

Factors influencing Kinetic Isotope Effects in Some Proton-transfer Reactions in Aprotic Solvents

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Kinetic studies have been carried out on the proton-transfer reactions of (i) 4-nitrobenzyl cyanide (4-NBC) with tetramethylguanidine (TMG) and (ii) 4-nitrophenylphenylcyanomethane (4-NPPCM) with 1,8-bis(dimethylamino)naphthalene (DMAN) in acetonitrile.

The reaction (i) has a moderate enthalpy of activation ($\Delta H^\ddagger = 25 \text{ kJ mol}^{-1}$) and a negative entropy of activation ($\Delta S^\ddagger = -98 \text{ J mol}^{-1} \text{ K}^{-1}$). The deuterium kinetic isotope effect is large.

The reaction (ii) of the more hindered molecule 4-NPPCM and DMAN has similar activation parameters ($\Delta H^\ddagger = 26 \text{ kJ mol}^{-1}$, $\Delta S^\ddagger = -140 \text{ J mol}^{-1} \text{ K}^{-1}$), but the kinetic isotope effect is considerably larger; also $\Delta H_D^\ddagger - \Delta H_H^\ddagger$ is large (13 kJ mol^{-1}) and A_H/A_D is small, indicating a considerable tunnelling effect. Evidence that the large isotope effects are not artefacts of hydrogen exchange is presented. The tunnelling factor is estimated.

Deuterium kinetic isotope effects and their dependence on various factors have been extensively studied for many years and several reviews are now available.¹⁻⁷ The observed value of the kinetic isotope effects has been found to be a result of two factors, one depending on the loss of zero-point energy for C-H and C-D bonds between the initial and transition states of the reaction, and the other concerned with the quantum-mechanical probability of tunnelling of the proton through the energy barrier. The former, according to the theory of Westheimer,¹ will depend on the 'symmetry' of the transition state.

In our previous papers⁸⁻¹⁰ we have demonstrated that even in polar solvents it is possible to observe high values of kinetic isotope effects and a significant contribution of the tunnelling of the proton. We observed $k_H/k_D = 10.7$ for the reaction of 4-nitrophenylphenylcyanomethane (4-NPPCM) with 1,1,3,3-tetramethylguanidine (TMG)⁸ and $k_H/k_D = 20.0$ for the reaction of the same C-acid with 2-phenyl-1,1,3,3-tetramethylguanidine (PhTMG),¹⁰ both in acetonitrile at 25 °C. The higher values of the kinetic isotope effect in this latter system were attributed to the more symmetrical transition state and to the increase in steric hindrance, both due to the phenyl group attached to the *sp*²-hybridised nitrogen in the PhTMG molecule.

The intention of the present paper is to show the important influence of steric factors in determining kinetic isotope effect values. In order to investigate this influence, we chose to study the reaction of 4-nitrobenzyl cyanide (4-NBC) with TMG, for comparison with the reaction of 4-NPPCM with PhTMG.¹⁰ The structures of the new reagents, compared with those of 4-NPPCM with PhTMG,¹⁰ mean that the C-acid is weaker and the base stronger, so that the symmetry of the transition state is not affected. Moreover, the reactions of C-acids show only a minor dependence of the kinetic isotope effects on the ΔpK_a values of the acids and bases used.¹¹⁻¹³ Thus, any differences between the observed kinetic isotope effect values for the 4-NBC and TMG reaction system and those observed for the reaction of 4-NPPCM with PhTMG¹⁰ may be attributed entirely to a reduction in steric hindrance.

The second reaction system reported in this paper consists of 4-NPPCM reacting with 1,8-bis(dimethylamino)naphthalene (DMAN). This system was designed to make the reaction centre extremely crowded. If steric hindrance is the most important factor influencing kinetic isotope effect values, one could expect

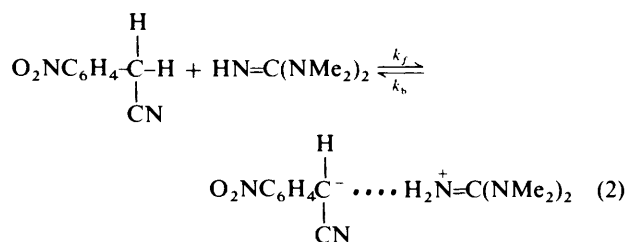
to observe high k_H/k_D values and possibly a large contribution of proton tunnelling in this reaction.

Results and Discussion

Reaction of 4-NBC with TMG in Acetonitrile.—The reaction system of 4-NBC and TMG in acetonitrile gives a red product of $\lambda_{\text{max.}} = 532.4 \text{ nm}$. The absorbance measurements of the product in equilibrium gave a good linear plot of a/A versus $1/b$, as required by equation (1), where a and b are the initial concentrations of the acid and base, respectively; A is the absorbance at equilibrium; ϵ is the molar extinction coefficient of the product; and K is the equilibrium constant of the reaction.

$$a/A = 1/Kb\epsilon + 1/\epsilon \quad (1)$$

Equation (1) is derived on the basis of the assumption that the product is an ion-pair,¹⁴ so the reaction of 4-NBC with TMG may be represented by equation (2).†



The equilibrium constant for this reaction system is $K_{\text{eq}}^{20} = 252 \pm 8 \text{ dm}^3 \text{ mol}^{-1}$ and the molecular extinction coefficient $\epsilon = 32\,700 \pm 1\,500$. The observed equilibrium constant is close to that previously found for the reaction system of 4-NPPCM and PhTMG¹⁰ ($K_{\text{eq}}^{20} = 400 \pm 30 \text{ dm}^3 \text{ mol}^{-1}$). This agreement gives support to our suggestion that the removal of a phenyl ring both from the acidic and the basic sites in the system 4-NPPCM + PhTMG does not greatly change the ΔpK_a value of the system, and hence the symmetry of the transition state remains almost unaffected.

The observed first-order rate constants and second-order rate constants for the proton- and deuterium-transfer reactions are collected in Table 1.

The reaction of 4-NBC and TMG has $k_H^{f,20} = 1\,839 \text{ dm}^3 \text{ mol}^{-1} \text{ s}^{-1}$ and is much slower than the reaction of 4-NPPCM and TMG⁸ ($k_H^{f,20} = 6\,640 \text{ dm}^3 \text{ mol}^{-1} \text{ s}^{-1}$), and of about the same

† Where k_f is the forward rate constant and k_b is the backward rate constant

Table 1. Observed and second-order rate constants for proton- and deuteron-transfer reactions between 4-nitrobenzyl cyanide and tetramethylguanidine in acetonitrileInitial conc. of 4-nitrobenzyl cyanide = 5×10^{-5} M

$T/^\circ\text{C}$	$10^3 b/\text{mol dm}^{-3}$	$k_{\text{obs}}/\text{s}^{-1}$	$k_f/\text{dm}^3 \text{ mol}^{-1} \text{ s}^{-1}$	k_b/s^{-1}	$k_f^{\text{H}}/k_f^{\text{D}}$
Proton-transfer reaction					
5	0.90—4.52	6.21—9.93	$1\,029 \pm 9$	5.2 ± 0.1	
10	0.90—4.52	7.39—12.19	$1\,306 \pm 3$	6.2 ± 0.1	
15	0.90—4.52	9.25—14.58	$1\,480 \pm 10$	7.9 ± 0.1	
20	0.90—4.52	11.10—17.75	$1\,839 \pm 6$	9.5 ± 0.1	
25	0.90—4.52	13.90—22.10	$2\,270 \pm 20$	11.8 ± 0.1	
30	0.90—4.52	18.39—27.57	$2\,545 \pm 20$	16.0 ± 0.1	
35	0.90—4.52	21.82—33.73	$3\,400 \pm 200$	18.8 ± 0.1	
Deuteron-transfer reaction					
5	0.90—4.52	0.073 ₅ —0.313	67 ± 4		15.4 ± 0.9
10	0.90—4.52	0.092 ₅ —0.415	89 ± 4		14.7 ± 0.7
15	0.90—4.52	0.116 ₅ —0.497	107 ± 3		13.8 ± 0.4
20	0.90—4.52	0.142—0.625	136 ± 5		13.5 ± 0.5
25	0.90—4.52	0.174—0.779	170 ± 6		13.3 ± 0.5
30	0.90—4.52	0.216 ₅ —0.975	214 ± 11		11.9 ± 0.6
35	0.90—4.52	0.264 ₅ —1.215	265 ± 12		12.8 ± 0.9

Equilibrium constants:

$$K_{\text{H}}^{20} = \frac{k_f}{k_b} = \frac{1\,839}{9.5} = 194 \pm 2 \text{ dm}^3 \text{ mol}^{-1}; K_{\text{H}}^{20} = 252 \pm 8 \text{ dm}^3 \text{ mol}^{-1}; \epsilon = 32\,700 \pm 1\,500 \text{ dm}^3 \text{ mol}^{-1} \text{ cm}^{-1}; \lambda_{\text{max.}} \text{ of ion-pair product} = 532.4 \text{ nm}.$$
Table 2. The activation parameters for the reaction of proton- and deuteron-transfer between 4-nitrobenzyl cyanide and tetramethylguanidine in acetonitrile

Parameter	Normal substrate	Deuterated substrate
ΔH^\ddagger (kJ mol ⁻¹)	25.0 ± 1.0	29.7 ± 0.5
E_A (kJ mol ⁻¹)	27.5 ± 1.0	32.2 ± 0.5
ΔS^\ddagger (J mol ⁻¹ K ⁻¹)	-98.0 ± 4.0	-102.0 ± 2.0
ΔG^\ddagger (kJ mol ⁻¹)	54.0 ± 2.0	60.0 ± 1.0
A (dm ³ mol ⁻¹ s ⁻¹)	$(1.30 \pm 0.6) 10^8$	$(8.02 \pm 1.83) 10^7$
$\Delta H_{\text{D}}^\ddagger - \Delta H_{\text{H}}^\ddagger$		5 ± 1
$\Delta S_{\text{D}}^\ddagger - \Delta S_{\text{H}}^\ddagger$		4 ± 4
$\Delta G_{\text{D}}^\ddagger - \Delta G_{\text{H}}^\ddagger$		6 ± 2
$A_{\text{H}}/A_{\text{D}}$		1.6 ± 0.8

rate as the reaction between 4-NPPCM and PhTMG¹⁰ ($k_{\text{H}}^{f,20} = 1\,708 \text{ dm}^3 \text{ mol}^{-1} \text{ s}^{-1}$).

The values of the equilibrium constants derived from equilibrium ($K_{\text{eq}}^{20} = 252 \pm 8 \text{ dm}^3 \text{ mol}^{-1}$) and kinetic measurements ($k_{\text{kin}}^{20} = 194 \pm 2 \text{ dm}^3 \text{ mol}^{-1}$) (Table 1) are in good agreement, indicating that the ion-pair product of $\lambda_{\text{max.}} = 532.4 \text{ nm}$ is not involved in any side reactions.

The kinetic curves for deuteron-transfer reactions are exactly first-order and the same values of observed rate constants were obtained when different parts of kinetic curves were used for calculations with Guggenheim's method. The equilibrium constant for the formation of the ion-pair product is high, and so the reverse reaction too slow for the isotopic exchange to make detectable changes in the shapes of the kinetic curves. According to Melander and Saunders,¹⁵ the use of the early part of kinetic curves for the study of deuteron-transfer reactions reduces the probability of the results being distorted by the effects of isotopic exchange. In our case, the reaction studied was slow enough to enable entire kinetic curves to be recorded and used in calculations. This additionally proves that the deuterium isotope effects (Table 1) are not artefacts representing the genuine and unperturbed values. Moreover, the contribution from isotopic 'scrambling'¹⁶ always leads to an increase in observed kinetic isotope effect values. The drop in the isotopic rate ratio observed in the system of 4-NBC with TMG, when

compared with the reaction of 4-NPPCM with PhTMG,¹⁰ cannot therefore be a result of this phenomenon.

The activation parameters for proton- and deuteron-transfer reactions are shown in Table 2.

The values both of enthalpy and of entropy of activation are very similar to those found for the reaction of 4-NPPCM with PhTMG.¹⁰ Although the reaction of 4-NBC with TMG has a ΔpK_a value comparable to that for the reaction of 4-NPPCM with PhTMG,¹⁰ the greater crowding in the latter reaction system should be reflected in smaller rate constants and bigger values for the enthalpy of activation, especially in the D-transfer reaction. The observed similarities of rates and enthalpies of activation, then, seem to be a result of 'additional' acceleration of the reaction between 4-NPPCM with PhTMG¹⁰ by tunnelling of the transferred proton. In our case (Table 2) the rate constants and enthalpies of activation are almost equal for the proton-transfer reaction, and substantially different for the deuteron-transfer reaction, when the reactions of 4-NPPCM with PhTMG¹⁰ and of 4-NBC with TMG are compared. These data give supplementary support to our earlier suggestion concerning the large contribution of tunnelling in the reaction of 4-NPPCM with PhTMG in acetonitrile ($k_{\text{H}}/k_{\text{D}} = 23$; $\Delta\Delta H^\ddagger = 12.4 \text{ kJ mol}^{-1}$; $A_{\text{H}}/A_{\text{D}} = 0.12$),¹⁰ and also suggest that the reaction system of 4-NBC and TMG shows no appreciable tunnelling (Table 2), since the values of the isotopic rate ratio

($k_H/k_D = 13$), the differences in the enthalpies of activation ($\Delta\Delta H^\ddagger = 5 \text{ kJ mol}^{-1}$), and the ratio of Arrhenius pre-exponential factors ($A_H/A_D = 1.6$) are large, but are all in the semi-classical region. We can thus conclude that, when comparing the reaction of 4-NPPCM with PhTMG and of 4-NBC with TMG, it is the reduction in steric hindrance which seems to be responsible for the dramatic decrease in observed kinetic isotope effects and in tunnelling in the latter reaction system.

Reaction of 4-NPPCM with DMAN in Acetonitrile.—The reaction system of 4-NPPCM and DMAN in acetonitrile gives a violet product of $\lambda_{\text{max.}} = 580 \text{ nm}$. Equilibrium measurements of the absorbance of the product show detectable dissociation of the ion-pair product. Therefore neither equation (1), nor the equation which was derived on the basis of the assumption that the product dissociates to separate ions,¹⁴ is fulfilled. Consequently, it is only possible to make an approximate estimate of the equilibrium constant and the molecular extinction coefficient of the product for this reaction system: $K_{\text{eq}}^{20} \approx 2 \text{ dm}^3 \text{ mol}^{-1}$ and $\epsilon \approx 35\,000$ were estimated for ion-pair product formation. Since the value of the extinction coefficient is compatible with those found for the other reactions carried out with 4-NPPCM,^{8,10} the approximation of the equilibrium constant within the same set of experiments seems therefore to be reliable. The much smaller equilibrium constant ($K_{\text{eq}}^{20} = 2 \text{ dm}^3 \text{ mol}^{-1}$) compared with those for the other reactions of this C-acid (K_{eq}^{20} varying from 400–6 000

$\text{dm}^3 \text{ mol}^{-1}$, with bases of comparable strength)^{8,10} is a manifestation of the enhanced steric hindrance in the reaction system. The energy of the ion-pair product is increased by steric inhibition of resonance stabilisation, due to the inability of this sterically hindered system to become planar. This may be the reason why the equilibrium constant is smaller than expected, and for the significant dissociation of the ion-pair product.

The observed and calculated rate constants for the forward and backward proton- and deuteron-transfer-reactions are collected in Table 3.

The comparison of the values of the equilibrium constant calculated from kinetic measurements at 20 °C with that calculated from equilibrium measurements (Table 3) shows that they are of the same order of magnitude; $K_{\text{kin}}^{20} = 7 \text{ dm}^3 \text{ mol}^{-1}$ and $K_{\text{eq}}^{20} = 2 \text{ dm}^3 \text{ mol}^{-1}$ respectively.

The forward rate constants k_f^{20} are 6.7, 6 640, and 1 700 $\text{dm}^3 \text{ mol}^{-1} \text{ s}^{-1}$ for DMAN, TMG,⁸ and PhTMG,¹⁰ respectively, all in acetonitrile. This differentiation of the rate constants is attributed to the increase in the energy of the transition state in the case of the sterically hindered reactions; this is reflected in the activation parameters (Table 4), particularly in the small values of the Arrhenius pre-exponential factor A .

Since the enthalpies for the reaction of 4-NPPCM with PhTMG¹⁰ and DMAN (Table 4) are equal ($\Delta H_H^\ddagger = 26.2 \pm 0.4$; $\Delta H_D^\ddagger = 39.0 \pm 1.0$; and $\Delta H_H^\ddagger = 26.0 \pm 0.8$; $\Delta H_D^\ddagger = 40.0 \pm 3.0 \text{ kJ mol}^{-1}$, respectively), the difference in the rate constants is clearly due to steric factors, reflected in the

Table 3. Observed and second-order rate constants for proton- and deuteron-transfer reactions between 4-nitrophenylphenylcyanomethane and 1,8-bis(dimethylamino)naphthalene in acetonitrile

Initial concentration of 4-nitrophenylphenylcyanomethane = $1 \times 10^{-4} \text{ M}$

$T/^\circ\text{C}$	$10^2 b/\text{mol dm}^{-3}$	$k_{\text{obs}}/\text{s}^{-1}$	$k_f/\text{dm}^3 \text{ mol}^{-1} \text{ s}^{-1}$	k_b/s^{-1}	k_f^H/k_f^D
Proton-transfer reaction					
15	2.02–8.06	0.811–1.150	5.7 ± 0.3	0.7 ± 0.1	
20	2.02–8.06	0.995–1.405	6.7 ± 0.9	0.9 ± 0.1	
25	2.02–8.06	1.209–1.716	8.2 ± 0.5	1.1 ± 0.1	
30	2.02–8.06	1.448–2.075	10.2 ± 0.5	1.2 ± 0.1	
35	2.02–8.06	1.768–2.509	12.4 ± 0.4	1.5 ± 0.2	
40	2.02–8.06	2.228–3.087	14.4 ± 0.3	1.9 ± 0.2	
Deuteron-transfer reaction					
10	0.506–2.024	0.003 85–0.005 98	0.14 ± 0.01		24.3 ± 1.4
15	0.506–2.024	0.004 70–0.008 22	0.23 ± 0.005		20.9 ± 2.9
20	0.506–2.024	0.006 10–0.010 89	0.32 ± 0.01		20.5 ± 1.6
25	0.506–2.024	0.007 91–0.013 98	0.40 ± 0.02		19.6 ± 1.2
30	0.506–2.024	0.010 05–0.017 95	0.52 ± 0.02		18.8 ± 0.8
35	0.506–2.024	0.012 78–0.022 82	0.66 ± 0.02		

Equilibrium constants:

$K_{\text{kin}}^{20} = \frac{k_f^H}{k_f^D} = \frac{6.7}{0.9} = 7 \pm 1 \text{ dm}^3 \text{ mol}^{-1}$; K_{eq}^{20} (estimated) = $2 \text{ dm}^3 \text{ mol}^{-1}$. $\epsilon \approx 35\,000 \text{ dm}^3 \text{ mol}^{-1} \text{ cm}^{-1}$. $\lambda_{\text{max.}}$ of product in acetonitrile = 580 nm.

Table 4. The activation parameters for the reaction of proton and deuteron transfer between 4-nitrophenylphenylcyanomethane and 1,8-bis(dimethylamino)naphthalene in acetonitrile solvent

Parameter	Normal substrate	Deuterated substrate
ΔH^\ddagger (kJ mol ⁻¹)	26.0 ± 0.8	40.0 ± 3.0
E_A (kJ mol ⁻¹)	28.5 ± 0.8	43.0 ± 3.0
ΔS^\ddagger (J mol ⁻¹ K ⁻¹)	-140.0 ± 3.0	-119.0 ± 9.0
ΔG^\ddagger (kJ mol ⁻¹)	68.0 ± 1.0	75.0 ± 9.0
A (dm ³ mol ⁻¹ s ⁻¹)	$(8.47 \pm 3.47) 10^5$	$(1.03 \pm 0.9) 10^7$
$\Delta H_D^\ddagger - \Delta H_H^\ddagger$		13 ± 2
$\Delta S_D^\ddagger - \Delta S_H^\ddagger$		20 ± 8
$\Delta G_D^\ddagger - \Delta G_H^\ddagger$		7 ± 4
A_H/A_D		0.08 ± 0.06

Arrhenius pre-exponential factors ($A = 2.1 \times 10^8$ and $A = 8.5 \times 10^5 \text{ dm}^3 \text{ mol}^{-1} \text{ s}^{-1}$, respectively).

The values of the kinetic isotope effects collected in Tables 3 and 4 are very large. The value of the isotopic rate ratio ($k_{\text{H}}/k_{\text{D}} = 21 \pm 1$ at 25 °C) is one of the largest reported. This value is only slightly smaller than the rate ratios $k_{\text{H}}/k_{\text{D}} = 24$ and 23 found for the reaction of 2-nitropropane with 2,6-lutidine and *sym*-collidine in a mixed Bu'OH-H₂O solvent.^{7a-c} In the case of the present reaction of 4-NPPCM with DMAN in acetonitrile, the values of $\Delta\Delta H^\ddagger = 13 \pm 2 \text{ kJ mol}^{-1}$ and $A_{\text{H}}/A_{\text{D}} = 0.08$, together with the isotopic rate ratio $k_{\text{H}}/k_{\text{D}} = 21 \pm 1$, indicate a significant contribution of tunnelling to the overall mechanism of the proton-transfer reaction.

The calculated $k_{\text{H}}/k_{\text{D}}$ values were fitted by a truncated Bell's equation with $\nu_{\text{H}}^\ddagger = 1.040 \text{ cm}^{-1}$ using the computer program of Saunders and Kaldor.¹⁷ The calculated value of the ratio of tunnelling factors $Q_{\text{H}}/Q_{\text{D}} = 2.35$ is larger than the values given by Caldin and Mateo¹⁸ for the reaction of 4-nitrophenylnitromethane with TMG: $Q_{\text{H}}/Q_{\text{D}} = 1.56, 1.65,$ and 1.75 in acetonitrile, dichloromethane, and tetrahydrofuran, respectively. Even the value of $Q_{\text{H}}/Q_{\text{D}} = 1.9$ given by Kresge¹⁹ for this reaction in toluene is lower. This result confirms our general conclusion⁸⁻¹⁰ that the contribution of the tunnelling effect is influenced by the polarity of the solvent to an extent much less than was formerly assumed.¹⁸

Experimental

Materials.—4-Nitrophenylphenylcyanomethane (4-NPPCM) was prepared by the procedure of Neresheimer and Ruppel²⁰ as previously described in detail.⁸

Deuteriated 4-NPPCM was obtained by isotopic exchange in dioxane-D₂O mixture in the presence of OD⁻ ions.⁸ The isotopic purity reached at least 98%, as shown by n.m.r. and m.s. analysis.

4-Nitrobenzyl cyanide (4-NBC). The commercial product by Fluka AG, Busch SG was recrystallised from 95% ethanol to give crystals of m.p. 114–115 °C. The deuteriated analogue 4-NBC-d₂ was obtained as above using a procedure identical to that for 4-NPPCM-d.⁸ The isotopic purity (n.m.r. and m.s. analysis) was at least 98%.

1,8-Bis(dimethylamino)naphthalene (DMAN). The commercial product from Aldrich was freshly crystallised from a mixture of methanol and ethylene glycol to give faintly yellowish crystals, m.p. 44–45 °C.

1,1,3,3-Tetramethylguanidine (TMG) was dried with KOH pellets then with a molecular sieve and fractionally distilled under reduced pressure. The middle fraction, about 25% of the total, was used. The water content, estimated by i.r. analysis, was about 0.5% by weight.

Acetonitrile. Reagent grade acetonitrile from BDH was purified by the method of O'Donnell *et al.*²¹

Equilibrium and Kinetic Measurements.—Optical density measurements were made on a Specord M-40 spectrophotometer at 20 ± 0.5 °C.

The kinetic runs were performed under pseudo-first-order

conditions with base always in at least 20-fold excess. The solvent acetonitrile was always freshly distilled and all solutions were freshly prepared.

The kinetic measurements for the normal and deuteriated *C*-acids were made by means of a stopped-flow spectrophotometer.

Pseudo-first-order rate constants were calculated by Guggenheim's method. The second-order rate constants were calculated from equation (3) where k_{obs} = pseudo-first-order rate constant.

$$k_{\text{obs}} = k_{\text{f}}b + k_{\text{b}} \quad (3)$$

The activation parameters were evaluated from the temperature dependence of the second-order rate constants by means of a least-squares fit to the transition-state theory equation.

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