Ionization of Nitroalkanes by Substituted Pyridines[1]

BY EDWARD S. LEWIS AND JAMES D. ALLEN

Pyridine bases promote the iodination of nitroethane and 2-nitropropane, and the rate-determining step is a proton transfer. Spectrophotometric rate measurements confirm earlier conductometric measurements by Pearson and Williams on nitroethane which showed a steric hindrance to proton transfer to 2- and 6-substituted pyridines. This effect is greatly increased with 2-nitropropane, and with 2-t-butylpyridine as the base. Deuterium isotope effects are large and appear to have unusually large temperature dependences corresponding to $A_D > A_H$ where A is the Arrhenius pre-exponential factor. Some conceivable but improbable alternatives to tunneling as an explanation for this observation are presented.

Introduction

The use of hydrogen isotope effects in helping to elucidate reaction mechanisms has been hindered by the fact that isotope effects are difficult to predict in reactions of even fairly well understood mechanism. This paper is a part of a program to study the variation of isotope effects in reactions of known mechanism, and represents a study of the effect of steric hindrance on proton transfer reactions. The model for this study has been the paper of Pearson and Williams,[2] in which they showed that the reaction of nitroethane with 2,6-lutidine, as measured by iodination of the resulting anion, is substantially slower than would be expected on the basis of a linear free energy relation with the base strengths.

Methods

Rates were measured by observing the disappearance of iodine spectrophotometrically in a solution of 30% aqueous ethanol containing a large excess of both the pyridine base and the nitro compound. The spectrophotometer then showed a linear fall in the concentration of iodine with time. Excess iodide was added, so that its concentration would be substantially constant; this makes the extinction coefficient of iodine constant throughout the run, and makes the absorbance vs. time curve linear.

Results and Discussion

The rate constants are given in Table I. The accuracy of these entries is of considerable pertinence to the discussion which follows, so a summary of the sources of error is appropriate. There are two sorts of errors, those which will affect the absolute rate constants, and those which affect also the isotope effects. In the first class are uncertainties about solvent composition, purity of the catalyzing base and the extent to which it is neutralized (to suppress lyate ion catalysis), temperature uncertainties, and uncertainty about the extinction coefficient of iodine. The latter may be here the most serious because we were at first unaware of the effect of the pyridine base on the extinction coefficient and did not establish the extinction coefficients with high accuracy, nor did we allow for variation of extinction coefficient among solutions containing different bases. One manifestation of this error, overlooked at the time of the measurements, is a small apparent dependence of second-order rate constants on base concentration. An example is shown in the table.

(1) This work was supported by a grant from the Robert A. Welch Foundation.

(2) R. G. Pearson and F. V. Williams, J. Am. Chem. Soc., **75**, 3073 (1953).

The same stock solutions of base, iodine, and iodide in the solvent were used for the protium and deuterium compounds, and the extinction coefficient is independent of the isotopic nature of the transparent nitro compound, so these errors all cancel when isotope effects are calculated. We attribute the difference between our results and those of Pearson and Williams to this first class of error, perhaps combined with some inherent in the conductometric work.

TABLE I

RATES OF IODINATION OF CH_3CHRNO_2 AND CH_3CDRNO_2 IN THE PRESENCE OF SUBSTITUTED PYRIDINES

R	Pyridine	Temp., °C.	$10^3 k_H$.[a] 1./mole min.	$10^3 k_D{}^a$	k_H/k_D
H	None	24.9	7.14 (6.5)	0.823	8.68
H	4-CH_3	24.9	20.2 (18.2)	2.21	9.15
H	3-CH_3	24.9	15.9 (13.2)	1.58	10.1
H	2-CH_3	24.9	27.4 (24.5)	2.83	9.69
H	2-t-Bu	24.9	2.13	0.205	10.4
H	2-t-Bu	30.2	4.19		
H	2-t-Bu	36.3	6.40	0.732	8.74
H	2,6-$(CH_3)_2$	24.9	36.0 (20.8)	2.98	12.1
CH_3	None	24.9	0.525[b]	0.0558[b]	9.40
			0.465[c]	.0500[c]	9.30
CH_3	3-CH_3	24.9	1.14	.108	10.7
CH_3	2-t-Bu	24.9	0.0316	...	...
CH_3	2,6-$(CH_3)_2$	15.2	.218	...	...
CH_3	2,6-$(CH_3)_2$	20.1	.389	...	...
CH_3	2,6-$(CH_3)_2$	24.9	.533	0.0527	10.1
CH_3	2,6-$(CH_3)_2$	30	.941		
CH_3	2,6-$(CH_3)_2$	36.3	1.58	0.190	8.42

[a] Each number is the average of the result of at least two runs with satisfactory agreement. The parenthetical numbers are the rates measured by Pearson and Williams[2] at 25°. [b] Average of runs at ca. 0.1 M pyridine. [c] Average of runs at ca. 0.4 M pyridine.

Contributors to errors in the isotope effect are differences in the purity of the deuterated and undeuterated materials, especially if a contaminant is reactive; error in the correction for iodination of the solvent, which is larger for the slower reacting materials; and contamination of the deuterium compound by protium compound. In some runs mentioned in the Experimental part but not included in the table, failure to attain temperature equilibrium caused an isotope effect error, but this error is absent in the reported data. We have no evidence that any impurities were contributing to the results. Although nitroethane did show impurity on the v.p.c., different batches, including one sample purified by v.p.c. and showing no contamination, gave the same rate constants. The existence of the large isotope effect indicates that the protium compounds do not contain unexchangeable rapidly reacting

compounds. If the deuterium compound is contaminated with a reactive compound, then the true isotope effect is even larger than we observe. There is no evidence for this, but if it were the case, then the arguments which follow are in no way vitiated. The technique used, in which only about 1% of the substrate is consumed, is especially sensitive to reactive impurities. A type of reactive impurity in the deuterium compound is the undeuterated material. When the extent of reaction is very small, it can be shown that eq. 1 holds, in which k_H and k_D are the rate constants for the pure protium and deuterium compounds, respectively, and k_{obsd} is the observed rate constant determined on a sample of deuterated compound containing the mole fraction f_H of hydrogen compound.

$$k_D = (k_{obsd} - k_H f_H)/(1 - f_H) \quad (1)$$

This correction is quite substantial when $k_H f_H$ is a significant fraction of k_{obsd}. In these reactions in which only an initial rate is measured and which have a large isotope effect, it is important to make f_H as small as possible, and to know it as accurately as possible. The values of k_D given are calculated by eq. 1 using values of f_H deduced from the n.m.r. spectrum. This analysis is straightforward for 2-nitropropane, but is of limited accuracy since the signal for the single proton is a septuplet, and therefore even in the case of the pure liquid, the signal to noise ratio with an extensively deuterated sample is unfavorable. The best estimates are based on peak heights. With 2-nitroethane, the signal from the single proton in CH_3CDHNO_2 is further split by the deuterium, and the use of peak heights is then difficult; integration is seriously limited by the small signal to noise ratio. Nevertheless, the analysis and correction is better than omitting the correction. The correction applied to nitroethane neglects any secondary isotope effect, which we estimate as about 10–20% in the reaction of the monodeuterio compound. These corrected isotope effects in our opinion are the best that can be derived from the data; it should be noted that the anomalous temperature dependencies are found even if the correction is not applied. Bell[3] has discussed the effect of this contamination on isotope effect temperature dependence in a more general case, although the smaller isotope effects pertinent to his discussion make the corrections smaller.

A further difficulty exists with 2-nitropropane. The reaction of iodine with 2-nitropropane has been shown to be reversible[4]; thus the consumption of iodine is incomplete. Furthermore, a consideration of the reaction mechanism at equilibrium leads to the conclusion that the 2-nitropropyl anion reacts with a proton at a rate comparable with its reaction with iodine, and thus the zero order approximation is quite poor in the neighborhood of equilibrium. Although we made no effort to measure this equilibrium and cannot calculate it from Bell's data because of solvent change, it was clear that under the reaction conditions there was a significant iodine concentration after very long reaction times. Rate constants given are taken from linear early portions of the absorbance vs. time curves, when the extent of reversal is negligible. Nevertheless, this reversal and the necessary consequence, a possibility of

some exchange of the deuterium compound with solvent, does constitute a limitation on the accuracy of the results.

The table shows that the steric effect found by Pearson and Williams can be made much more conspicuous. Thus, 2-t-butylpyridine, although about as strong a base as the methylpyridines,[5] reacts more slowly with nitroethane than does pyridine itself; with 2-nitropropane, 2,6-lutidine reacts at about the same rate as pyridine in spite of its greater base strength, and 2-t-butylpyridine reacts almost too slowly to measure.[6]

Table I shows that the isotope effects are large. They apparently increase with the base strength, for pyridine has a smaller isotope effect than any methylpyridine (with either nitro compound) and the 2,6-lutidine has the largest effect (with nitroethane). A similar effect was observed by Reitz, who found that the isotope effect in the ionization of nitromethane was about 3.6 with water as the base (at 70°), 4.4 with chloroacetate, and 6.4 with acetate (at 25°).[7] Although this effect is not large, it suggests that the transition state is not quite symmetrical with respect to the stretching force constants for the making and breaking bonds and contains some zero point energy in the "symmetrical" stretching mode.[8]

Under these circumstances the large isotope effects are unexpected, and suggest either that the bending vibrations are quite small in the transition state, or that there may be tunneling which makes k_H unexpectedly large. The complete loss of bending vibrations in the transition state could easily provide enough zero point energy loss to give these isotope effects when combined with a modest loss of stretching zero point energy, but there seems no particular reason why these bonds should be unusually weak; in other proton transfers it is unnecessary to call upon any loss of bending zero point energy.

If we consider the evidence for tunneling, aside from the large isotope effects, there is also the possibility of observing deviation from the Arrhenius equation (as observed by Hulett and by Catlin)[9] and unusually small A_H/A_D values, where the A's are the Arrhenius pre-exponential factors, as explained by Bell.[3] Because of the uncertainty of the extinction coefficient and its temperature dependence, it is difficult to interpret the temperature variation of our rate constants. The three points for the 2-t-butylpyridine and nitroethane do not fit the Arrhenius equation well, but the deviation is in the wrong direction to be attributed to tunneling. The five points for the 2,6-lutidine and 2-nitropropane reaction fit adequately, yielding an apparent activation energy of about 16.7 kcal.

The isotope effects are free from extinction coefficient difficulties. From the data one can calculate for the 2,6-lutidine reaction with 2-nitropropane a value of

(3) R. P. Bell, "The Proton in Chemistry," Cornell University Press, Ithaca, N. Y., 1959, p. 204.
(4) R. P. Bell and E. Gelles, Proc. Roy. Soc. (London), A210, 310 (1952).
(5) H. C. Brown and X. Mihm, J. Am. Chem. Soc., 77, 1723 (1955).
(6) It may be noted that with models even 2-t-butyl-6-methylpyridine with 2-nitropropane shows no conspicuous hindrance either with reagent-like or product-like structures. Perhaps the hindrance is connected with transition-state solvation.
(7) O. Reitz, Z. physik. Chem., A176, 363 (1938).
(8) L. Melander, "Isotope Effects on Reaction Rates," Ronald Press, New York, N. Y., 1962, Chapter 2; F. H. Westheimer, Chem. Rev., 61, 265 (1961).
(9) J. R. Hulett, Proc. Roy. Soc. (London), A251, 274 (1959); E. F. Caldin and E. Harbron, J. Chem. Soc., 3454 (1962); E. F. Caldin and M. Kasparian, Abstracts, XIXth Intern. Congr. Pure and Appl. Chem., 1963, Sect. A1, p. 103.

A_H/A_D of about 0.14 and for the 2t-butylpyridine and nitroethane reaction, A_H/A_D = 0.091.

These values are both well under any value derived from the classical absolute reaction rate picture, and certainly then support a suggestion of tunneling. There is no evidence that the steric hindrance is related to the small A_H/A_D factors, although some preliminary evidence did lead us to believe this and hence to concentrate on the two hindered examples. It does appear that the slowness of the reactions and the high barrier may indeed be connected to the existence of tunneling. Our rate constants of about 2 × 10⁻⁵ l./mole sec. are smaller (at 25°) than those of many reactions studied at this temperature. These reactions very likely have at this temperature a higher-than-average barrier, and this is certainly a reasonable prerequisite for the significant contribution of tunneling.

An alternative explanation not involving tunneling also depends on having unusually low rates. If the pre-exponential factor is small (rather than the barrier high), and if the small A factor can be accounted for by a very constricted pathway for the proton, it is reasonable that the deuteron, being effectively smaller than the proton, would pass the constriction more readily, giving a greater transmission coefficient for the deuterium compound, and hence $A_D > A_H$.[10] A constriction along the reaction coordinate near the maximum in the potential energy diagram can also conceivably change the position of the maximum in total energy (potential energy + zero point energy) along the reaction coordinate. In polar reactions the extent of solvation, for example, then may depend upon the isotope used, and there is no reason why A_H and A_D should be nearly equal. This would appear to be a significant problem only when the charge separation changes very rapidly with reaction coordinate in the neighborhood of the maximum.

There does not appear to be any clear experimental way to distinguish between a mass dependence of the transmission coefficient and tunneling. The comparison between deuterium and tritium isotope effect could help to identify these cases, but there would have to be a realistic and mathematically tractable model for both. The curvature of the Arrhenius plot should also in principle distinguish, but grosser changes of mechanism also will cause deviation in the same direction, so that the curvature is not always convincing evidence for tunneling.

Experimental

Materials.—Commercial nitroethane showed 0.5% water and 3.5% other volatile impurity by gas chromatography after fractional distillation. The impurity was not identified, but appeared not to interfere with the kinetics, since the rate constants were unchanged when a far purer sample, made by preparative gas chromatography, was used.

Nitroethane-1-d_2 was prepared by the method of Leitch[11] by three successive exchanges with deuterium oxide. It contained 3% total impurity by chromatography, and was between 97 and 99.5% deuterated, as shown by its n.m.r. spectrum.

Distillation of commercial 2-nitropropane gave a sample 99.5% pure by gas chromatography; the impurity was not identified.

2-Nitropropane-2-d-was prepared by exchange. Heavy water (17.6 g.) and 2-nitropropane (15 g.) were mixed and 0.2 g. of sodium was added. The mixture was refluxed for 17 hr. and the organic layer was separated and subjected to two further exchanges with fresh heavy water. The distilled product contained 2% impurity by gas chromatography and contained only about 1% hydrogen at the tertiary position by n.m.r.

Pyridine (98%), 2-methylpyridine (99.5%), 3-methylpyridine (98%), and 4-methylpyridine (99%) were good commercial materials, purified by distillation, in some cases after refluxing with barium oxide. The parenthetical numbers represent the fraction of the major peak in the gas chromatographic analysis. It is interesting to note that water was a significant contaminant even when the barium oxide treatment was used; apparently this treatment is either not as effective as is reported, or the bases are extremely hygroscopic. A mixture of 54 g. of a good commercial grade of 2,6-lutidine and 7 g. of boron fluoride etherate was fractionally distilled to remove less hindered bases. It assayed 99.5% by gas chromatography.

2-t-Butylpyridine was prepared from 2-methylpyridine following Brown and Murphy.[12] The product, after two methylations, although apparently homogeneous on gas chromatography, was shown by n.m.r. to be a mixture of 2-isopropyl- and 2-t-butylpyridine. Atmospheric pressure distillation through a spinning-band column yielded 2-t-butylpyridine, homogeneous both by chromatography and n.m.r.

The solvent was made by diluting 700 ml. of water to a liter with ethanol at 25°, allowing time for the heat of mixing to be dissipated. This is apparently not identical with the solvent used by Pearson and Williams,[2] the preparation of which is not described, since iodine with pyridine was not as soluble in our solvent as they report.

Rate measurements used a solution containing a weighed amount of the base (enough to make about 0.03 M solution) made up to volume with a solution 0.100 M in iodide ion, 3 × 10⁻⁴ M in iodine, and 0.003 M in perchloric acid in the aqueous ethanol. A weighed sample of nitro compound (30- to 100-fold excess over the iodine) in a 50-ml. volumetric flask was made up to volume with the thermostated base solution and, after mixing, the solution was pipetted into a 10-cm. cell which was then placed in a thermostated jacket in the spectrophotometer and the decrease in absorbance at 471 mμ was measured. The slope of the straight-line of absorbance $vs.$ time was then converted to a pseudo-zero-order rate constant by the use of the extinction coefficient of 666 for iodine in this medium. This, divided by the concentration of base and that of nitro compound, gives the second-order constants in the table. A slow reaction with the solvent was measured in blank runs, and used to correct the slowest rates.

The temperature of the cell contents was shown to be constant and indistinguishable within the reading accuracy of a thermometer from that of the air space in the cell compartment, which is more readily measured, when thermostated water was circulated both through the walls of the cell compartment and through a jacket surrounding the cell. The cell temperature deviated toward room temperature from the thermostat temperature because of heat loss in the circulating system; the temperatures reported are actual cell temperatures. In some of the earlier runs errors in isotope effects occurred because the reaction time of the hydrogen compound was comparable to the time constant for approach to the equilibrium temperature. The time for approach to equilibrium is quite dependent on the size of the cell, the thermostating system, and doubtless some undetermined factors. In our system, the approach to equilibrium temperature was approximately exponential, with a half-time of 4–5 min. The magnitude of error introduced depends on the reaction rate, its temperature dependence, and the difference between the initial and the equilibrium temperatures, so no generalizations can be made. We believe that all the reported rates are free from significant error from this source.

(10) We are indebted to Dr. M. Wolfsberg for pointing out this possibility in more elegant terms for a hypothetical potential energy surface.
(11) L. C. Leitch, *Can. J. Chem.*, **33**, 400 (1955).
(12) H. C. Brown and W. A. Murphy, *J. Am. Chem. Soc.*, **73**, 3308 (1951).