Kinetic Isotope Effect and Tunnelling in the Proton-transfer Reaction between 4-Nitrophenylnitromethane and Tetramethylguanidine in Toluene: A Reinvestigation

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The reaction of the deuterated analogue of 4-nitrophenylnitromethane with tetramethylguanidine in toluene shows complex kinetics compared to the corresponding proton-transfer reaction. The complex kinetics can be accounted for by an H–D exchange mechanism. Comparison of experimental data and data calculated from the assumed reaction mechanism suggests a kinetic isotope effect of about 11 at 30 °C which is confirmed in experiments using deuterated tetramethylguanidine. The results are not in agreement with previously reported values and suggest that the isotope effect and degree of tunnelling is much less than previously supposed.

The proton-transfer reaction (1) between 4-nitrophenylnitromethane (4-NPNM) and the strong base tetramethylguanidine [TMG; $\text{HN}=\text{C}(\text{NMe}_2)_2$] has been found exceptionally suitable for studies of the tunnel effect.^{1–3}

In solvents of low polarity such as toluene and chlorobenzene, large isotopic rate ratios ($k^{\text{H}}/k^{\text{D}} \approx 50$ at 25 °C) are observed. These isotope effects and their temperature variations are only explainable in terms of tunnelling.

The isotope effect in the reaction of 4-NPNM with TMG in toluene is among the highest so far recorded for a simple proton-transfer in solution, and is generally accepted as some of the most convincing evidence for tunnelling in such reactions.^{4,5} It would therefore be of interest to have it confirmed in similar reactions. This has so far proved unsuccessful. Thus,

for the reaction of 4-NPNM in toluene with the following bases: tributylamine, triethylamine, quinuclidine,⁶ *N,N*-diethyl-*n*-alkylamidines,⁷ 1,5-diazabicyclo[5.4.0]undec-5-ene (DBU),⁸ 1,5-diazabicyclo[4.3.0]non-5-ene (DBN)⁹ and pentamethylguanidine,¹⁰ the isotope effects are *ca.* 10–15.

The large effects observed with TMG as compared to trialkylamines have been attributed to an unusually narrow potential energy barrier due to the sp^2 hybridisation of the basic nitrogen atom.³ Since no similar effects are observed with any of the last four bases mentioned above, this explanation must be questioned, and the rather special position of TMG among the bases so far studied must be regarded as largely unexplained.

In previous studies^{11,12} we have observed that deuterium-transfer reactions of $[^2\text{H}_2]$ -4-NPNM exhibit complex kinetics as a result of isotopic exchange. Such exchange may give rise to apparent deuterium-transfer rate constants which are too small and hence to erroneously large isotope effects. These complications are particularly pronounced in reactions with bases containing an exchangeable proton on the basic nitrogen atom such as the amidines. In view of the special position of TMG noted above, and of the fact that TMG also has an exchangeable proton on the basic nitrogen atom, the possibility arises that the deuterium-transfer reaction of TMG is affected by exchange and that the original data are in error. We have therefore reinvestigated the reaction of 4-NPNM with TMG in toluene² at 30 °C with particular emphasis on the kinetic behaviour of the deuterium-transfer reaction.

EXPERIMENTAL

Materials. 4-Nitrophenylnitromethane was prepared by the method of Cooke and MacBeth,¹³ m.p. 90–91 °C (lit. 91 °C), and the deuterated analogue was prepared from this by exchange with sodium methoxide-methan(²H)ol in deuterium oxide.¹⁴ The ¹H NMR spectrum of the deuterated acid was identical to that for the proton acid except for the absence of the methylene proton signal.

Tetramethylguanidine (Koch-Light) was dried with potassium hydroxide and fractionally distilled at reduced pressure, b.p. 23 °C/0.4 mmHg. Deuteration was accomplished by shaking a few milliliter in light petroleum with an excess of D₂O. Sufficient NaOD in D₂O was then added to extract the base into the organic phase, and the aqueous phase discarded. This operation was repeated four times. The solution was then cooled in ice and the solvent evaporated under vacuum. These operations yielded deuterated material containing about 98 % D on the imine nitrogen as judged from the ¹H NMR spectrum.

Toluene was refluxed over sodium with a Dean-Stark trap and fractionally distilled under dry nitrogen.

Apparatus and procedure. Rate constants were generally determined by following the increase with time of the absorbance at 435 nm, using a Canterbury SF-3A stopped-flow spectrophotometer (Nortech Laboratories Ltd.). The signal from the stopped-flow apparatus was digitalized and read out on a typewriter by an Inter technique Didac 800 digital data-processing system. All kinetic measurements were made under first-order conditions with

the base in excess. First-order rate constants were calculated by fitting 15–20 readings of approximately equally spaced absorbance to the first-order rate equation by the LSKINI programme of DeTar.¹⁵

Theoretical runs from the H–D exchange mechanism shown in Scheme 1 were calculated as previously described¹² from the variation with time of the concentrations of the four ion pairs I–IV in Scheme 1 by the REMECH programme of DeTar¹⁶ after assigning rate constants to each step and a set of initial concentrations for the acid and the base. Assignment of rate constants to the various steps in Scheme 1 was done as follows. Since the proton-transfer reaction is free from complications, the forward (k_f^H) and backward (k_b^H) rate constants for this reaction are known. These give values for $k_9 = k_f^H$ and $k_5 = k_{10} = k_b^H$. By assuming a value for the isotope effect equal for the forward and backward reaction (i.e. equilibrium isotope effect = 1), values for the forward (k_f^D) and backward (k_b^D) deuterium transfer reaction can be calculated. This gives value for $k_1 = k_f^D$. In the half-deuterated species a statistical factor of 2 is assumed so that $k_2 = k_7 = \frac{1}{2}k_b^D$, $k_3 = k_8 = \frac{1}{2}k_b^H$, $k_4 = \frac{1}{2}k_f^H$ and $k_6 = \frac{1}{2}k_f^D$. A secondary isotope effect of 15 % was initially included in the appropriate rate constants; this had, however, only a small effect on the calculated results (3–4 %) and was therefore subsequently omitted.

To prevent H–D exchange with the glass in the reaction with deuterated TMG all glass apparatus was treated with dimethyldichlorosilane followed by a methanol rinse and drying.

Scheme 1.

RESULTS

The proton-transfer reaction showed good first-order kinetics in runs with the base in excess, and gave rate constants in agreement with published values.² This reaction was therefore not studied further.

The deuteron-transfer reaction shows small systematic deviations from first-order kinetics in a manner similar to that observed previously in the reaction of 4-NPNM with alkylamidines.^{11,12} The departure from accurate first-order kinetics is not easily detected from the oscilloscopic trace of the reaction, but becomes apparent when the data are fitted to the first-order expression by the least-squares program LSKIN1 of De Tar.¹⁵ This program generates a plot of the residuals, ($A_{\text{obs}} - A_{\text{calc}}$) vs. percent of reaction, which is particularly convenient for visual examination of systematic deviations from first-order behaviour.¹⁷ An example is shown in Fig. 1 for the reaction of 4-[²H₂]-NPNM with TMG in toluene at 30 °C with concentrations of acid and base equal to 2×10^{-5} M and 7.83×10^{-3} M, respectively (filled circles). The dashed lines represent about two standard deviations for a normal first-order proton-transfer reaction. If the data conformed to the first-order expression, there should be no trend.

The kinetic behaviour of the deuteron-transfer reaction can be reproduced by the H-D exchange mechanism shown in Scheme 1. Theoretical runs can be calculated from Scheme 1 by the REMECH program of DeTar if the forward, k_f^H , and backward, k_b^H , rate constants for proton-transfer are known, and if a value for the isotope effect is assumed.¹² The open circles in Fig. 1 illustrate data from a cal-

Fig. 1. Plot of residuals against percent reaction for an experimental (filled circles) and a calculated run (open circles). Total change in A is ca. 0–900.

culated run based on published values² for $k_f^H = 2544 \text{ mol}^{-1} \text{ dm}^3 \text{ s}^{-1}$ and $k_b^H = 19.2 \text{ s}^{-1}$ in toluene at 30 °C, an assumed isotope effect of 11, and the same concentrations of acid and base as in the experimental run. The isotope effect of 11 was found by trial and error to give the best quantitative reproduction of the experimental data. A significantly worse fit was obtained with a variation of ± 2 in the assumed isotope effect. In our stopped-flow apparatus about 3–15 % of the initial reaction is lost due to the dead-time of the apparatus and the sampling mode of the data-acquisition system. In the experimental run in Fig. 1, 15 % was lost and the theoretical run was therefore adjusted accordingly. Thus the two runs illustrated in Fig. 1 represent the last 85 % of the complete reaction. The assumed isotope effect of 11 corresponds to a value for $k_f^D = 231 \text{ dm}^3 \text{ mol}^{-1} \text{ s}^{-1}$, in contrast to the reported value² of $67.3 \text{ dm}^3 \text{ mol}^{-1} \text{ s}^{-1}$ at 30 °C.

The S-shaped plot of the residuals in Fig. 1 is characteristic for the deuteron-transfer reaction and is independent of the concentration of the reactants. The quantitative deviation from first-order kinetics as measured by the standard deviation of the fit of the data does, however, decrease with increasing base concentration. Thus the standard deviation is reduced by a factor of 2–3 for concentrations of base above 0.04 M compared to those below 0.02 M.

Since the data show systematic deviations from first-order kinetics, the apparent first-order rate constant will depend systematically on the extent of reaction covered. It is nevertheless convenient to use the first-order expression,¹⁷ and provided all data refer to the same extent of reaction within a few

Fig. 2. Plot of k_{obs}^D against base concentration. Filled circles are experimental points and dashed line is calculated from the Scheme with $k^H/k^D = 11$. Open circles are values at 30 °C from Ref. 18.

Fig. 3. Plot of $k_{\text{obs}}^{\text{D}}$ against base concentration. Filled circles are experimental points using ordinary TMG, open circles are experimental points using deuterated TMG. Full line and dashed line are calculated from eqn. (2) and Scheme 1, respectively.

percent, valid comparisons between observed and calculated rate constants can be made.

Figs. 2 and 3 show experimentally determined apparent first-order rate constants at various base concentrations (filled circles) and calculated values from Scheme 1 based on an assumed isotope effect of 11 (dashed line). The filled triangle in Fig. 2 illustrates the value of the apparent first-order rate constant obtained for the highest base concentration if only the last 30 % of the reaction is used. For comparison, the data^{2,18} of Caldin and Mateo at 30 °C are shown in Fig. 2 as open circles. The open circles in Fig. 3 are the experimentally observed first-order rate constants obtained when deuterated TMG (DN=C(NMe₂)₂) is used in place of ordinary TMG. A least-squares treatment of these data gives $k_{\text{f}}^{\text{D}} = 244 \pm 8 \text{ mol}^{-1} \text{ dm}^3 \text{ s}^{-1}$ and $k_{\text{b}}^{\text{D}} = 1.3 \pm 0.4 \text{ s}^{-1}$. The straight line in Fig. 3 is calculated from eqn. (2).

$$k_{\text{obs}}^{\text{D}} = k_{\text{b}}^{\text{D}} + k_{\text{f}}^{\text{D}}B \quad (2)$$

which follows from eqn. (1) when the base is in large excess, and with values of $k_{\text{f}}^{\text{D}} = 231 \text{ mol}^{-1} \text{ dm}^3 \text{ s}^{-1}$ and $k_{\text{b}}^{\text{D}} = 1.74 \text{ s}^{-1}$ as used in Scheme 1 to calculate the dashed line.

Although better first-order kinetics were obtained with deuterated TMG than with ordinary TMG, we find it impossible to get completely satisfactory kinetics in the deuterion-transfer reaction as com-

pared to the proton-transfer reaction. We attribute this to difficulties in maintaining TMG fully deuterated in solution and to the presence of adventitious protons in the solvent.

DISCUSSION

The reaction of 4-NPNM and its deuterated analogue with TMG in toluene has been shown by kinetic data, ¹H NMR and absorption spectroscopy to be a reversible proton- or deuterion-transfer giving rise to an ion-pair.² The kinetics and spectrophotometric determination of the equilibrium constant for the proton-transfer reaction is consistent with the mechanism in eqn. (1). Similar results have been obtained for the reaction of 4-NPNM with butylamidine⁷ and DBU⁸ in toluene, and with triethylamine in acetonitrile.¹⁴ No evidence indicates that the deuterion reaction gives other or additional products than the proton reaction.

The kinetic behaviour of the deuterion-transfer reaction between 4-[²H₂]-NPNM and TMG is not consistent with the simple mechanism of eqn. (1). In runs with the base in excess the deuterion-transfer is not first-order in acid (Fig. 1). If the deviations from first-order kinetics are ignored, the reaction is apparently also not first-order in base (Fig. 2), and inconsistent with eqn. (2). The same behaviour was observed in the reaction with alkylamidines and attributed to H–D exchange as shown in Scheme 1.^{11,12} The same mechanism can account for the observed kinetics in the present reaction if an isotope effect of 11 at 30 °C is assumed, as shown by the good agreement between calculated and observed data in Figs. 1, 2 and 3. The fact that improved first-order kinetics as well as a linear relation between k_{obs} and base concentration are obtained with deuterated TMG is consistent with the proposed mechanism. In this case no exchange can occur and Scheme 1 reduces to eqn. (1) where the observed first-order rate constant is related to the forward and backward rate constants and base concentration through eqn. (2). Fig. 3 shows that the observed first-order rate constants obtained with deuterated TMG agree with the line calculated from eqn. (2) with the same values of k_{f}^{D} and k_{b}^{D} as were used in Scheme 1 to reproduce the experimental data obtained with ordinary TMG. It is evident from Fig. 3 that the discrepancy between the observed value for $k_{\text{obs}}^{\text{D}}$ and the value expected if the mechanism was that of eqn. (1) decreases as

the base concentration increases. Thus at base concentrations above 0.05 M almost the same value for $k_{\text{obs}}^{\text{D}}$ is calculated either from Scheme 1, or from eqn. (2), as obtained experimentally using either TMG or deuterated TMG. This is consistent with the assumed H–D exchange mechanism since as the base concentration increases the relative importance of the back reaction will decrease and the observed rate will be dominated by the k_1 or k_f step in Scheme 1 and eqn. (1), respectively. Unfortunately the most convenient base concentrations for the present type of studies are usually below 0.01–0.02 M, and thus fall in the range where the back reaction, and hence exchange, become important.

In the previous study of the present reaction² it was found that the plots of $k_{\text{obs}}^{\text{D}}$ vs. base concentration had intercepts close to zero, and that k_{b}^{D} could therefore not be obtained reliably. An example, with data at 30 °C from the original thesis,¹⁸ is shown in Fig. 2 where $k_f^{\text{D}} = 67.3 \pm 2.3 \text{ dm}^3 \text{ mol}^{-1} \text{ s}^{-1}$ and $k_{\text{b}}^{\text{D}} = 0.11 \pm 0.02 \text{ s}^{-1}$. We believe that the small intercepts and k_{b}^{D} values are misleading and a consequence of H–D exchange by the mechanism in Scheme 1. The small k_{b}^{D} value at 30 °C is inconsistent with the value estimated from $k_{\text{b}}^{\text{D}} = k_f^{\text{D}}/K^{\text{D}}$. At 30 °C $K^{\text{D}} = 120 \pm 50 \text{ dm}^3 \text{ mol}^{-1}$ and hence $k_{\text{b}}^{\text{D}} = 0.56 \pm 0.23 \text{ s}^{-1}$. Alternatively, since the isotope effect on the equilibrium constant is small,² $K^{\text{H}} = 125 \pm 4 \text{ dm}^3 \text{ mol}^{-1}$ may be used in place of K^{D} , in which case $k_{\text{b}}^{\text{D}} = 0.54 \pm 0.02 \text{ s}^{-1}$. Such a value for k_{b}^{D} is not in agreement with the intercept of the straight line in Fig. 2. Thus the original data are either internally inconsistent, or there is a large inverse equilibrium isotope effect ($K^{\text{H}}/K^{\text{D}} = 0.19$). The latter is unreasonable and contrary to the statement that the equilibrium isotope effect is small. A similar estimate of k_{b}^{D} as above with $k_f^{\text{D}} = 231 \text{ dm}^3 \text{ mol}^{-1} \text{ s}^{-1}$, i.e. corresponding to an isotope effect of 11, gives $k_{\text{b}}^{\text{D}} = 1.8 \text{ s}^{-1}$, in reasonable agreement with the intercept of 1.3 in the $k_{\text{obs}}^{\text{D}}$ vs. base plot for the reaction with deuterated TMG (Fig. 3).

The present results show that the deuterium-transfer rate constants for the reaction of TMG with 4-NPNM in toluene are considerably larger, and hence the isotope effects smaller, than previously suggested.² Thus the degree of tunnelling will also be less than supposed. At 30 °C the results indicate an isotope effect of about 11, a value about the same as that observed in other reactions of 4-NPNM in toluene.^{6–10}

It is to be expected that the complications due to H–D exchange will diminish with increasing

polarity of the solvent. As the solvent polarity increases the ion-pair will be increasingly better stabilized and the importance of the back reaction, and exchange, will be reduced. Thus it seems likely that the isotope effects of about 30–50 reported² for the present reaction in cyclohexene, mesitylene, dibutyl ether and chlorobenzene in addition to toluene, are also affected by scrambling. On the other hand, the results in the more polar solvent acetonitrile, dichloromethane and tetrahydrofuran, where $k^{\text{H}}/k^{\text{D}}$ is ca. 11–13, are probably much more reliable.

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