.026[7d] and 0.014[7e] units. This has been attributed to greater electron release from the carbon–deuterium bond through the operation of a normal inductive effect.

A steric deuterium isotope effect[8] has been proposed as an alternative explanation for the effects of α-[9] and β-deuterium substituents upon the rates of carbonium ion reactions. According to this proposal, hydrogen atoms behave as if they were larger than deuterium atoms and exert stronger repulsions on neighboring atoms as a consequence of the greater amplitude of vibration of their bonds. Accordingly, steric assistance to ionization[10] favors more rapid reaction of the protium species.

This interpretation of β-deuterium isotope effects has been severely criticized[6j] principally on the basis of a sensitivity to conformational effects. However, the concept has been applied to account for the enhancements in the rates of racemization of 9,10-dihydro-4,5-dimethylphenanthrene which accompanies the introduction of deuterium into the methyl groups and the bridge positions,[11a] and for the partial asymmetric alcoholysis of α-phenylbutyric anhydride in pyridine with (+)-(*S*)-2-propanol-1-d_3.[11b] Moreover, inverse secondary isotope effects observed in the reactions of deuterated ketones with 2,4-dinitrophenylhydrazine have been attributed to decreased steric crowding in the transition states for the reactions of the labeled ketones.[12]

Although the steric model affords a common interpretation for a great variety of secondary deuterium isotope effects observed in widely differing reactions, it has received comparatively little attention. The principle itself is quite simple. It is postulated that deuterium is effectively a smaller atom than hydrogen.[8] That is to say, the steric requirements of deuterium and of a deuterium-containing group are smaller than those of the corresponding hydrogen moieties. Consequently, if a reaction proceeds with relief of strain, the hydrogen derivative should be more strained in the ground state and react at a faster rate than the deu-

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(1) Chemical Effects of Steric Strains. XIX.

(2) Based on a thesis submitted by Gerald J. McDonald in partial fulfillment of the requirements for the degree of Doctor of Philosophy at Purdue University, 1964.

(3) Research assistant, 1959–1961, 1962–1963, on grants provided by the National Science Foundation, G-6273 and G-19878.

(4) Dow Chemical Co. Fellow, 1961–1962.

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terium derivative. On the other hand, if the reaction involves the formation of a sterically crowded transition state, the reaction of the hydrogen compound should be retarded relative to the deuterium analog. Similarly, in an equilibrium situation, the reaction should shift in the direction of minimizing the steric interactions, *i.e.*, placing the deuterium in the more crowded environment. It is of course obvious that the isotopes must be in the vicinity of the reaction center for the effect to be significant.

These concepts have long been applied to the interpretation of steric influences in organic chemistry. As previously applied, the effects of the usual steric interactions are far larger than those which can possibly arise from the minor differences in the steric requirements of deuterium and hydrogen. However, there would appear to be no reason not to expect similar phenomena to be observed, although on a greatly reduced scale.

Previously, when we were faced with a critical test of the significance of the steric factor in organic chemistry, we found that a study of the heats of reaction of pyridine bases with Lewis acids and the rates of reaction with alkyl halides provided data that proved convincing even to the most reluctant skeptic.[13] Accordingly, we decided to utilize the same approach. We synthesized 2-, 3-, and 4-picoline and 2,6-lutidine containing trideuteriomethyl groups and examined their rates of reaction with alkyl iodides, reported in the present paper, and their heats of reaction with boron trifluoride and diborane, reported in the following paper.[14,15]

Results

Syntheses. 2,6-Dimethyl-d_6-pyridine and 4-methyl-d_3-pyridine were prepared by an exchange procedure with liquid ammonia-d_3. However, the incorporation of 9% of deuterium in the 4 position of the labeled dimethylpyridine together with the time-consuming nature of the repetitive exchange experiments prompted the development of an alternative procedure for the preparation of 2- and 3-methyl-d_3-pyridine. Lithium aluminum deuteride reduction of the appropriate ester was followed by treatment with thionyl chloride to obtain the corresponding chloromethyl-d_2-pyridine hydrochloride. Exchange of the proton with deuterium oxide, followed by reduction with zinc and acetic acid-*d*, afforded the methyl-d_3-pyridine. The over-all yields of 2- and 3-methyl-d_3-pyridine were 40 and 64%, respectively.

The properties and deuterium compositions of these pyridine derivatives are summarized in Table I.

Commercial samples of the normal methylpyridines were subjected to careful purification for use in the kinetic and calorimetric experiments. Their physical properties are also summarized in Table I.

Finally, it appeared desirable to examine also the effect of ring deuteration. Accordingly, the kinetic isotope effects in the reactions of pyridine-4-d_1 and pyridine-d_5 were determined. These materials were commercially available.

Table I. Properties of the Pyridine Bases

Pyridine	Bp, °C (mm)	$n^{20}D$	D atoms per molecule[a]	D atoms per methyl group[a]
Pyridine	115.0 (749)	1.5099		
Pyridine-4-d_1			1.00	
Pyridine-d_5			4.90	
4-Methyl	145.4 (743)	1.5057		
4-Methyl-d_3	144.9 (742)	1.5042	2.82	2.82
3-Methyl	143.6 (745)	1.5065		
3-Methyl-d_3	143.1 (747)	1.5053	2.97	2.97
2-Methyl	129.0 (735)	1.5010		
2-Methyl-d_3	127.9 (741)	1.4998	2.96	2.96
2,6-Dimethyl	144.2 (752)	1.4976		
2,6-Dimethyl-d_6[b]	142.7 (747)	1.4956	5.81	2.86

[a] By nmr analysis. [b] Contains 9% deuterium in the 4 position of the ring.

All of the pyridines were examined by gas chromatographic analysis. The labeled and normal pyridines, 2-methylpyridines and 2,6-dimethylpyridines, were estimated to be at least 99.8 mole % pure. Only a single peak was observed for the 3-methyl- and 4-methylpyridines. However, these have such close retention times that this does not prove the absence of the other isomer. However, 3-methylpyridine was estimated to be at least 99.7 mole % pure by cryoscopic examination. The synthesis of 3-methyl-d_3-pyridine from pure methyl nicotinate establishes its isomeric purity. Finally, a large sample of 4-methylpyridine, indicated to have a purity of 98.9 mole % by cryoscopic examination, was distilled through packed column rated at 53 plates. A center cut was collected and used for the measurements, as well as for the synthesis of the deuterium analog. Consequently, we believe that 1% represents the maximum amount of the isomeric 3 derivative that can be present. However, since the reactivities of the 3- and 4-methylpyridines are so similar, any uncertainty introduced into the results by this factor is far smaller than the normal experimental variation.

Kinetics. The rates of reaction of methyl iodide with all of the pyridine bases were determined at 25.0° in nitrobenzene solution. In addition, the two pyridine bases with methyl substituents in the α position were examined with alkyl iodides of larger steric requirements. Thus, the rates of reaction of the labeled and normal 2-methylpyridines with ethyl and isopropyl iodides were measured, as well as those of the 2,6-dimethylpyridines with ethyl iodide. Elevated temperatures were required for these reactions, and the experimental uncertainty is somewhat greater than for the reaction at 25° with methyl iodide. It was decided that there was no point in examining the reaction of isopropyl iodide with 2,6-lutidine. The reaction is so slow that elevated temperatures are required and side reactions, such as elimination, complicate the interpretation of the results.

The reactions were followed by measuring the rate of formation of iodide ion by the usual Volhard procedure. Individual determinations of the rate constants were made with each corresponding pair of labeled and normal pyridine base. A reaction with the normal compound was always run under the same conditions as a reaction with the corresponding labeled compound, using the same stock solution of the alkyl

(13) For a review, with pertinent literature references, see H. C. Brown, *J. Chem. Soc.*, 1248 (1956).

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(15) The present two studies were undertaken and largely completed before we learned of the related convincing studies by K. Mislow and his associates.[11]

Table II. Kinetic Isotope Effects in the Reactions of Labeled Pyridine Bases with Methyl Iodide at 25.0°[a]

Pyridine[b]	Rate constant × 10^4 (l. mole^{-1} sec^{-1}) k_H	k_D		k_D/k_H
4-Methyl-d_3[c]	7.819 ± 0.064	7.797 ± 0.031		0.997
	7.807 ± 0.058	7.810 ± 0.038		1.000
	7.852 ± 0.054	7.898 ± 0.036		1.006
			Mean	1.001 ± 0.003
3-Methyl-d_3[c]	7.317 ± 0.042	7.354 ± 0.053		1.005
	7.302 ± 0.048	7.367 ± 0.050		1.009
	7.341 ± 0.060	7.428 ± 0.045		1.012
			Mean	1.009 ± 0.002
2-Methyl-d_3[c]	1.619 ± 0.010	1.664 ± 0.012		1.028
	1.588 ± 0.010	1.642 ± 0.009		1.034
	1.603 ± 0.004	1.647 ± 0.010		1.027
			Mean	1.030 ± 0.003
2,6-Dimethyl-d_6[d]	0.1313 ± 0.0007	0.1434 ± 0.0007		1.092
	0.1298 ± 0.0004	0.1427 ± 0.0006		1.099
	0.1302 ± 0.0005	0.1424 ± 0.0007		1.094
			Mean	1.095 ± 0.003
Pyridine-4-d_1[c,e]	3.470 ± 0.041	3.506 ± 0.035		1.010
	3.448 ± 0.025	3.487 ± 0.036		1.011
	3.484 ± 0.035	3.540 ± 0.019		1.016
			Mean	1.012 ± 0.002
Pyridine-d_5[c,e]	3.470 ± 0.041	3.545 ± 0.033		1.022
	3.448 ± 0.025	3.570 ± 0.032		1.035
	3.484 ± 0.035	3.612 ± 0.024		1.037
			Mean	1.031 ± 0.006

[a] Reaction in nitrobenzene solution. [b] Initial concentration of the pyridine base was 0.1 *M*. [c] Initial concentration of methyl iodide was 0.3 *M*. [d] Initial concentration of methyl iodide was 1.0 *M*. [e] Values for the rate constants for pyridine, pyridine-4-d_1, and pyridine-d_5 were determined in sets of three made up of one of each pyridine base.

iodide in nitrobenzene. The reactions were run side by side in the constant temperature bath, if they were sufficiently slow to permit concurrent analyses. If this was not possible, they were staggered, or the second run was begun immediately following completion of the first. Values for the kinetic isotope effect were calculated for each set of runs and then averaged.

The values of the rate constants for the reactions with methyl iodide are listed in Table II, for ethyl iodide in Table III, and for isopropyl iodide in Table IV, together with the observed values for the kinetic isotope effects at the temperature of the measurement.

Table III. Kinetic Isotope Effects in the Reactions of 2-Methyl-d_3- and 2,6-Dimethyl-d_6-pyridine with Ethyl Iodide[a]

Pyridine[b]	Temp, °C	Rate constant × 10^5 (l. mole^{-1} sec^{-1}) k_H	k_D	k_D/k_H
2-Methyl-d_3	75.0	23.80 ± 0.12	24.58 ± 0.15	1.033
		23.66 ± 0.24	24.55 ± 0.24	1.038
			Mean	1.036
2,6-Dimethyl-d_6	75.0	1.622 ± 0.004	1.755 ± 0.018	1.082
		1.639 ± 0.020	1.739 ± 0.022	1.061
			Mean	1.072
2,6-Dimethyl-d_6	100.0	8.571 ± 0.110	9.173 ± 0.133	1.070

[a] Reaction in nitrobenzene solution. [b] Initial concentration of the two reactants 0.1 *M*.

Table IV. Kinetic Isotope Effect in the Reaction of 2-Methyl-d_3-pyridine with Isopropyl Iodide at 100.0°[a]

Pyridine[b]	Rate constant × 10^5 (l. mole^{-1} sec^{-1}) k_H	k_D	k_D/k_H
2-Methyl-d_3	3.619 ± 0.038	3.833 ± 0.079	1.059
	3.537 ± 0.063	3.734 ± 0.070	1.056
		Mean	1.058

[a] Reaction in nitrobenzene solution. [b] Initial concentration of the two reactants was 0.1 *M*.

The isotope effects in the reactions of all of the labeled pyridine bases with methyl iodide and in the reaction of 2-methyl-d_3-pyridine with ethyl iodide are estimated to be precise to within ±1%. In the reaction of 2,6-dimethyl-d_6-pyridine with ethyl iodide, the isotope effect is estimated to be precise to within ±2%. The larger uncertainties in the individual values for the rate constants result in an estimated precision of only ±3% for the kinetic isotope effect in the reaction of 2-methyl-d_6-pyridine with isopropyl iodide.

While the literature of secondary isotope effects is littered with overly optimistic estimates of the reliability of the observed effects, we hope and we believe that the above represents a conservative evaluation of the limits of the experimental uncertainty.[16]

Discussion

For convenience in following the discussion, the observed secondary isotope effects are summarized in Table V, together with the values calculated for 25° to provide a common temperature for comparing the magnitude of the effects.

The major conclusions which may be drawn from the data appear to be the following.

1. A methyl-d_3 group, either in the 4 position (k_D/k_H = 1.001) or in the 3 position (k_D/k_H = 1.009), has no effect on the rate of reaction over and above the experimental uncertainty.

2. Methyl-d_3 groups in the 2 position bring about enhanced rates of reaction well beyond the experimental uncertainty. Thus the system exhibits an inverse secondary isotope effect.

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[16] One of the referees, who disagreed strongly with our conclusions, recommended that the data be subjected to a statistical treatment to determine if the differences observed were significant. The results of this statistical analysis, reported in the Experimental Section, support these conclusions and indicate that the estimated experimental uncertainty, reported above, may actually be overly conservative.

Table V. Summary of the Kinetic Isotope Effects

Pyridine	Alkyl iodide	Temp, °C	$(k_D/k_H)_T$	$(k_D/k_H)^a$ at 25°
4-Methyl-d_3	Methyl	25.0	1.001	1.001
3-Methyl-d_3	Methyl	25.0	1.009	1.009
2-Methyl-d_3	Methyl	25.0	1.030	1.030
	Ethyl	75.0	1.036	1.042
	Isopropyl	100.0	1.058	1.073
2,6-Dimethyl-d_6	Methyl	25.0	1.095	1.095
	Ethyl	75.0	1.072	1.085
	Ethyl	100.0	1.070	1.088
Pyridine-4-d_1	Methyl	25.0	1.012	1.012
Pyridine-d_5	Methyl	25.0	1.031	1.031

[a] Calculated with aid of the expression, $k_D/k_H = e^{(E_H-E_D)/RT}$.

3. In the case of methyl iodide, the two methyl groups of 2,6-dimethyl-d_6-pyridine (k_D/k_H = 1.095) appear to exert significantly more than twice the effect of one methyl group in 2-methyl-d_3-pyridine (k_D/k_H = 1.030). However, within the larger uncertainty of the ethyl iodide measurements, the effects appear additive (k_D/k_H = 1.085, 1.042).

4. The value of the secondary isotope effect appears to increase in 2-methyl-d_3-pyridine as the alkyl iodide is changed from methyl (k_D/k_H = 1.030), to ethyl (k_D/k_H = 1.042), to isopropyl (k_D/k_H = 1.073). However, the same trend is not evident in the abbreviated series involving 2,6-dimethyl-d_6-pyridine with methyl (k_D/k_H = 1.095) and ethyl (k_D/k_H = 1.085).

5. Finally, ring deuteration in the 4 position of pyridine appears to exhibit an effect (k_D/k_H = 1.012) which is of the same order of magnitude as the estimated uncertainty (1.00 ± 0.01). However, pyridine-d_5 exhibits a small inverse isotope effect (k_D/k_H = 1.031) that is three times the estimated uncertainty.

An interpretation of these results requires an analysis of the nature and relative magnitudes of the isotope effects to be expected in these reactions on the basis of the electronic and steric hypotheses which have been advanced to account for secondary isotope effects. The steric hypothesis suggests that the deuterium atom behaves as though it were smaller than the hydrogen atom.[8] Indeed, it is well established that the molar volumes of deuterium and methane-d_4 at their triple points are considerably smaller than for their hydrogen analogs.[17] On this basis, the steric requirements of methyl-d_3 groups should be significantly smaller than normal methyl groups.

The reactivity of the alkyl pyridines has been shown to be sensitive to the steric requirements of the alkyl substituents in the α position.[18] It follows that if the postulated difference in the steric requirements of the methyl-d_3 and methyl-d_0 groups is valid, an enhanced reactivity should be observed for 2-methyl-d_3- and 2,6-dimethyl-d_6-pyridine over the normal compounds. This is actually the case for all of the alkyl iodides examined (Table V).

It is a consequence of the steric interpretation that the presence of these substituents in the 3 and 4 positions, relatively remote from the reaction center, should have no influence on the observed rate.

The very small factor observed for the 4-methylpyridine derivatives, k_D/k_H = 1.001, clearly supports the conclusion that the 4-methyl-d_3 substituent exerts no significant electronic effect on the reaction rate. In the case of the 3-methylpyridine derivatives, the observed ratio for k_D/k_H = 1.009 is borderline. The deviation from 1.000 is significantly larger than the average deviation of the individual measurements, but falls within our estimated uncertainty of ±0.01 which includes variations of ±0.5% in the individual rate constants. For that reason we have concluded that in neither case can the results be considered to indicate that the methyl-d_3 substituent exerts a significant electronic effect on the reaction. Consequently, this second condition for a steric deuterium isotope effect may also be considered to be fulfilled.

With regard to the ring-labeled pyridines, the 1.031 isotope effect for pyridine-d_5 is considered to be beyond the experimental uncertainty, but the 1.012 effect for pyridine-4-d_1 is just at the limit of the estimated uncertainty. If the latter effect is real, an electronic isotope effect would be indicated. However, in that event, it would be impossible to account for a k_D/k_H value as small as 1.031 for the cumulative electronic effect of five deuterium substituents, four of them much closer to the reaction center than the original 4-deuterium. It appears more reasonable that the 1.031 isotope effect is predominantly a reflection of the smaller steric requirements of the two deuterium atoms in the α positions.

A further consequence of the steric interpretation is the prediction that the isotope effects in the reactions of the pyridine bases containing α-methyl-d_3 substituents should increase with the increasing steric requirements of the alkyl iodide. This trend is indeed evident in the isotope effects of 1.030, 1.042, and 1.073 observed in the reactions of 2-methyl-d_3-pyridine with methyl, ethyl, and isopropyl iodide, respectively. A slight reversal of this trend is seen in the reactions of 2,6-dimethyl-d_6-pyridine with methyl and ethyl iodide. However, the values of 1.095 and 1.086 may well be reversed and still be within the experimental uncertainties of the measurements.

Finally, in the case of steric effects of the more customary magnitudes, it is observed that two *ortho* substituents produce an effect considerably larger than twice that of one such substituent. However, we do not know whether this exponential growth of steric interactions will also be observed when we are dealing with very minute effects. Unfortunately, the present results are ambiguous on this point. Thus, nonadditivity is suggested in the reactions of methyl iodide with 2-methyl-d_3- and 2,6-dimethyl-d_6-pyridine, with k_D/k_H = 1.030 and 1.095, respectively. However, additivity is indicated in the corresponding reactions with ethyl iodide, with k_D/k_H = 1.042 and 1.086. It must be apparent that we are operating at the limits of the precision of the data.

In spite of these minor uncertainties, it must be concluded that the present data are indeed consistent with the predictions based on a steric origin for the secondary isotope effect.

Predictions resting on a postulated electronic origin for the secondary isotope effect are complicated by opposing theories now in the field. In this system, a prediction based on a hyperconjugation contribution gives a different answer from one based on an inductive effect.

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(17) K. Clusius and K. Weigand, *Z. Physik. Chem.*, **B46**, 1 (1940).

(18) H. C. Brown and A. Cahn, *J. Am. Chem. Soc.*, 77, 1715 (1955).

Since the nitrogen atom of the various pyridine bases represents a center of developing positive charge in the transition states for the reactions with the alkyl iodide, it might be expected that the positive charge could be stabilized by hyperconjugative contributions from methyl substituents in the 2 and 4 positions. If so, the introduction of deuterium in these methyl groups would be expected to result in a smaller hyperconjugative contribution and a reduced rate. The effect sould be much smaller or absent in the 3 position. Since the observed effect of deuterium substitution is a rate enhancement restricted to the 2 position, hyperconjugation cannot be the basis of the observed secondary isotope effect in the present system.

The hypothesis of an inductive isotope effect proposes an enhanced electron-donating ability of deuterium relative to hydrogen. Consequently, a methyl-d_3 group would be expected to stabilize a developing positive center more effectively than a normal methyl group through the operation of an inductive effect. Thus, this hypothesis also predicts an inverse isotope effect, similar to that predicted by the steric interpretation.

The main point of difference in the two proposals as they apply to the reactions under consideration is the requirement of the steric proposal that the isotope effect be operative only in the α position, in the neighborhood of the reaction center, whereas the inductive effect should operate in all three positions of the ring.

Both 4-picoline (pK_a = 6.02) and 2-picoline (pK_a = 5.97) are considerably stronger bases than pyridine (pK_a = 5.17).[19] Obviously the increase must be associated with the electronic effect of the methyl group. Since the effects are comparable for the 4-methyl and 2-methyl substituents, it would appear that on an electronic basis we should anticipate similar effects in the 4 and 2 positions for methyl-d_3 and methyl-d_0 substituents. However, the observed isotope effects of 1.001 for the 4 and 1.030 for the 2 derivatives are not in accord with this expectation.

It must be concluded that there are some serious discrepancies with the predictions based on the inductive interpretation. On the other hand, the results are consistent on all counts, within the limitations of the experimental uncertainties, with the predictions based on a steric origin for the secondary isotope effect. Consequently, as discussed in the following paper,[14] this reaction provides still another member of the enormous number now available which are consistent with the steric interpretation.

Experimental Section

Materials. The small effects we were examining made it essential that the substances we used were as pure as possible, without contamination by isomers. The normal pyridine bases were commercial materials which were purified by standard methods, but with especial care. The general methods followed are illustrated by the procedure used in the purification of 2,6-lutidine, described below. The physical properties are summarized in Table I.

Pyridine-4-d_1 and pyridine-d_5 were commercial samples (Merck) which were stored over barium oxide, but were otherwise used without purification. Gas chromatographic examination on a Ucon Polar column, 54°, showed but a single peak. Nmr analysis indicated that the pyridine-4-d_1 was isotopically pure. The pyridine-d_5 analyzed for 4.90 deuterium atoms per molecule, with the α positions 99% labeled, β 97%, and γ 98%.

The alkyl iodides were dried overnight (anhydrous magnesium sulfate or calcium sulfate) and then distilled under nitrogen from copper shot through a column packed with Heli-Pak into receivers containing copper shot and wrapped with aluminum foil to exclude light. The physical properties observed were: methyl iodide, bp 43° (746 mm), n^{20}D 1.5310; ethyl iodide, bp 73.1°, n^{20}D 1.5136; isopropyl iodide, bp 90.1°, n^{20}D 1.4993. In each case the materials exhibited only a single peak on gas chromatographic examination (tricresyl phosphate, 30°). Stored over copper shot under nitrogen, with exclusion of light, the materials remained completely colorless.

Nitrobenzene was distilled; a center cut taken and stored over calcium hydride.

2,6-Lutidine. The following procedure is representative of the methods used to purify the pyridine bases. 2,6-Lutidine (Reilly) (500 g) was dried overnight over calcium hydride. The hydride was filtered off and 44 g of boron trifluoride etherate was added with cooling and magnetic stirring. (This is a convenient means of selectively removing less hindered, more reactive isomers.) A white precipitate formed which dissolved on heating. The material was distilled in a Todd column packed with glass helices. The fractions collected were individually examined by gas chromatography (Ucon Polar, 135°). The best cuts (385 g) were combined, treated with 22 g of boron trifluoride etherate, and redistilled. The best cuts (240 g) from this distillation were combined and stored in an amber bottle over calcium hydride and under nitrogen, bp 144.2° (752 mm), n^{20}D 1.4976 (lit.[20] bp 144.0° (760 mm), n^{20}D 1.49767). Analysis by the cryoscopic method, using a platinum resistance thermometer with automatic recorder, indicated a purity of 99.86 mole %. The observed freezing point was −6.12°. Corrected to 100 mole % purity, the freezing point was −6.04° (lit.[20] fp −6.10°).

2,6-Dimethyl-d_6-pyridine. Ammonia-d_3 was prepared by the following procedure. In a 250-ml autoclave was placed 70 g (0.69 mole, 48% excess) of magnesium nitride (Anderson Chemical Co.) and 56.1 g (2.8 moles) of 99.5% deuterium oxide (General Dynamics) in a thin-walled glass capsule containing a steel roller bearing. The autoclave was sealed and vigorously shaken to break the glass container. A vigorous exothermic reaction ensued. The ammonia-d_3 was withdrawn through a valve in the head of the autoclave and used directly for a single exchange.

The ammonia was condensed in a 100-ml three-neck flask and 0.23 g of potassium and a pinch of anhydrous ferric oxide were added to form the potassium amide catalyst. The 2,6-lutidine (50 g, 0.467 mole) was added through a dropping funnel. An orange-red color developed immediately, changing to brown-red over the course of the reaction. After 5 hr the ammonia was distilled off and the lutidine was recovered. A total of eleven exchange reactions were run, the first five for 5 hr each and the last six for 10 hr each. After five reactions 50% exchange had taken place, after eight reactions 85%, after 10 reactions 93%, and after eleven reactions 96%. The product (34 g) was fractionated, bp 142.7° (747 mm), n^{20}D 1.4956, and stored in an amber bottle over barium oxide. Its infrared spectrum showed new bands at 4.51 (m), 4.65 (w), 4.85 (w), and 11.20 μ (s) and the disappearance of bands at 3.43 (s), 6.90 (vs), 7.28 (s), 7.83 (m), and 8.17 μ (m) compared to the starting material. Nmr analysis indicated 2.86 deuterium atoms per methyl group and 9% labeling of the γ-ring position. Mass spectral analysis[21] indicated the following isotopic composition: d_4, 3.6%; d_5, 23%; d_6, 66%; d_7, 7.4%; and d_8, 0.2%.

4-Methyl-d_3-pyridine. The exchange procedure was very similar. The product exhibited bp 144.9° (742 mm), n^{20}D 1.5042. Nmr analysis indicated the presence of 2.82 deuterium atoms in the methyl group. Mass spectral analysis[21] indicated: d_1, 1.3%; d_2, 18.5%; d_3, 80%; and d_4, 0.2%.

3-Methyl-d_3-pyridine. Methyl nicotinate (Reilly) was purified by two successive vacuum sublimations, mp 40–42°. The material was then reduced to 3-hydroxymethyl-d_2-pyridine by lithium aluminum deuteride in tetrahydrofuran solution in 91% yield. Nmr analysis indicated 1.98 deuterium atoms in the methylene group.

The carbinol (48.7 g, 0.439 mole) in 345 ml of dry benzene was treated with dry hydrogen chloride. 3-Hydroxymethyl-d_2-pyridine hydrochloride precipitated as a white solid. Washed with benzene and anhydrous ether, the yield was 63.6 g, 98%, mp 118–119.5°.

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[19] H. C. Brown and X. R. Mihm, *J. Am. Chem. Soc.*, 77, 1723 (1955).

[20] D. P. Biddiscombe, E. A. Coulson, R. Handley, and E. F. G. Herington, *J. Chem. Soc.*, 1957 (1954).

[21] We are indebted to R. Gohlke of the Dow Chemical Co. for the mass spectral analysis.

The carbinol hydrochloride (63.5 g, 0.43 mole) was dissolved with cooling in 300 ml of distilled thionyl chloride. The mixture was heated under reflux for 4 hr, then excess thionyl chloride was distilled off. To the warm, concentrated solution 275 ml of dry benzene was added. The hydrochloride precipitated. The reaction mixture was cooled to −11°, and the solid was separated and washed with benzene and dry ether. The yield was 70.1 g, 98%, mp 137–139°.

The product was dissolved (almost completely) in 25 ml of deuterium oxide. After standing overnight, the water was pumped off. A fresh portion of deuterium oxide was added and the process was repeated. A third and a fourth exchange finally yielded 68.5 g of 3-chloromethyl-d_2-pyridine hydrochloride-d, mp 136–142°. Nmr analysis indicated a minimum of 96% exchange.

3-Chloromethyl-d_2-pyridine hydrochloride-d (67.8 g, 0.406 mole) was dissolved in 250 ml of acetic acid-d. This solution was placed in a dropping funnel and added over 8 hr to a stirred mixture of 135 ml (7.41 moles) of deuterium oxide (>99.7%), 170 ml of acetic acid-d, and 83 g (1.27 g-atoms) of zinc dust, maintaining the temperature at 25°. After stirring overnight, the mixture was heated to reflux and maintained there for 1 hr. The product was recovered by standard isolation procedures. There was obtained 29.8 g (76%) of 3-methyl-d_3-pyridine, bp 143.1° (747 mm), $n^{20}\mathrm{D}$ 1.5053. Nmr analysis indicated 2.97 deuterium atoms in the methyl group.

2-Methyl-d_3-pyridine. Picolinic acid (Aldrich, mp 136–137°) was converted to the ethyl ester, reduced to 2-hydroxymethyl-d_2-pyridine, bp 60° (0.4 mm), converted to the hydrochloride, mp 108.5–110°, and finally to 2-methyl-d_3-pyridine by reduction of the chloromethylpyridine hydrochloride with zinc, as above. There was obtained 13.2 g (80%) of 2-methyl-d_3-pyridine, bp 127.9° (741 mm), $n^{20}\mathrm{D}$ 1.4998. (The over-all yield from the ester was 40%.) Nmr analysis indicated 2.96 deuterium atoms in the methyl group.

Kinetic Procedures. Stock solutions of the alkyl iodides in nitrobenzene were standardized regularly during use. For each analysis three aliquots of the stock solution and three aliquots of nitrobenzene were treated with equal aliquots of an alcoholic silver nitrate solution. The mixtures were allowed to stand overnight, and the excess silver nitrate was titrated with standard potassium thiocyanate. From the difference between the average titers for the blanks and the halide solutions, the concentration of the alkyl iodide solutions could be determined.

The nitrobenzene solutions of the pyridine bases were prepared by weighing out the required amount of the pyridine base into a calibrated volumetric flask and diluting to the mark. In the case of the labeled bases, the molecular weights calculated from the nmr analyses were used.

The reactions of pyridine bases with alkyl iodides in nitrobenzene solution have been shown previously to exhibit simple second-order kinetics.[18] Standard solutions of the alkyl iodide and pyridine base were mixed and maintained at constant temperature, and aliquots were removed at appropriate time intervals for analysis for iodide ion by the usual Volhard titrimetric procedure.

In order to minimize the possible effects of random errors, a reaction with the normal base was always run under the same conditions as a reaction with the corresponding labeled base, using aliquots from the same standard solution of alkyl iodide. The reactions were run side by side in the constant temperature bath, if they were slow enough to be followed simultaneously. If this was not possible, they were staggered, or the second run was begun immediately after the first had been completed. Nine aliquots were analyzed for each run. The first was used to establish the kinetic zero point, and values for the rate constant were calculated at each of the other eight points. The eight individual values for each run were averaged, and the two average values for the rate constants for the reactions of the corresponding labeled and normal bases (Tables II–IV) were used to calculate a value for the kinetic isotope effect (Tables II–IV). Generally, two or three values for the kinetic isotope effect were determined and averaged (Table V).

The reactions with methyl iodide were run at 25° in long-necked flasks. Special techniques were utilized to handle the methyl iodide solutions to avoid loss of the halide through volatilization. Convenient reaction rates were achieved by appropriate choice of the initial concentration of the iodide, maintaining the pyridine base at 0.1 *M*. Thus for pyridine and the picolines, the methyl iodide concentration was 0.3 *M*, and for the less reactive 2,6-lutidine, 1.0 *M*.

The reactions with ethyl and isopropyl iodide were run at 75 and 100° in sealed ampoules. The initial concentrations of the pyridine base and alkyl iodide were equal and approximately 0.1 *M* each. The concentrations were corrected for the volume expansion of the solvent, using the values for the density of nitrobenzene at various temperatures.[18]

The reactions of methyl iodide with pyridine and 3- and 4-picoline were carried to 60% completion, but the slower reactions with 2-picoline and 2,6-lutidine were followed only to 35 to 40% completion. Finally, the reactions with ethyl iodide were followed to 30% completion and isopropyl iodide to 15%.

Statistical Analysis.[22] The Student's *t* test was used to determine whether there was a significant difference between the mean of the ratio k_D/k_H and 1.000 for the reactions of the bases with methyl iodide, utilizing the data summarized in Table II. Standard methods were used[23] and the confidence levels were obtained from the usual *t* table.[23]

The results are summarized in Table VI.

Table VI. Statistical Analysis of the Data for the Reaction of Methyl Iodide with the Pyridine Bases

Pyridine	Mean of k_D/k_H	Std dev $s \times 10^3$	Evaluated t	Confidence level,[a] %
4-Methyl-d_3	1.001	4.58	0.308	60
3-Methyl-d_3	1.009	3.54	3.58	96
2-Methyl-d_3	1.030	3.16	13.4	>99
2,6-Dimethyl-d_6	1.095	3.61	37.1	>99
Pyridine-4-d_1	1.012	3.24	5.22	98
Pyridine-d_5	1.031	8.15	5.36	>98

[a] For the question whether there is a significant difference between the ratio k_D/k_H and 1.000 for each pair of bases.

The question whether the differences in the k_D/k_H values for various pairs of bases were significant was also explored. The results are summarized in Table VII.

Table VII. Statistical Analysis of the Significance of the k_D/k_H Values for the Reactions of Various Pairs of Pyridine Bases with Methyl Iodide

Pyridine bases compared	Evaluated t	Confidence level, %	Conclusion: Means
3-Methyl-d_3 and 4-methyl-d_3	1.95	<95	Not significantly different
2-Methyl-d_3 and 4-methyl-d_3	7.37	99	Significantly different
2-Methyl-d_3 and 3-methyl-d_3	6.26	99	Significantly different
2,6-Dimethyl-d_6 and 2-methyl-d_3	19.2	99	Significantly different
Pyridine-4-d_1 and -d_5	3.07	97	Borderline

These results support the five major conclusions presented in the discussion which were based on the estimated uncertainty of 1% in the k_D/k_H values for the methyl iodide reactions.

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(22) We are indebted to W. J. Hammar and D. VanderJagt of the Department of Chemistry, Purdue University, for this analysis.

(23) P. G. Hoel, "Introduction to Mathematical Statistics," 3rd ed, John Wiley and Sons, Inc., New York, N. Y., 1954.