Rates and Isotope Effects in the Proton Transfer Reactions of Methyl 4-Nitrovalerate(1)

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The rates of proton transfer from methyl 4-nitrovalerate to pyridine and 2,4,6-trimethylpyridine have been measured by iodination and by racemization. The iodination rates closely resemble those for 2-nitropropane, except for a larger term for solvent catalysis. Rates from racemization and iodination are the same where both can be measured, but iodination becomes less useful as the rate drops, and is least valuable in the dilute solutions necessary for water solutions. The deuterium isotope effect for the racemization of methyl 4-nitrovalerate-*4-d* by 2,4,6-trimethylpyridine is in the excess of 20 at 30°.

The nitroalkanes have been popular substrates for the study of slow proton transfers to a variety of bases, because they are accessible, they have easily measurable acid dissociation constants, and they deviate about as far as any acids from the ideal Eigen behavior.[3] The hydrogen isotope effects have also been of interest from the beginning of such studies.[4] More recent studies have on the one hand borne on the variation of isotope effect with acid and base strength,[5,6] and with the contribution of tunneling to the isotope effect.[5,7,8]

The evidence for tunneling was based primarily on a very large deuterium[5,7] or tritium[8] isotope effect in the reaction of 2-nitropropane with 2,6-dimethyl- and 2,4,6-trimethylpyridine measured mostly by iodination methods. These large isotope effects are rather central to any arguments on the importance of tunneling in proton transfer reactions, although they are not the only evidence.[9] It appeared necessary to take criticisms of the results seriously and to attempt to get independent confirmation. A study of the isotope effect in the 2,6-dimethylpyridine–2-nitropropane reaction in aqueous ethanol[10] contradicts the results of ours in aqueous *tert*-butyl alcohol[7] and of Bell's in water. We have previously expressed an uncertainty about the significance of results in ethanolic solution and indeed abandoned our earlier groundwork in this solvent[11] because it is not inert to iodine, and therefore leads to a substantial blank reaction which is especially serious with the slower reactions, but we nevertheless felt that an independent demonstration would be valuable.

We here study methyl 4-nitrovalerate, which is accessible in optically active form[12] but is in most respects very similar to 2-nitropropane, and compare iodination rates with those of 2-nitropropane, to see how close the resemblance is, and compare iodination rates with racemization rates, to ascertain that the rate-determining step is indeed the same.

Results

The iodination of methyl 4-nitrovalerate, reaction 1, was followed spectrophotometrically at 30° in aqueous *tert*-butyl alcohol (54% *t*-BuOH by weight) and in water.

$$\mathrm{B + CH_3CHNO_2CH_2CH_2CO_2CH_3 + I_2 \longrightarrow BH^+ + CH_3CINO_2CH_2CH_2CO_2CH_3 + I^-} \quad (1)$$

The absorbance at 468 nm was not a linear function of time, as noted before,[7] because of the variable iodide ion concentration. Using suitable correction for varying extinction coefficients, plots of concentration of total iodine *vs.* time were linear. The pseudo-zero-order rate constants derived from these plots were proportional to ester concentrations and increased linearly with base concentration, showing a rate law of the form of eq 2, differing only by the detectable term in k_s from our earlier work.[7]

$$-\mathrm{d}(\mathrm{I_2})/\mathrm{d}t = k_\mathrm{B}(\mathrm{B})(\mathrm{ester}) + k_\mathrm{s}(\mathrm{ester}) \quad (2)$$

The absence of a lyate ion term was demonstrated as before by the insensitivity of the rate to the presence of a small amount of perchloric acid. The results are shown in Table I, which also shows some rate of iodination of methyl 4-nitrovalerate-*4-d*.

Table I also includes rate constants for reaction of 2-nitropropane with the same bases at 25° where available. It is clear that the ester resembles the 2-nitropropane closely; most of the factor of about two discrepancy is attributable to the 5° temperature difference. The larger solvent term appears real, although the entry for 2,4,6-trimethylpyridine, larger than for pyridine itself, probably only reflects the fact that blank corrections with this base are so large that results are quite uncertain. We were unable in water to get an iodination rate of the deuterated compound because of excessive blank correction and other problems described in the Experimental Section. This difficulty is not due to worse behavior in the solvent water than in the *tert*-butyl alcohol solvent, but only due to the fact that measured zero-order rates are necessarily very slow because the concentration of ester is solubility limited, as is also that of collidine.

The k_s in *tert*-butyl alcohol was not found in the earlier work with 2-nitropropane;[7] in water a value of 4×10^{-9} sec^{-1} has been reported,[5] which is clearly smaller than the value of 4×10^{-7} in Table I. We suggest that the larger k_s term may arise from neigh-

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TABLE I

IODINATION OF METHYL 4-NITROVALERATE AT 30°

Solvent	Base	Isotope	k_B, M^{-1} sec^{-1} [a]	k_s, sec^{-1} [a]	k_B^{2NP}, M^{-1} sec^{-1} [b]
54% t-BuOH–H_2O	Pyridine	H	3.9 ± 0.2 × 10^{-6}	1.4 × 10^{-7}	1.9 × 10^{-6}
54% t-BuOH–H_2O	Pyridine	D[c]	4.3 ± 0.1 × 10^{-7} [c]	0.7 × 10^{-7} [c]	2.1 × 10^{-7} (k_D)
H_2O	Pyridine	H	4.3 ± 0.3 × 10^{-5}	3.9 × 10^{-7}	1.7 × 10^{-5}
H_2O	Pyridine	D[c]	3.6 ± 0.1 × 10^{-6} [c,d]	2.0 × 10^{-7} [c,d]	1.7 × 10^{-6} (k_D)
H_2O	Collidine[e]	H	1.9 ± 0.2 × 10^{-4} [e]	9.3 × 10^{-7} [e]	
H_2O	OAc^-	H	1.3 ± 0.1 × 10^{-5}	[f]	3 × 10^{-6}
54% t-BuOH–H_2O	OAc^-	H	4.0 ± 0.3 × 10^{-5}	[f]	

[a] The data were fitted to eq 2, with k_B the slope, together with the standard error, and k_s the intercept. Because extrapolation to k_s is fairly long and puts greatest emphasis on the slowest runs, where other errors become important, no estimates of error are given. [b] Rate constants for attack of the same base in the same solvent on 2-nitropropane at 25° from ref 5 and 7. [c] This sample contained 1.2% protium compound; the values of k_B are appropriately corrected. [d] All runs in water have substantial blank corrections and are therefore less accurate than the runs in t-BuOH, in spite of similar level of reproducibility. [e] Collidine is 2,4,6-trimethylpyridine; these data are of low precision, see text. [f] These data are not complete enough to warrant extrapolation to give k_s; k_B was calculated using k_s from the runs with pyridine.

TABLE II

RATES OF RACEMIZATION OF METHYL 4-NITROVALERATE AT 30°

Solvent	Base (M)[a]	Isotope	k_{obsd}, sec^{-1}	k_B, M^{-1} sec^{-1}	k_B (Iod)[b]
54% t-BuOH	Py (0.292)	H	1.3 × 10^{-6}	4.1 × 10^{-6}	3.9 × 10^{-6}
54% t-BuOH	Py (0.390)	H	1.5 × 10^{-6}	3.8 × 10^{-6}	
H_2O	Coll (0.0815)	H	1.48 × 10^{-5}	1.77 × 10^{-4}	1.9 × 10^{-4}
H_2O	Coll (0.0798)	H	1.57 × 10^{-5}	1.91 × 10^{-4}	
H_2O	Coll (0.0565)	D	8.2 × 10^{-7}	6.8 × 10^{-6}	
H_2O	Coll (0.0720)	D	9.4 × 10^{-7}	6.7 × 10^{-6}	
H_2O	Coll (0.0870)	D	1.01 × 10^{-6}	6.5 × 10^{-6}	

[a] Py = pyridine, Coll = 2,4,6-trimethylpyridine. [b] Values of k_B for iodination from Table I.

boring-group participation by the ester group analogous to that found in the carboxylate ion,[13] but we refrain from guessing whether solvent is involved essentially and in what position. The substantial uncertainty of k_s (see Table I, footnote a) makes extensive discussion unfruitful. Some efforts were made to measure k_s directly, but these were frustrated by the reversibility of reaction 1 in the absence of added base, which led to more complex kinetics and small iodine consumption.

The isotope effects with the base pyridine are not surprising; in t-BuOH (k_H/k_D = 9.1 for k_B) is, within experimental error, the same as that reported for 2-nitropropane (k_H/k_D = 8.9[7]), and in water (k_H/k_D = 11.8), considering the rather larger uncertainty, is also probably indistinguishable from the 2-nitropropane value (k_H/k_D = 10.3).[5] The isotope effect on k_s (k_H/k_D = 2.3 in t-BuOH, 2.0 in water) does appear smaller than that reported by Bell and Goodall[5] (k_H/k_D = 4 in water), possibly again reflecting a different mechanism for the k_s terms, but uncertain because of the k_s uncertainty.

It proved advisable to demonstrate that reaction 1 really represented the reaction. The methyl 4-iodo-4-nitrovalerate proved to be very sensitive, presumably because of the ready reversibility of reaction 1. However, spectrophotometric measurements (rough because of the volatility of bromine) showed that the rates of iodination and bromination were about the same, and bromination did produce a substance clearly identified as methyl 4-bromo-4-nitrovalerate.

Table II presents the racemization data under various conditions. The reactions are all very slow and it was impractical to extrapolate to zero base concentration. The racemization followed a first-order course with a pseudo-first-order constant k_{obsd} and was assumed to be first order in base. The deuterated compound showed the presence of protium compound by a faster initial rate; rates reported are for the later stages of the reaction.

The first four entries show that the polarimetric rates are reproducible within better than 10%, and are within this same precision the same as the rates measured by iodination. The last three entries show that the deuterium compound reacts far more slowly than the protium compound. The k_B values shown are calculated using k_s from the iodination rates, since the evaluation of k_s polarimetrically is unreliable. The isotope effect using these values then gives the average $k_B^H = 1.84 \times 10^{-4}$, $k_B^D = 6.7 \times 10^{-6}$, $k^H/k^D = 27$. The result is quite sensitive to the value of k_s chosen, especially for the deuterated compound, but the presence of a very large isotope effect in reasonable agreement with the earlier result is unequivocal; even if $k_s = 0$, the isotope effect, at 30°, based on the more concentrated solutions, is over 15.

We conclude that the earlier very large isotope effect in the hindered proton transfer is real; it is not an artifact of the iodination method used before.[5,7] The iodination method, however, does become less accurate as the reactions get slower and side reactions get faster, and is very close to its practical limit with some of the deuterated cases with the highly methylated pyridines, the earlier conditions.[7]

Experimental Section

Materials.—The *tert*-butyl alcohol used was of commercial grade and of good melting point. For reproducibility it was found preferable to prepare the solvent gravimetrically (54%

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[13] H. Wilson and E. S. Lewis, *J. Amer. Chem. Soc.*, **94**, 2283 (1972).

tert-butyl alcohol by weight). All aqueous solutions were made up using glass distilled water.

Analytical grade pyridine was dried over molecular sieve and distilled through a Nester-Faust spinning band column. Purity was checked by an analysis on a Perkin-Elmer gas chromatograph using a 20-ft Carbowax column (<1% impurity).

1,3,5-Trimethylpyridine (commercial sample 99.9% purity claimed) was distilled after treatment with boron trifluoride etherate.

Methyl 4-nitrovalerate was prepared by a triethylamine-catalyzed Michael reaction of nitroethane and methyl acrylate according to published procedure.[14] The procedure used for preparation and analysis of the D ester was essentially that of Allen,[11] except that sodium carbonate was used as the base. Protio ester was combined with a large excess of D_2O (99.8%) and a small quantity of sodium carbonate to effect exchange. The mixture was heated at 45° for 24 hr, being stirred continuously. The organic layer was separated and fractionally distilled after each exchange. Four such exchanges were usually necessary. Yields were poor because of a competing reaction leading to the formation of levulinic acid. The extent of deuteration was readily estimated by nmr, approximately by disappearance of the 1 H sextet at τ 5.1–5.7, more accurately by the change of the 3 H doublet at τ 8.4–8.6 into a symmetric triplet.

Optically active ester was prepared by Fischer esterification of the optically active acid, which was prepared by published procedures.[7] Resolution of the deuterated acid (obtained by acid hydrolysis of the D ester) was found to be possible with only a small amount of exchange by the same method. Fischer esterification gave the optically active D ester.

All the materials had nmr spectra consistent with their assigned structures.

Rate Measurements.—All iodinations were carried out exactly according to the earlier procedure.[7]

Racemization data were obtained using a Bendix automatic polarimeter; a jacketed cell was thermostated at 30°.

Solutions for observation were made by mixing thermostated solutions of reagents, of known concentration, in a definite ratio. Prior to this the polarimeter had been zeroed with solvent in the cell. The cell was rinsed four or five times with the reaction mixture before being filled for measurement. The change of rotation with time was recorded automatically. Reactions were normally followed (where possible) over 3 half-lives.

With slower reactions ($t_{1/2}$ >1 week) an offset zero method was used to follow the change more accurately. The scale was chosen so that a change in rotation of 10 millidegrees would give readings across the full scale, *i.e.*, a full-scale deflection = 10 millidegrees, and the zero was set at the end of the chart instead of the middle. This increased sensitivity enabled measurements to be made a little more accurately, but prevented scale changes.

Product Studies.—Attempted iodination of methyl 4-nitrovalerate under the same conditions as those used in the kinetic studies were not fruitful because of equilibration. It was believed that bromination would overcome the problem of reversibility and that the position of bromination would be analogous to that of iodination, and rough rate measurements confirmed this.

Bromine was added, dropwise, to an alkaline solution of the ester until no additional bromine was consumed. The mixture was twice extracted with ether. After drying, the ether was removed and a gc analysis of the residue was made. This indicated the formation of a new higher boiling product which was purified by preparative gc on a 2.5 ft × 0.5 in. column (25% SE-30 on 60/80 mesh Chromosorb P) at 200°. It was identified as methyl 4-bromo-4-nitrovalerate by spectral methods: nmr, 3 H singlet τ 7.8, 3 H singlet 6.4, 4 H irregular multiplet 7.2–7.7; ir 1370, 1560 cm^{-1}, characteristic of the NO_2 group; mass spectrum showed the characteristic bromine doublets and the heaviest ion corresponded to loss of NO_2 only. The ester was independently synthesized by esterification of the corresponding acid[13] and was found to have the same spectral characteristics.

Registry No.—Methyl 4-nitrovalerate, 10312-37-5.

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Structural Directivity in the Diels–Alder Reaction. Dependence on Dienophile Cis–Trans Geometry

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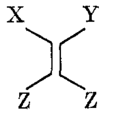
Citracononitrile and mesacononitrile were treated with six unsymmetrical dienes, and the structural isomer ratios were determined. Substantial differences between the ratios obtained from citracononitrile and mesacononitrile were observed in the reactions with 1,3-pentadiene and 3-phenyl-1,3-pentadiene. Determination of structural isomer ratios involved a one-step degradation of the dinitrile adducts to mixtures of substituted benzonitriles by treatment with potassium *tert*-butoxide and anthraquinone. This is a new reaction apparently involving the quinone dehydrogenation of carbanions.

The wealth of information available concerning structural directivity in the Diels–Alder reaction deals almost exclusively with orienting effects of diene and dienophile substituent groups as they vary in electronic character and size.[2] In general, any substituents X and Y located on the same olefinic carbon atom of the dienophile **1**, regardless of their electronic character, reinforce each other's structural directing influence in Diels–Alder reactions with unsymmetrical dienes. On the other hand, dienophiles **2** and **3**, with substituents X and Y located on opposite ends of the olefinic bond, whether they be cis or trans to each other in any particular compound, compete for structural directivity.



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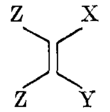

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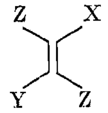

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The possibility that dienophile geometry may play a significant role in determining structural directivity is suggested by an example reported by Bachmann, who found that diene **4** reacted with citraconic anhydride (**5**) to give predominantly structural isomer **6**, while mesaconic acid (**7**) gave predominantly isomer **8**.[3] The opposing structural directing substituents are a methyl group and a hydrogen atom in both of these dienophiles. If one considers only the nature of these opposing groups, without regard to geometry or nature of the

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