

RATES OF HYDROGEN EXCHANGE AND KINETIC ISOTOPE EFFECTS IN THE REACTION OF *p*-NITROPHENYLNITROMETHANE WITH AMINE BASES IN TOLUENE SOLUTION: ABSENCE OF INTERNAL RETURN

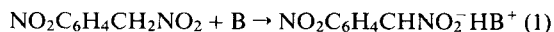
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Rates of loss of tritium from *p*-nitrophenylnitromethane- α -*t* in toluene solution catalyzed by a series of amine bases show that hydrogen exchange in this system occurs at the same rate as ionization of the carbon acid, and that internal return is not taking place. This substantiates a previous suggestion that very large deuterium isotope effects reported for some of these reactions and attributed to extensive tunnelling were determined under conditions where the isotopic label was being lost and are therefore artifacts. This study provides isotope effects which are generally much smaller than those reported previously, but some tunnelling may still be taking place in some of these reactions.

INTRODUCTION

Quantum mechanical penetration of an energy barrier, or tunnelling, is more probable for light than for heavy particles, and it can therefore produce kinetic isotope effects that are larger than those predicted by semi-classical isotope effect theory.¹ Such very large isotope effects, some as great as $k_H/k_D = 50$ at 25°C, have been reported for hydron transfer from the carbon acid *p*-nitrophenylnitromethane to a series of amine bases in non-polar solvents, giving ion-pair products:²



Since isotope effects as large as this exceed by a considerable margin the maximum value that can be attributed to complete loss of all of the zero-point energy of a carbon—hydrogen bond, these large isotope effects soon came to be regarded as good evidence for quantum mechanical tunnelling at a time when convincing evidence for this phenomenon in proton transfer reactions was rare.

Reinvestigation of some of these reactions, however, revealed deviations from expected kinetic behavior which could be attributed to loss of isotopic label from the deuterated substrate through exchange with adventitious protium. Detailed kinetic analysis taking such exchange into account lowered the large isotope effects to values within the limits of semi-classical theory.³

This criticism of the original work was countered⁴ by

the argument that rates of hydrogen exchange in these systems were not known, and internal return,⁵ which occurs in some carbon acid ionization reactions, could well make exchange much slower than proton transfer. In that case, the isotopic integrity of the deuterated substrate would be maintained. It was further proposed that the kinetic deviations that were observed might be explained as an influence of adventitious water, which is very difficult to keep out of some of the systems used; this might affect the rate law without changing the isotope effect. If this were so, then the original claim of very large isotope effects would stand.

In order to supply the missing information, we have determined rates of hydrogen exchange in these systems by measuring rates of loss of tritium from *p*-nitrophenylnitromethane- α -*t*. The results we obtained have been reported in preliminary form;⁶ we now describe our work in full.

EXPERIMENTAL

Materials. *p*-Nitrophenylnitromethane was prepared as reported in the literature⁷ by treating *p*-nitrobenzyl bromide with silver nitrite.⁸ This material was labelled with tritium through hydrogen exchange with tritiated water. A mixture of 50 mg of *p*-nitrophenylnitromethane, 100 μ l of tritiated water (0.1 Ci ml⁻¹) and sufficient 1,4-dioxane to make a homogeneous solution

(ca 100 μ l) was allowed to stand at room temperature for 1 week. The solvents were then removed by applying high vacuum and heating at 50 °C for 24 h. The residue was found to be pure by gas chromatography. An analogous experiment using D₂O in place of tritiated water followed by examination of the product by mass spectrometry and proton and carbon-13 NMR showed that isotope incorporation had taken place, as intended, only in the methylene group.

Literature methods were used to prepare pentamethylguanidine⁹ and *n*-butyl- and *n*-nonyl-*N,N*-diethylamine.¹⁰ All other materials were of the best available commercial grades. Amines were purified by drying over anhydrous sodium or potassium hydroxide followed by distillation under reduced pressure (triethylamine and tri-*n*-butylamine) or preparative gas chromatography (tetramethyl- and pentamethylguanidine, *n*-butyl- and *n*-nonyl-*N,N*-diethylamine, 1,5-diazabicyclo[4.3.0]non-5-ene and 1,5-diazabicyclo[5.4.0]undec-5-ene), except for quinuclidine, which was purified by vacuum sublimation. Toluene was dried and purified by heating ACS-grade material under reflux over molten sodium for several hours followed by distillation in a dry nitrogen atmosphere. The first and last 10% of the distillate were discarded and the middle 80% was stored under nitrogen in brown bottles.

Kinetics. Rates of detritiation of *p*-nitrophenylnitromethane- α -*t* were measured by radioactive assay of the labelled substrate. Solutions of amine catalysts in toluene were prepared by weight and molar concentrations at the reaction temperatures were calculated using the known density-temperature relationship for toluene.¹¹ Appropriate volumes, usually 50 ml, of these solutions were allowed to come to temperature equilibrium with a constant-temperature bath controlled to ± 0.02 °C, and reactions were then initiated by adding 2 μ l of *p*-nitrophenylnitromethane- α -*t* stock solution and shaking the resulting mixtures vigorously. At appropriate times, aliquots of reaction mixture were removed by volumetric pipette and were quenched in an excess of aqueous hydrochloric acid. The toluene and aqueous layers were separated, and the toluene layers were washed three times with aqueous hydrochloric acid, were dried with anhydrous calcium chloride, and were assayed for radioactivity by liquid scintillation counting.

p-Nitrophenylnitromethane concentrations in the reaction mixtures were 2.5×10^{-7} M, and concentrations of the labelled material, *p*-nitrophenylnitromethane- α -*t*, were ca 10^{-5} times lower. Amine concentrations, chosen to give convenient rates of exchange, ranged from 10^{-2} M for the slower systems to 10^{-5} M for the faster systems. Even so, some of the more reactive systems required the use of a special sampling device,¹² which was patterned after a gas-driven rapid-operating pipette.¹³

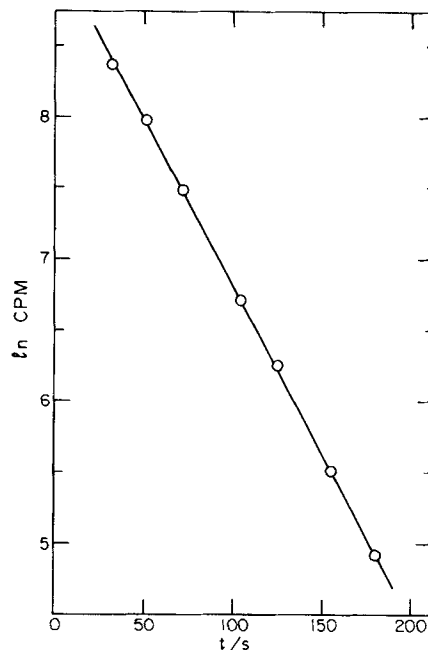


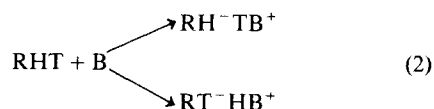
Figure 1. First-order plot for the detritiation of *p*-nitrophenylnitromethane- α -*t* by 9.9×10^{-4} M tetramethylguanidine in toluene solution at 5.0 °C

Reactions were followed for 3–4 half-lives and data obtained in this way obeyed the first-order kinetic law accurately; an example is shown in Figure 1. Observed first-order rate constants were obtained by least-squares fitting to a linear expression using 'infinite time' radioactivities measured after 15 half-lives.

RESULTS

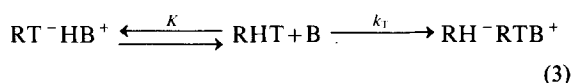
First-order specific rates of loss of tritium from *p*-nitrophenylnitromethane- α -*t* to nine different amine bases were determined at 25 °C and for three of these additional measurements were made at 2–4 other temperatures. In each case the base concentration was varied, generally by a factor of five, and 4–6 different concentrations were usually used. These data are summarized in the thesis upon which this paper is based.¹²

p-Nitrophenylnitromethane has two acidic hydrogens, but, at the tracer level of radioactivity used, the concentration of doubly tritiated molecules is negligibly small and only the singly labelled substrate, RHT, need be considered. This substance can reach in either one of two ways, by transferring a triton or by transferring a proton:



The latter reaction is a 'dead-end' process which puts tritium into a non-exchanging position, and it will not contribute to the rate of loss of tritium directly. It will, however, provided it occurs to a significant extent, deplete the concentration of RHT and affect the rate of detritiation indirectly.

This dead-end reaction involves the transfer of proton, whereas that leading to exchange involves transfer of tritium; the dead-end reaction will therefore be faster than exchange by a tritium isotope effect. Isotope effects on these reactions are large (see below), and this rate difference will therefore be appreciable. Since the ion pairs are formed reversibly, this dead-end reaction will also be reversible, and formation of the dead-end ion pair can consequently be treated as a rapidly established non-productive side-equilibrium:



This conclusion is supported by calculations involving numerical integration of the differential form of the rate law using values of the necessary parameters (rate and equilibrium constants and isotope effects) consistent with experimental observation.¹² The rate law for such a process is

$$k_{\text{obs}} = k_T [\text{B}] / (1 + K[\text{B}]) \quad (4)$$

It predicts that the exchange reaction will show base catalysis at low $[\text{B}]$, with k_{obs} directly proportional to $[\text{B}]$, but, as $[\text{B}]$ increases, this catalysis will diminish and eventually will become saturated. As Figure 2 shows, this proves to be the case experimentally.

The relationship of equation (4) can be linearized by taking reciprocals of both sides. This leads to the

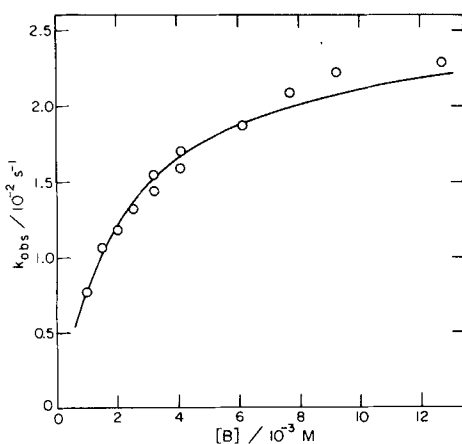


Figure 2. Relationship between tetramethylguanidine concentration and observed rate constants for the detritiation of *p*-nitrophenylnitromethane- α -*t* in toluene solution at 5.0 °C

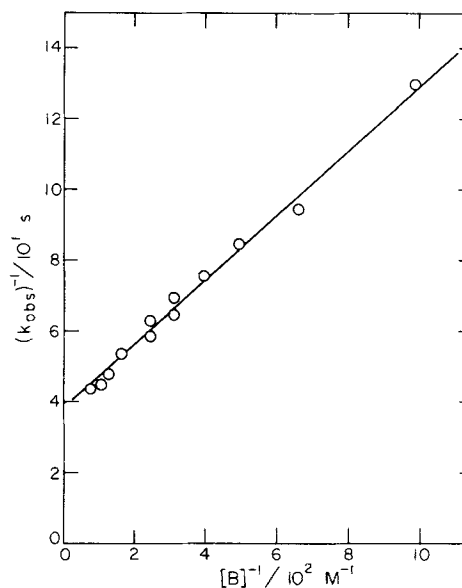


Figure 3. Reciprocal plot of the data shown in Figure 2

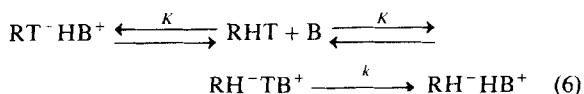
equation

$$1/k_{\text{obs}} = (K/k_T) + 1/k_T [\text{B}] \quad (5)$$

which predicts that a plot of $1/k_{\text{obs}}$ vs $1/[\text{B}]$ will be linear and that both k_T and K may be evaluated from the slope and intercept of such a plot. Figure 3 shows that this relationship is also obeyed. Least-squares analysis of the data gives $(k_{\text{obs}})^{-1} = (3.86 \pm 0.14) \times 10 + (9.04 \pm 0.32) \times 10^{-2} [\text{B}]^{-1}$, from which $k_T = (\text{slope})^{-1} = 11.1 \pm 0.4 \text{ M}^{-1} \text{ s}^{-1}$ and $K = (\text{intercept})/(\text{slope}) = 427 \pm 22 \text{ M}^{-1}$. If, as seems probable, there is little or no isotope effect on ion pair formation, i.e. if the two ion pairs shown in equation (3) are formed in similar amounts, the equilibrium constant K should be equal to half of the ion-pair formation constant for the system: $K = K_{\text{IP}}/2$. Such ion-pair formation constants have been measured,² and that for the process under discussion is $K_{\text{IP}} = 839 \text{ M}$ (This value was calculated from ΔH° and ΔS° for ion-pair formation determined from spectrophotometric measurement of K_{IP} over the temperature range 10–30 °C^{2b}); this makes $K_{\text{IP}}/2 = 420 \text{ M}^{-1}$, which is in very good agreement with the value of K determined from the data in Figures 2 and 3.

This analysis presumes that the triton transfer step in equation (3) is not reversible, and that internal return is therefore not taking place. An analogous treatment may be carried out for a process in which internal return does occur. The kinetic scheme for such a situation will have the formation of both ion pairs as rapid and reversible steps, and loss of radioactive label from the tritium-

transferred ion pair will be rate determining:



The rate law for this case is

$$k_{\text{obs}} = kK[\text{B}]/(1 + 2K[\text{B}]) \quad (7)$$

A curvilinear relationship between k_{obs} and $[\text{B}]$ with saturation of base catalysis at high $[\text{B}]$ is again predicted, as is also a linear reciprocal plot:

$$1/k_{\text{obs}} = (2/k) + 1/kK[\text{B}] \quad (8)$$

However, now the parameters that may be obtained from the slope and intercept of the reciprocal plot are different; in particular, the intercept divided by the slope is now equal to $2K$ instead of just K as was the case for no internal return. Since the definition of K has not changed, and $K = K_{\text{IP}}/2$ still holds, $2K = K_{\text{IP}}$ and, if the internal return mechanism is correct, the intercept divided by the slope should be equal to K_{IP} . The fact that (in-

tercept)/(slope) = $427 \pm 22 \text{ M}^{-1}$ is different from $K_{\text{IP}} = 839 \text{ M}^{-1}$ may therefore be taken as evidence that internal return is not occurring. Additional support for a mechanism without internal return is given below.

The reciprocal expression of equation (5) was used to analyze the relationship between k_{obs} and $[\text{B}]$ for all of the amines studied here. In all cases this method determined the rate constant k_{T} well; the results are listed in Table 1. Statistically significant values of the equilibrium constant K , on the other hand, often could not be obtained because the reactions were fast, and low values of $[\text{B}]$ had to be used to put k_{obs} into a measurable range; in such situations the product $K[\text{B}]$ was small compared with 1, and the significant curvature in plots of k_{obs} vs $[\text{B}]$ needed to evaluate K was not achieved. However, the accurate determination of K was not the purpose of this work.

For three of the bases, detritiation rate measurements were made over a range of temperatures, and Arrhenius plots were constructed. The activation energies, E_{a} , and pre-exponential factors, A , so obtained are listed in Table 2.

Table 1. Summary of rate constants for detritiation of *p*-nitrophenyl-nitromethane- α -*t* by amine bases in toluene solution

Base	$T/^\circ\text{C}$	$k_{\text{T}}/\text{M}^{-1} \text{s}^{-1}$
Tetramethylguanidine	5.0	11.1 ± 0.4
	15.0	18.6 ± 0.2
	25.0	30.3 ± 0.5
	35.0	41.9 ± 0.6
	45.0	61.2 ± 1.0
Triethylamine	0.4	1.31 ± 0.03
	15.0	2.28 ± 0.03
	25.0	3.17 ± 0.04
Quinuclidine	5.0	28.1 ± 0.6
	15.0	45.2 ± 0.4
	25.0	63.8 ± 0.6
Tri- <i>n</i> -butylamine	25.0	0.715 ± 0.010
<i>n</i> -Butyl- <i>N</i> , <i>N</i> -diethylamidine	25.0	11.1 ± 0.1
<i>n</i> -Nonyl- <i>N</i> , <i>N</i> -diethylamidine	25.0	32.8 ± 0.1
Pentamethylguanidine	25.0	469 ± 2
1,5-Diazabicyclo[4.3.0]non-5-ene	25.0	3100 ± 40
1,5-Diazabicyclo[5.4.0]undec-5-ene	25.0	2480 ± 30

Table 2. Activation energies and pre-exponential factors for detritiation of *p*-nitrophenylnitromethane by amine bases in toluene solution

Base	$E_{\text{a}}/k_{\text{cal}} \text{ mol}^{-1}$	Log A	$E_{\text{a}}^{\text{T}} - E_{\text{a}}^{\text{H}}/k_{\text{cal}} \text{ mol}^{-1 \text{a}}$	$A_{\text{T}}/A_{\text{H}}^{\text{a}}$
Tetramethylguanidine	7.46 ± 0.28	7.22 ± 0.20	3.25 ± 0.28	5.9 ± 2.8
Triethylamine	5.83 ± 0.09	5.08 ± 0.07	1.73 ± 0.11	0.92 ± 0.19
Quinuclidine	6.81 ± 0.46	7.11 ± 0.35	1.68 ± 0.47	0.99 ± 0.81

^aParameters for protio reaction taken from Ref. 2c.

DISCUSSION

Internal return

The objective of this work was to determine whether hydrogen exchange and carbon acid ionization occur at comparable rates in the reaction of *p*-nitrophenyl-nitromethane with certain amine bases in toluene solution, or whether exchange is markedly slower than ionization, i.e. whether or not internal return is taking place in these reactions. This can be accomplished by comparing the rates of ionization of the protio substrate measured in previous studies^{2,3} (whose values appear to be reliable; questions have been raised only about rates of ionization of the deuterio substrate) with rates of hydrogen exchange measured here. Such a comparison should be made using the same isotope of hydrogen for both processes, in order to eliminate the influence of isotope effects, and we have therefore translated the specific rates of ionization of the protio substrate into rate constants for tritium transfer, using tritium isotope effects calculated by the Swain–Schaad relationship¹⁴ from reported deuterium effects. The results are listed in Table 3.

It may be seen that in no case are rates of ionization estimated in this way, $(k_T)_{est}$, greater than the rates of exchange, $(k_T)_{obs}$. For the first three entries there is in fact good agreement between the two kinds of rate constant. Therefore, since rates of ionization are not higher than rates of exchange, hydron transfer must lead directly to exchange and internal return cannot be taking place in these reactions.

This conclusion, however, would seem to be spoiled by the last five entries in Table 3. These show rates of exchange that are significantly faster than rates of ionization, which is an impossible situation if exchange occurs as expected through hydron transfer from the

carbon acid to the amine acceptor. However, there is a reasonable explanation. If internal return is not occurring, then, provided there is a pool of exchangeable protium in the reaction medium, the deuterated substrate will lose its isotopic label every time it ionizes. Such a transformation of deuterio to protio substrate is known to depress the observed rate constants and lead to erroneously large deuterium isotope effects.³ This would make the isotope effects used in calculating values of $(k_T)_{est}$ too large, and that would lead to artificially small estimates of this rate constant.

Evidence for the existence of the pool of exchangeable protium needed for such an explanation comes from the very fact that hydrogen exchange does take place; i.e. that the tritiated substrate does lose radioactivity, as shown, for example, by the kinetic run illustrated in Figure 1. In this case, an obvious source of exchangeable protium is the N–H bond of the amine triton acceptor, present in great excess over the tritiated substrate. Some of the amines used here and in the earlier studies,^{2,3} however, have completely alkylated basic nitrogen atoms and possess no N–H bonds, and yet the labelled substrate loses radioactivity to toluene solutions of these amines just as it does to solutions of amines which do have N–H bonds. There must therefore be another source of exchangeable protium, and it is likely that this is adventitious water. Most of the amines used in these studies are highly hygroscopic, and it is very difficult to keep toluene solutions of these substances absolutely dry; we are sure that, despite strenuous efforts, we were not able to do so. Very little water, moreover, is needed to produce the effects observed. We estimate, for example, that water concentrations of the order of 10^{-5} M would be sufficient to account for the extents of exchange we have seen with amine acceptors possessing no N–H bonds,

Table 3. Rate constants and isotope effects for the reaction of *p*-nitrophenylnitromethane with amine bases in toluene solution at 25°C

Base	$k_H/M^{-1} s^{-1a}$	k_H/k_D^a	$(k_T)_{est}^b$	$(k_T)_{obs}^c$	k_H/k_T	$(k_H/k_T)^{1/1.442}$
Pentamethylguanidine	45 000 ^d	14 ^d	520	470	48	14.6
1,5-Diazabicyclo[5.4.0]undec-5-ene	270 000 ^e	13 ^e	3200	3100	54	16.0
<i>n</i> -Butyl- <i>N,N</i> -diethylamidine	685 ^f	13 ^f	9.9	11	31	10.8
Tri- <i>n</i> -butylamine	43 ^g	14 ^g	0.48	0.72	30	10.6
Triethylamine	132 ^g	11 ^g	2.1	3.2	21	8.2
<i>n</i> -Nonyl- <i>N,N</i> -diethylamidine	790 ^f	8 ^f	20	33	12	5.6
Quinuclidine	2200 ^g	16 ^g	22	64	17	7.2
Tetramethylguanidine	2290 ^g	45 ^g	4.8	30	38	12.4

^a Observed values reported in references indicated.

^b $(k_T)_{est} = k_H/2(k_H/k_D)^{1.442}$

^c This work.

^d Ref. 3b.

^e Ref. 2f.

^f Ref. 2e.

^g Ref. 2c.

and it is reported that water concentrations in the region of 10^{-3} M were frequently found in previous studies using "dry" toluene as the solvent.⁴ Each of these water concentrations is many orders of magnitude greater than the concentration of isotopically labelled substrate generally used, and each therefore represents an appreciable pool of exchangeable protium.

The argument has been advanced that adventitious water present in sufficient concentrations will mimic the deviations from kinetic behavior previously attributed to loss of isotopic label from the deuterated substrate through exchange.⁴ This claim is based on the observation that the strongly basic amines used in these studies react with water in toluene solution to form quaternary ammonium hydroxide ion pairs:



The hydroxide ions so generated, being strong bases themselves, will react with *p*-nitrophenylnitromethane:



and, if this reaction is sufficiently fast, upward deviations from a linear dependence of observed rate constants on base concentration will result, and perhaps even departures from first-order kinetics will occur.

These arguments should apply both to rates of detritiation and to rates of deuterium transfer, but we have found no such effects, even with reactions conducted in toluene containing deliberately added water. Figure 4 illustrates the situation for a water-saturated toluene solvent (ca. 0.02 M H_2O).¹⁵ Each of the runs shown there was accurately first order, and a

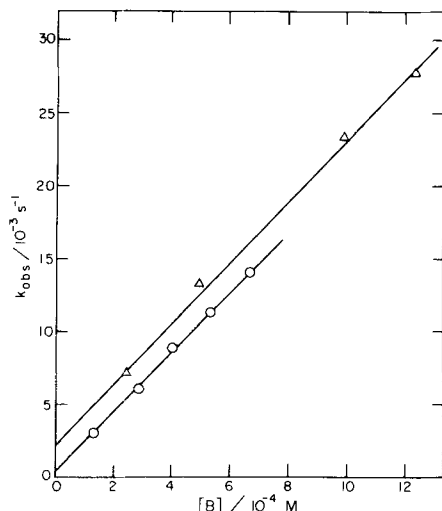


Figure 4. Effect of water on rates of detritiation of *p*-nitrophenylnitromethane- α -*t* catalyzed by tetramethylguanidine in toluene solution at 25.0°C . Δ , 'Dry' solvent; O , H_2O -saturated solvent (0.02 M H_2O)

linear dependence of k_{obs} on $[\text{B}]$ was maintained, just as in the 'dry' medium (at the base concentrations used for the runs shown in Figure 4, the extent of dead-end ion-pair formation is small and the curvilinear relationship expected between k_{obs} and $[\text{B}]$ degenerates into a linear relationship). Similar behavior has been observed for the ionization reactions of *p*-nitrophenylnitromethane with tetramethylguanidine and *N,N*-diethyl-*n*-pentylamine in dry and water-saturated toluene solution.^{3b}

It is likely that the expected kinetic deviations⁴ did not materialize because the rate constant for the reaction of *p*-nitrophenylnitromethane with quaternary ammonium hydroxide ion pairs used in the prediction was too large. This rate constant could not be measured, and that determined for a related ion pair, tetrabutylammonium hydroxide, was used instead. It is unlikely, however, that these two rate constants are similar. The quaternary ammonium groups of the ion pairs formed by reaction of water with amines [equation (9)] will all possess at least one N-H bond, and these N-H bonds will provide sites at which hydroxide ions can bind tightly, through hydrogen bonding, to their ammonium ion partners. No such sites are available in the tetrabutylammonium ion, and hydroxide ions associated with this species will be much more loosely bound, and therefore much more kinetically effective. The tetrabutylammonium hydroxide ion pair can therefore be expected to react with *p*-nitrophenylnitromethane much faster than, and thus be a poor model for, ion pairs generated by the reaction of amines with adventitious water.

Comparison of rates of ionization with rates of hydrogen exchange thus indicates that the two are the same, and that ionization leads directly to exchange and internal return is not taking place in these reactions. This conclusion is supported by results obtained from analysis of the curvilinear relationship between observed rates of exchange and base concentration, as discussed above. It is also consistent with expectation based on the fact that the acid ionization of nitro compounds, such as *p*-nitrophenylnitromethane, is an intrinsically slow process.¹⁶ This means that, in approximately ergoneutral systems such as those investigated here and in previous studies,^{2,3} rates of hydrogen transfer will be slow in both directions; reformation of the carbon acid from the ion-pair hydron transfer product is therefore unlikely to be sufficiently faster than exchange of hydrogen in the ion pairs, which is probably a diffusion-controlled process, to give internal return.

Isotope effects

In the absence of internal return, isotope exchange and ionization occur through the same rate-determining step, and the detritiation rate constants determined here

may be combined with published specific rates of ionization of the protio substrate^{2,3} to provide tritium isotope effects. Such isotope effects, together with their deuterium equivalents, are given in the last two columns of Table 3. These isotope effects are generally smaller than those reported before; an especially marked reduction is found for tetramethylguanidine acting as the hydron acceptor. There is good agreement, however, for pentamethylguanidine, in the ionization of which loss of deuterium label was suppressed by carrying out the measurements in D₂O-saturated toluene solution.^{3b} The value obtained here for tetramethylguanidine is also consistent with $k_H/k_D \approx 11$ at 30 °C estimated for this base from detailed analysis of the non-first-order kinetics observed for the ionization of the deuterio substrate in the presence of the protio isotopomer of this base.^{3a}

Although the isotope effects determined here are generally less than previous values, some are still fairly large. However, none is larger than the semi-classical maximum limit, $k_H/k_D = 15-20$, that may be estimated for complete loss of all of the zero-point energy of the stretching and both bending vibrations of a carbon—hydrogen bond, with no contribution from tunnelling.¹⁷ The completely unbound transition state that this would require, however, is implausible, and a more realistic upper limit is judged to be $k_H/k_D = 10$.¹⁸ By this criterion, tunnelling could be taking place in several of the reactions in Table 3, notably that with tetramethylguanidine as the base. This idea receives some support from the activation energy difference and ratio of pre-exponential factors which may be obtained for this system by combining the results from this study with values reported for the protio substrate;^{2c} the resulting isotopic differences (Table 2) are just outside the limits generally considered to signify no tunnelling; they contrast with the 'normal' results found for triethylamine and quinuclidine, for which the isotopic effects themselves are also well below the semi-classical limit.

ACKNOWLEDGEMENTS

We are grateful to the Natural Sciences and Engineering Research Council of Canada and the Donors of the Petroleum Research Fund, administered by the American Chemical Society, for financial support of this work.

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