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Primary kinetic hydrogen isotope effects in deprotonations of a nitroalkane by intramolecular phenolate groups

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Rate constants and kinetic isotope effects have been determined for the formation of nitronate anions from the ethers 1-(2-methoxyphenyl)-2-nitropropane, 7(X = H, L = H and D) and 1-(2-methoxy-5-nitrophenyl)-2-nitropropane, 7(X = NO_2, L = H and D), and from the corresponding phenols, 1-(2-hydroxyphenyl)-2-nitropropane, 3(X = H, L = H and D), and 1-(2-hydroxy-5-nitrophenyl)-2-nitropropane, 3(X = NO_2, L = H and D), in aqueous basic medium. For the ethers 7, rates of deprotonation by hydroxide are comparable with those found for deprotonations of 2-nitropropane, with k^H/k^D (25 °C) = 7.7 and 7.8, respectively. In both the cases, the isotope effects are conventionally temperature dependent. For the corresponding phenols 3, conditions have been established under which the deprotonations of the nitroalkane are dominated by intramolecular deprotonation by the kinetically first-formed phenolate anion, with an estimated effective molarity EM ~ 250. For 3 (X = H, L = H or D), k^H/k^D (25 °C) = 7.8, with $E_a^D - E_a^H = 6.9\ kJ\ mol^{-1}$ and $A^H/A^D = 0.5$. For 3(X = NO_2, L = H or D), rates of intramolecular deprotonation are reduced 30-fold, and an elevated kinetic isotope effect is found (k^H/k^D (25 °C) = 10.7). Activation parameters ($E_a^D - E_a^H = 17.8\ kJ\ mol^{-1}$ and $A^H/A^D = 0.008$) are compatible with an enhanced tunnelling contribution to reactivity in the H-isotopomer.

Keywords: effective molarity; intramolecular deprotonation; nitroalkanes; primary kinetic hydrogen isotope effect; temperature dependences

INTRODUCTION

In this paper, we describe our continuing study on hydrogen kinetic isotope effects (kies) in intramolecular deprotonations of carbon acids. A fuller introduction may be found in our initial papers on the subject.[1,2] In the present paper, we note that our experiments have been prompted, firstly, by the very unusual kies reported for some enzyme-catalysed deprotonations[3] and secondly, by the dearth of comparable measurements in intramolecular transfers in small molecules,[4] which might model the active-site chemistry in those enzymes. (For a rationale of the use of small molecule chemistry in the modelling of active sites, see Reference [5,6].)

Particular enzymic examples are the rate-limiting deprotonations of a Schiff base by an active site carboxylate in the oxidative deamination of primary amines by dehydrogenases exploiting tryptophan tryptophylquinone cofactors. The case of reaction of methylamine catalysed by MADH,[7] **1**, is shown in Fig. 1. In this case $k^H/k^D = 16.8$ at 25 °C, and this ratio is only weakly temperature dependent with an Arrhenius treatment giving $E_a^D - E_a^H = 0.5$ (± 0.5) kJ mol^{-1} and $A^H/A^D = 13.5$. Such behaviour is not compatible with a kinetic isotope effect arising only from changes in the isotopically induced ground state zero-point energy differences,[8] and has been rationalised in terms of hydron transfer mechanisms involving quantum mechanical tunnelling of the transferring nuclei through the potential energy barrier. Complete absence of temperature dependence, indeed, represents an extreme case where tunnelling dominates the transfer processes for both the proton and deuteron. Controversially, it has been suggested that enzymes may have evolved to exploit tunnelling mechanisms in maximising reaction efficiency,[9,10] and much computational and experimental effort has been devoted to discover how enzyme structures promote tunnelling.[3] Certainly, such large temperature independent isotope effects are rare in 'small-molecule' chemistry, but then measurements of kies for intramolecular deprotonations of carbon acids are even rarer, so that experiments with model compounds currently neither support nor refute any postulate as to the special nature of the enzyme-catalysed proton transfers.

In our first papers, we reported experimental and computational studies of the deprotonation of the nitroalkane **2**(R = Ph) by an intramolecular carboxylate, arguing that the extensive charge reorganisation involved in forming the nitronate anion had some parallels with the extensive charge shifts accompanying the proton transfer in the MADH-catalysed reaction. This small molecule chemistry may also model that occurring in an oxidative conversion of nitroalkanes to corresponding aldehydes or ketones catalysed by the flavoenzyme, nitroalkane oxidase (NAO), shown to involve deprotonation of an enzyme-bound nitroalkane by the carboxylate group of an aspartate residue,[11] with a remarkable 10^9-fold rate enhancement over the acetate induced reaction. A kie, k^H/k^D (25 °C) = 7.9, has been reported for the NAO-catalysed reaction of 1,1-dideuterionitroethane,[12,13] but with conventional Arrhenius parameters ($E_a^D - E_a^H = 5.6\ kJ \cdot mol^{-1}$, and $A^H/A^D = 0.89$). In the event, both the kie for the intramolecular

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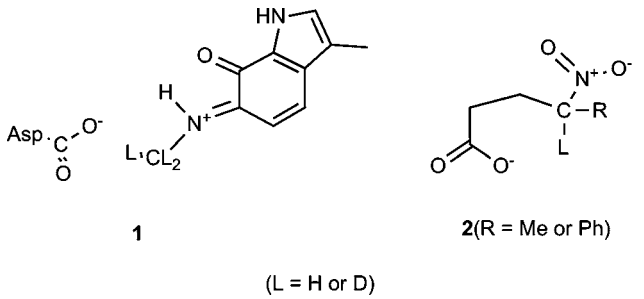

Figure 1. Deprotonations of carbon acids by carboxylate anions in the active site of MADH and in small molecule model

transfer in **2**(R = Ph), k^H/k^D (25 °C) = 5.8, and its Arrhenius parameters ($E_a^D - E_a^H = 5.5\ kJ\ mol^{-1}$, and $A^H/A^D = 0.63$) were also resolutely conventional, giving no indications of a major tunnelling contribution to this simple model reaction.

Catalysis by the intramolecular carboxylate in **2** was not efficient, with an effective molarity (EM) of only 13.7. Although low EMs are not unusual in deprotonations of carbon acids, we have been seeking molecules in which structure places and retains the catalysing basic group in a more favourable position with respect to the nitroalkane. Additionally, theory at any level suggests that an energetic balance in the transfer favours tunnelling, and this is not the case in the reactions of **2**, with the net transfer of proton from nitroalkane to carboxylate being endothermic by *ca* 17.8 kJ mol^{-1} (based on the pK_as of the carboxylic acid and nitroalkane being 4.5 and 7.5 respectively). We have, therefore, also sought molecules, which might permit a systematic adjustment of the energetics of the intramolecular reaction, as well as offering a more effective positioning of the catalysing group.

RESULTS AND DISCUSSION

Experimental design

The compounds we have selected are 2-nitroalkanes carrying substituted phenolic groups, **3**, shown in Fig. 2. In the parent compound **3**(X = H), the anticipated pK_a s of phenol and nitroalkane sites are 10.2 (the pK_a of *o*-cresol) and 7.9, respectively,[14,15] so that intramolecular proton transfer, conversion of **4** to **5**, remains energetically unbalanced, but now with an anticipated exotherm of *ca* 14 kJ mol^{-1}. In principle at least, this raises difficulties with the observability of the process. However, phenols are 'normal' acids and deprotonations of the phenolic hydroxyl group by hydroxide in water, to generate the intramolecular phenolate, are expected to occur at rates controlled by diffusion or solvent reorganisation (>10^{10} M^{-1} s^{-1}),[16] while deprotonations of nitroalkanes are slow, reflecting the extensive reorganisations of charge, bonding, and solvation, which must occur before the full stabilising effect of the delocalising nitro group comes into play.[17–19] Despite the higher thermodynamic acidity of the nitroalkane residue, the anticipated sequence of proton transfers in aqueous medium at pH > 10.5 is, therefore, that outlined in Fig. 2, with the final product being the di-anion **6**. We expect, therefore, to be able to observe the behaviour of the phenolate anion and characterise the intramolecular proton transfer involved in the conversion of phenoxide **4** to nitronates **5** and **6**.

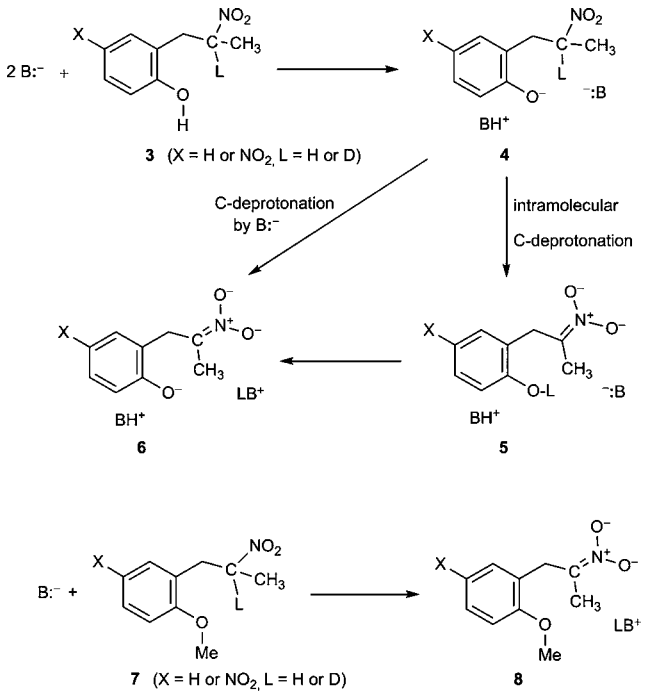

Figure 2. The phenolic nitroalkanes and the anticipated sequence of proton transfers in aqueous basic medium

Introduction of a nitro substituent on the benzene ring to produce **3**(X = 4-NO$_2$) is expected to enhance the acidity of the phenolic hydroxyl group by a factor of *ca* 10^3 (pK_a of 2-methyl-4-nitrophenol is 7.1[20]). The effect of the substitution on the acidity of the nitroalkane residue is expected to be much smaller and a likely upper limit is a factor of 5.5 (estimated using $\sigma_m = 0.710$ for the nitro group and $\rho = 1$ for the equilibrium deprotonation). Therefore, the pK_as of the oxygen and carbon acids should be much better balanced ($\Delta pK_a < 0.5$), and comparison of the behaviours of **3**(X = H) and **3**(X = NO$_2$) should permit a simple examination of the effects of the net reaction energetics on the efficiency of the intramolecular catalysis and the kies. As far as possible, the behaviour of these phenolic compounds is to be also compared with those of the corresponding methyl ethers **7**, so that the contributions of the intramolecular base can be assessed.

Preparative considerations and preliminary reactivity studies

1-(*o*-Methoxyphenyl)-2-nitropropane,[21] **7**(X = H) is a distillable liquid, available in two steps from *o*-anisaldehyde by Henry condensation with nitroethane[22] to yield 1-(*o*-methoxyphenyl)-2-nitropropene, then by selective reduction of the electron deficient double bond with sodium borohydride (Scheme 1). Its ^{1}H-NMR spectrum shows a 6-line multiplet (1H) at δ4.95, associated with the hydrogen attached α-to the nitro group, with coupling to the methyl group and to the adjacent diastereotopic pair whose signals appear as doublets of doublets at δ3.33 and δ3.09, respectively. Nitration of **7**(X = H) proceeded with preference for substitution *para* to the ethereal position to yield **7**(X = NO$_2$), showing similar signals for the methine and methylene hydrogens of the nitropropane side chain. Treatment of **7**(X = H) or **7**(X = NO$_2$) with d$_4$-methanol and a catalytic amount of pyridine

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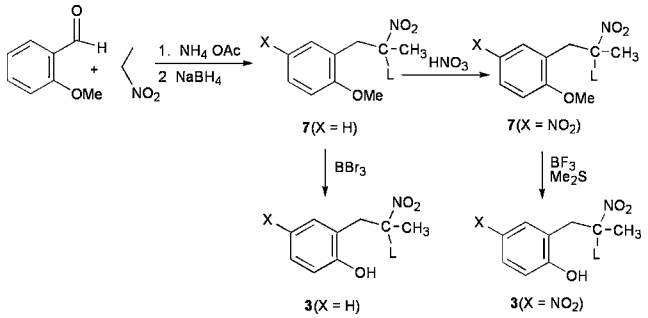


Scheme 1. Preparation **7** and **3** (X = H and X = NO_2)

cleanly exchanged the hydrogen attached to the stereogenic carbon α- to the nitro group for deuterium with loss of the associated six-line multiplet and simplification of the signals from the adjacent methyl group and diastereotopic pair. Extents of deuteriation were readily estimated from ^{1}H-NMR spectra by integration of the residual methine signal, using the signal of the non-exchanging hydrogens at the methyl group as an internal reference. Demethylations with BBr_3 in the case of **7**(X = H), or BF_3;SMe_2 in the case of **7**(X = NO_2),[23] yielded the required phenolic nitroalkanes **3**(X = H, L = H or D) and **3**(X = NO_2, L = H or D). As anticipated from the established stability of nitroalkanes to acidic medium,[24,25] there was no measurable loss of isotopic label from deuteriated samples, provided that conditions remained acidic throughout the reaction, isolation, and chromatography.

Methyl ether, **7** (X = H) was only moderately soluble in water but, at 30 °C, solutions could be obtained showing a peak at 273 nm(ε_{max} = 1500) and end absorption at 220 nm(ε = 7000). Addition of a few drops of sodium hydroxide solution to make the solution *ca* 0.01 M in base induced a growth in absorbance at wavelengths below 260 nm with $t_{½} \sim 3$ min. For the optimum balance between background absorbance and growth, the changes were monitored at 235 nm and shown to be of the first order. When solutions were acidified, the spectra slowly reverted to those of the original nitroalkane, and we associate the growth with the formation of the anticipated nitronate anion in **8**(X = H). Methyl ether, **7**(X = NO_2) was also sparingly soluble in pure water, but solutions could be obtained showing a peak at 320 nm (ε_{max} = 6000) and a shoulder at 228 nm(ε = 4900). Addition of base induced growth of the shoulder at 228 with $t_{½} \sim 2$ min, and again, spectra reverted slowly to those of the original nitroalkane on acidification of the solution.

Phenol **3**(X = H) was much more soluble in water and UV–Vis spectra showed a shoulder at 209 nm (ε = 7050) and a peak at 273 (ε_{max} = 1200). Addition of sodium hydroxide solution to make the solution *ca* 0.01 M in base induced immediate bathochromic shift and increase in extinction producing peaks at 292(ε_{max} = 8700) and 233(ε_{max} = 1800) nm, and then a slower first order growth with $t_{½} \sim 5$ seconds, most evident at 230 nm. We associate these changes with the anticipated diffusion-controlled formation of the phenolate **4**(X = H) and then slower formation of the nitronate anion 6(X = H). Nitrophenol **3**(X = NO_2) exhibited a similar pattern, with solutions in water showing a shoulder at 223 nm(ε = 9800) and a peak at 320 nm(ε_{max} = 10,100). Addition of sodium hydroxide solution induced immediate enhanced end absorption, and replacement of the peak at 320 nm by a new peak at 408 nm(ε_{max} = 18,000), followed by slower first-order growth with $t_{½} \sim 2$ min, to develop a distinct new peak at 223 nm. Again, we associate the behaviour with the diffusion-controlled formation of the nitrophenolate anion **4**(X = NO_2) and then slower formation of the nitronate anion, **6**(X = NO_2).

For both **6**(X = H) and **6**(X = NO_2), basic solutions were stable for prolonged periods as long as they were protected from atmospheric oxygen. Acidification to pH 4 regenerated the originating nitroalkanes *via* the nitronic acids **9**(X = H or NO_2). If, however, solutions were not deoxygenated, and then protected from molecular oxygen, these recoveries were not clean, with ketonic products also being formed in variable amounts (Scheme 2). A larger scale experiments with **3**(X = H) permitted isolation of the known ketone **10**(X = H)[26,27] and indicated that the new compounds were the products of an oxidative Nef reaction similar to that encountered first in the reactions of the 4-nitro-4-butanoic acids **2**(R = Ph and R = Me) by Lewis *et al.*,[28,29] and confirmed in our earlier work.[1] The mechanism of this process is not yet understood, but evidently it occurs readily in the presence of a suitably placed intramolecular carboxylic acid group, as in **2**, or a phenolic hydroxyl as in **3**(X = H or X = NO_2).

Although we considered it unlikely that this degradation could interfere with the rate measurements described below since they involved the use of basic solutions, in all our detailed kinetic studies, solutions were degassed, stored under nitrogen and then the deprotonation reactions were run under nitrogen.

Reaction kinetics

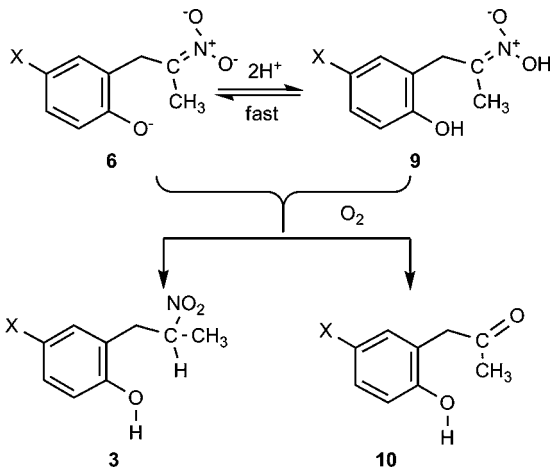
Rates of deprotonation in basic aqueous medium were first measured. In all cases, reactions were followed by monitoring first order absorbance growths at 235 nm. Table 1 shows the rate constants for nitronate ion formation from both ethers and phenols.

For the ethers, **7**(X = H) and **7**(X = NO_2), first order rate constants are proportional to base concentration, with no significant background reaction (see Eqns (1) and (2) respectively and Figs 3A and B).

$$k_{obs} = 0.356(\pm 0.018) \times [\mathrm{NaOH}] + 8.5\,(\pm 10.1) \times 10^{-4} \quad (1)$$

$$k_{obs} = 0.877(\pm 0.006) \times [\mathrm{NaOH}] - 9.0\,(\pm 3.0) \times 10^{-4} \quad (2)$$

The second order rate constants might be compared with those reported for similar deprotonations of 2-nitropropane[30]



Scheme 2. Regeneration of nitroalkanes on acidification, and competing oxidative degradations

Table 1. Rates of nitronate ion formation from 7 and 3(X = H, L = H) and from 7 and 3(X = NO_2, L = H) in aqueous basic medium at 30.1 °C

	10^2 k_{obs}[c] (s^{-1})				
[Na^+]/M	**7**(X = H)[a]	**3**(X = H)[a]	**7**(X = NO_2)[a]	**3**(X = NO_2)[a]	**3**(X = NO_2)[b]
0.02	0.760	23.3	1.66	1.11	0.794
0.04	1.52	23.7	3.39	1.37	0.797
0.06	2.31	23.4	5.19	1.80	0.799
0.08	2.87	23.6	6.91	2.05	

[a] NaOH solution, $\mu = 0.1$ using KCl;
[b] Sodium carbonate buffer at pH 10.2, $\mu = 0.08$ with KCl.
[c] Rate constants are means of at least two separate determinations whose values agreed to within 2%.

($k_2 = 0.353\ M^{-1}\ s^{-1}$ at 25 °C) and of 1-phenyl-2-nitropropane[31] ($k_2 = 1.74\ M^{-1}\ s^{-1}$ at 30 °C) to gauge the effect of introduction of the phenyl group, and then of substituted phenyl groups at the 1-position the 2-nitropropane. A simple phenyl group has a rate enhancing effect (*ca* 3-fold), but the combined electronic and steric effects of the *o*-methoxy group in **7**(X = H) reduce the effect of the phenyl substitution *ca* 5-fold. Interestingly, the second order rate constant for deprotonation of **7**(X = NO_2) by hydroxide ($0.877\ M^{-1}\ s^{-1}$) is a factor of 2.5 higher than for **7**(X = H), an acceleration presumably reflecting an enhancement in the acidity of nitroalkane grouping by the additional nitro group on the benzene ring. A two-point Hammett plot yields $\rho = 0.51$ for the electronic effect of a remote substituent on the rate of nitroalkane deprotonation.

Reactions of the phenol **3**(X = H) are faster (*ca* 8-fold in 0.08 M NaOH) than the corresponding ether **7**(X = H), but dependence on base concentration is much reduced (Eqn (3) and Fig. 3A). Presumably, the change in the electronic nature of the substituent from an electron-withdrawing methoxy group to an electron-donating phenolic oxyanion ($\sigma_I = 0.24$ and -0.16, respectively) is sufficient to reduce the reactivity in the intermolecular deprotonation of the nitroalkane by hydroxide by a factor of about 10. Importantly, the linear plot now has a substantial intercept (Eqn (3) and Fig. 3A), consistent with the contribution from the intramolecular deprotonation by the oxyanion of the phenolate, with $k_{intra} = 0.234\ s^{-1}$. From Eqn (3), the intramolecular contribution to the formation of nitronate from **3**(X = H) is >98% of the total reaction, even in 0.1 M sodium hydroxide solution.

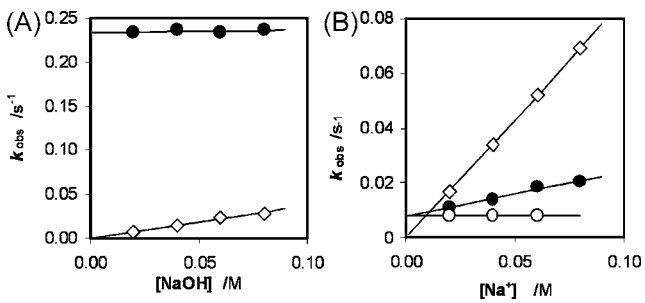


Figure 3. The effects of variation of base concentration on rates on nitronate formation. Plot A compares reactions of **7**(X = H) (◇) and **3**(X = H) (●), in deprotonations by NaOH. Plot B compares the reactions of 7(X = NO_2) (◇) with NaOH with those of **3**(X = NO_2) with NaOH (●) and in carbonate buffer at pH 10.2 (○). Data are taken from Table 1

$$k_{obs} = 0.030(\pm 0.040) \times [NaOH] + 2.34(\pm 0.03) \times 10^{-1} \quad (3)$$

$$k_{obs} = 0.165(\pm 0.018) \times [NaOH] + 7.7(\pm 0.7) \times 10^{-3} \quad (4)$$

For the phenol, **3**(X = NO_2), rates show a distinct dependence ($k_2 = 0.165\ M^{-1}s^{-1}$) on base concentration (Eqn (4) and Fig. 3B) and a reduced, but clearly discernable, background reaction ($7.7 \times 10^{-3}\ s^{-1}$), which we associate the intramolecular deprotonation by the phenolate grouping. Compared with **3**(X = H), the slope is larger by at least 15-fold, and the intercept reduced 30-fold and Brőnsted treatment (using the estimated pK_a s of the phenols) yields $\beta = 0.48$. Second order rate constants for deprotonations of simple secondary alkyl nitroalkanes by other phenolate anions are not available, but those for deprotonations of 2-nitropropane by hydroxide and by acetate have been reported[32] and a Brőnsted plot (2-points again) yields $\beta = 0.46$ for these oxyanionic bases so that there is a degree of consistency. Both the enhanced slope and the reduced intercept in the behaviour of **3**(X = NO_2) compared with that of **3**(X = H) are consistent with the reduced ability of the much less basic intramolecular phenolic oxyanion in **3**(X = NO_2) to compete with the external hydroxide anion in the deprotonation of the nitroalkane.

The behaviour of **3**(X = NO_2) was also examined in an aqueous carbonate buffer at pH 10.2. In this medium, both nitronate and nitrophenolate anions are expected to be stable. Rates of nitronate anion formation were independent of the buffer concentration (Eqn (5) and Fig. 3B) and agreed, within experimental uncertainty, with the extrapolation to zero base concentration for the hydroxide-induced reaction. In the buffered medium, the intramolecular deprotonation accounts for no less than 99.9% of the total reactivity

$$k_{obs} = .00125(\pm 0.00914) \times [Na^+] + 7.92(\pm 0.06) \times 10^{-3} \quad (5)$$

A measure of the effectiveness of the intramolecular catalysis in phenols may be obtained by comparing the second order rate constant for deprotonation of ethers **7**(X = H) and **7**(X = NO_2) by hydroxide with the first order rate constants for the intramolecular reaction of **3**(X = H) and in **3**(X = NO_2), but allowance must be made for the difference in the basicity between the hydroxide and phenolate oxyanions, on the one hand, and of the nitroalkanes on the other hand. Using the Bronsted $\beta = 0.46$

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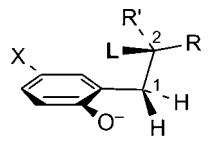
calculated above, permits extraction of second order rate constants for intermolecular deprotonation of the 2-nitroalkanes residues in **7**(X = H) by phenolate, and in **7**(X = NO_2) by *p*-nitrophenolate as 9.0×10^{-4} and 3.3×10^{-5} M^{-1} s^{-1}, respectively. Comparison with first order rate constants for the intramolecular deprotonations of **3**(X = H) and **3**(X = NO_2) gives effective molarities for the phenolate groupings of 261 and 234 M, respectively. These are very crude estimates, since no allowance has been made for the much smaller substituent induced shifts in the acidity of the nitroalkane. Even as order-of-magnitude values, these EMs are quite large for carbon acid deprotonations,[33–35] which are only exceptionally significantly larger than 10, and then in sterically compressed systems,[36,37] where the full solvation of the intramolecular base is not possible.[38] They are certainly larger than those found for the intramolecular deprotonations (*ca* 14 M) of the nitroalkane by carboxylate anion in the carboxylic acid **2** (R = Ph).[1] In all these cases, the O-to-C proton transfers occur in a six-centre array, and the improved catalytic efficiency in the phenols must reflect the locking of one of the bonds in that ring by its incorporation as a part of a phenolic array. Additionally, inspection of molecular models and empirical force field calculation suggests that, in the ground state conformation of the phenols, the 1,2-carbon–carbon bond of the nitroalkane lies orthogonally to the plane of the benzene ring, and that the optimum staggered arrangement of substituents on that bond places the nitroalkane hydron (L) within *ca* 3.0 Å of the phenolic oxygen (Fig. 4). Only minor adjustments of the dihedral angles about the aryl-C1 and C1—C2 bonds are then required to bring the anionic oxygen and nitroalkane hydrogen to Van der Waals contact (2.6 Å).

Although effective molarities in lactonisations are much larger, a similar trend is evident in the comparison of lactonisations of derivatives of 5-hydroxypentanoic acid[39] and *o*-hydroxyhydrocinammic acid.[40] The similarity in the effective molarities of the catalysing groups in **3**(X = H) and in **3**(X = NO_2) suggests that there is little enhancement in the catalytic efficiency associated exclusively with balancing the pK_a of the catalysing and substrate groups.

Solvent kinetic isotope effects, k^{H2O}/k^{D2O}, for the intermolecular and intermolecular deprotonations were determined to probe for possible involvement of hydrons derived from the water molecules in the deprotonations. The rate data are collected in Tables 2 and 3. In the case of the methyl ethers, **7**(X = H, L = H) and **7**(X = NO_2, X = H), values of k^{H2O}/k^{D2O}(at 25 °C) are 0.75(±0.04) and 0.71(±0.04), respectively. These values are only a little less inverse than that reported for the deprotonations of 2-nitropropane by hydroxide in water ($k^{H2O}/k^{D2O} = 0.68$),[30] and, within experimental uncertainty, equal to the fractionation factor for isotopic distribution between bulk water and water hydrogen-bonded to hydroxide or deuteroxide ($\phi = 0.74$).[41] The rate ratios are, therefore, consistent with the isotopically induced



R,R' = Me and NO_2

X = H or NO_2

Figure 4. The ground state conformation of the phenolic nitroalkanes

Table 2. Solvent isotope effects for deprotonations of 1-(2-methoxyphenyl)-2-nitropropane, 7 (X = H, L = H) and of 1-(2-methoxy-5-nitrophenyl)-2-nitropropane 7 (X = NO_2, L = H)

Solvent	*T* (°C)	k_2[b,c] (M^{-1} s^{-1})	k^{H2O}/k^{D2O} at 25 °C
7(X = H, L = H)[a]			
H_2O	19.9	1.44×10^{-1}	
H_2O	29.8	3.24×10^{-1}	
H_2O[b]	25.0	2.20×10^{-1}	0.75(±0.04)
D_2O	19.9	1.93×10^{-1}	
D_2O	29.8	4.26×10^{-1}	
D_2O[b]	25.0	2.92×10^{-1}	
7(X = NO_2, L = H)[a]			
H_2O	19.9	3.45×10^{-1}	
H_2O	29.8	7.32×10^{-1}	
H_2O[b]	25.0	5.12×10^{-1}	0.71(±0.04)
D_2O	19.9	4.78×10^{-1}	
D_2O	29.8	1.05×10^{0}	
D_2O[b]	25.0	7.20×10^{-1}	

[a] Base concentrations were [NaOH] = 0.00890 M and [NaOD] = 0.01285 M.
[b] Interpolated values.
[c] Rate constants are means of at least two separate determinations whose values agreed to be within 2%.

Table 3. Solvent isotope effects for deprotonations of 1-(2-hydroxyphenyl)-2-nitropropane, 3 (X = H, L = H) and of 1-(2-hydroxy-5-nitrophenyl)-2-nitropropane 3 (X = NO_2, L = H)

Solvent	*T* (°C)	k_{obs}[c] (s^{-1})	k^{H2O}/k^{D2O} at 25 °C
3(X = H, L = H)[a]			
H_2O	20.2	7.35×10^{-2}	
H_2O	24.8	1.33×10^{-1}	
H_2O	29.5	2.19×10^{-1}	0.91(±0.05)
H_2O	34.5	3.82×10^{-1}	
H_2O[d]	25.0	1.32×10^{-1}	
D_2O	22.6	1.09×10^{-1}	
D_2O	27.4	1.93×10^{-1}	
D_2O	34.6	4.35×10^{-1}	
D_2O[d]	25.0	1.45×10^{-1}	
3(X = NO_2, L = H)[b]			
H_2O	19.9	2.29×10^{-3}	
H_2O	29.8	7.32×10^{-3}	
H_2O[d]	25.0	4.18×10^{-3}	0.99(±0.05)
D_2O	19.9	2.28×10^{-3}	
D_2O	29.8	7.49×10^{-3}	
D_2O[d]	25.0	4.22×10^{-3}	

[a] [NaOH] = 0.00890 M and [NaOD] = 0.01285 M.
[b] Carbonate buffer, pH 10.2.
[c] Rate constants are means of at least two separate determinations, whose values agreed to be within 2%.
[d] Interpolated values.

differences in the desolvation of the oxyanionic base prior to its involvement in the abstraction of a proton from the nitroalkane. Involvement of a solvent-derived hydron in covalent bonding changes in the rate-limiting step would generate a larger 'normal' primary effect working against the inverse fractionation factor and the values here, therefore, do not support any involvement of water molecules as relays in the proton transfer.

Interestingly, the solvent isotope effects for intramolecular deprotonations in **3**(X = H, L = H) and in **3**(X = NO_2, X = H) are $k^{H2O}/k^{D2O} = 0.91$ (±0.05) and $k^{H2O}/k^{D2O} = 0.99$ (±0.05), respectively, both significantly less inverse than those for the intermolecular deprotonations. Initially, we speculated that this reduction might signal some involvement of a solvent-derived hydron in the process and are still not able to completely exclude this possibility. We note, however, that there is a factor of *ca* 10^5 in the basicity between hydroxide and phenoxide, and *ca* 10^7 between hydroxide and *p*-nitrophenoxide, and that inverse relationships between the basicity and hydrogen-bond energies have been demonstrated for phenolates, both in solution[42] and in the gas phase.[43] A reduction in hydrogen-bond strength should be associated with a reduction in depth and a widening of the potential well describing the bond, both of which would reduce isotopically-induced energy differentials. It does not seem unreasonable, therefore, that the fractionation factor for isotopic distribution between bulk water and water hydrogen-bonded to hydroxide or deuteroxide ($\phi = 0.74$) might be more inverse than that for distribution between bulk water and water hydrogen-bonded to phenoxides. We suggest that the reduced ability of the phenoxides as hydrogen-bond acceptors (compared with hydroxide) is a more likely explanation of the less inverse solvent isotope effects, which simply signal that desolvation of the less strongly hydrogen-bonded intramolecular phenoxide anion must again precede engagement in abstraction of the nitroalkane hydrogen.

Primary kinetic isotope effects

Our intention was to measure kinetic isotope effects for the deprotonations over as wide a temperature range as practical. For the ethers **7**(X = H) and 7(X = NO_2), we have already noted that solubility of these compounds in water is not high. Problems arising from this were not severe in the preliminary experiments described above, but it soon became evident that, with the apparatus available to us, problems of low solubility and slow rates of solution might cause problems if we continued to work with pure water, especially at lower temperatures. Our kinetic isotope measurements for these compounds were, therefore, made using a mixed solvent, 2:1 w/w dimethoxyethane (DME): water which, on a molar basis, is 71.24% water. This is a mixture we used earlier in the deprotonations of nitroalkanes[1] and found that solubilities and rates of solution are much improved while the reactivity patterns found in the fully aqueous solutions are not strongly modified. The rate data for the isotopomers of ethers **7**(X = H) and 7(X = NO_2) are collected in Tables 4 and 5. Reactivities are enhanced by the change from water to 2:1 DME water by a factor of 1.5 in the case of 7(X = H), and 2.3 in the case of 7(X = NO_2), presumably reflecting reduced solvation of the hydroxide of the by the more organic medium. Generally, the kinetics and temperature dependences are well behaved, and we find activation parameters similar to those reported by Amin and Saunders[31] for deprotonations of 1-phenyl-2-nitropropane in water and in aqueous alcoholic mixtures. In all cases, entropies of activation are large and negative, as might be expected for a bimolecular process, and our values for both the H-isotopomers

Table 4. Rates of deprotonations of 1-(2-methoxyphenyl)-2-nitropropane, 7 (X = H, L = H or D) in 2:1 (w/w) DME: water mixture

T (°C)	k_{obs}[b] (s^{-1})	k_2 ($M^{-1}\,s^{-1}$)	Activation parameters
7(X = H, L = H) in DME: H_2O[a]			
12.4	1.17×10^{-2}	1.24×10^{-1}	$\Delta H^{\ddagger} = 56.2$ (±0.3) kJ mol^{-1}
20.6	2.33×10^{-2}	2.48×10^{-1}	$\Delta S^{\ddagger} = -63.4$ (±0.8) J K^{-1} mol^{-1}
28.2	4.33×10^{-2}	4.60×10^{-1}	$\Delta G^{\ddagger} = 75.6$ (±0.5) kJ mol^{-1}
34.0	6.66×10^{-2}	7.09×10^{-1}	
40.6	1.10×10^{-1}	1.17×10^{0}	ln *A* = 22.9 (±0.2)
46.1	1.63×10^{-1}	1.74×10^{0}	$E_a = 59.2$ (±0.1) kJ mol^{-1}
25.0[c]		$3.53(\pm0.04) \times 10^{-1}$	
7(X = H, L = D) in DME: H_2O[a]			
12.6	1.72×10^{-3}	1.83×10^{-2}	$\Delta H^{\ddagger} = 59.8$ (±01.6) kJ mol^{-1}
20.6	3.32×10^{-3}	3.5×10^{-2}	$\Delta S^{\ddagger} = -69.0$ (±5.4) J K^{-1} mol^{-1}
25.5	4.78×10^{-3}	5.09×10^{-2}	$\Delta G^{\ddagger} = 80.4$ (±0.3.2) kJ mol^{-1}
30.4	6.54×10^{-3}	6.96×10^{-2}	
31.5	8.01×10^{-3}	8.52×10^{-2}	ln *A* = 22.2 (±0.7)
37.9	1.31×10^{-2}	1.39×10^{-1}	$E_a = 62.4$ (±1.7) kJ mol^{-1}
43.3	2.0×10^{-2}	2.18×10^{-1}	
52.0	4.14×10^{-2}	4.41×10^{-1}	
25.0[c]		$4.56 (\pm0.38) \times 10^{-2}$	

[a] [NaOH] = 0.0940 M.
[b] Rate constants are means of at least two separate determinations whose values agreed to within 2%.
[c] Interpolated values.

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Table 5. Rates of deprotonations of 1-(2-methoxy-5-nitrophenyl)-2-nitropropane, 7 (X = NO_2, L = H or D) in 2:1 (w/w) DME: water mixture

T (°C)	[b]k_{obs} (s^{-1})	k_2 ($M^{-1}\,s^{-1}$)	Activation parameters
7(X = H, L = H) in DME: H_2O[a]			
11.2	2.25×10^{-3}	4.31×10^{-1}	$\Delta H^{\ddagger} = 56.4\ (\pm 1.8)$ kJ mol^{-1}
20.5	4.64×10^{-3}	8.89×10^{-1}	$\Delta S^{\ddagger} = -53.6\ (\pm 4.5)$ J K^{-1} mol^{-1}
29.7	9.84×10^{-3}	1.88×10^{0}	$\Delta G^{\ddagger} = 72.3\ (\pm 2.7)$kJ mol^{-1}
39.1	2.07×10^{-2}	3.96×10^{0}	ln $A = 24.7\ (\pm 0.6)$
			$E_a = 58.8\ (\pm 1.4)$ kJ mol^{-1}
25.0[c]		$2.59\ (\pm 0.05) \times 10^{0}$	
7(X = H, L = D) in DME: H_2O[a]			
11.2	2.45×10^{-4}	5.26×10^{-2}	$\Delta H^{\ddagger} = 61.0\ (\pm 2.6)$ kJ mol^{-1}
20.5	6.13×10^{-4}	1.17×10^{-1}	$\Delta S^{\ddagger} = -54.9\ (\pm 5.4)$ J K^{-1} mol^{-1}
29.7	1.28×10^{-3}	2.43×10^{-1}	$\Delta G^{\ddagger} = 77.3\ (\pm 8.6)$ kJ mol^{-1}
39.1	3.10×10^{-3}	5.93×10^{-1}	ln $A = 24.5\ (\pm 1.1)$
			$E_a = 63.5\ (\pm 2.6)$ kJ mol^{-1}
25.0[c]		$3.31\ (\pm 0.23) \times 10^{-1}$	

[a] [NaOH] = 0.00522 M.
[b] Rate constants are means of at least two separate determinations whose values agreed to within 2%.
[c] Interpolated values.

(−63.4 and −53.6 J K^{-1} mol^{-1}) and D-isotopomers (−69.0 and −55.0 J K^{-1} mol^{-1}), and are comparable with the −57.4 J K^{-1} M^{-1} reported for deprotonation of 1-phenyl-2-nitropropane in water.

The kies and their temperature dependences are presented in Table 8, and it is apparent that those for the ethers, $k^H/k^D = 7.1$ (±0.4) and 7.6 (±0.6) at 25 °C, do not differ significantly, and are within the range expected for rate ratios associated with loss of ground state isotopic zero-point energy differences. They are also similar to kies reported for deprotonation of 2-nitropropane[44] (7.4) and 1-phenyl-2-nitropropane (7.5) by hydroxide in aqueous medium.[31] For both the ethers, the dominant contributor to the kies is different in activation energy, with ratios of pre-exponential factors being well within the range $(1/\sqrt{2} < A^H/A^D < \sqrt{2})$[8] associated with an absence of significant tunnelling of either isotope.

Table 6. Rates of deprotonations of 1-(2-hydroxyphenyl)-2-nitropropane, 3 (X = H, L = H or D) in water

T (°C)	[b]k_{obs} (s^{-1})	Activation parameters
3(X = H, L = H) in H_2O; [NaOH] = 0.100 M		
15.9	4.28×10^{-2}	$\Delta H^{\ddagger} = 83.9\ (\pm 0.9)$ kJ mol^{-1}
20.2	7.35×10^{-2}	$\Delta S^{\ddagger} = +19.6\ (\pm 2.9)$ J K^{-1} mol^{-1}
24.8	1.33×10^{-1}	$\Delta G^{\ddagger} = 78.1\ (\pm 1.7)$ kJ mol^{-1}
29.5	2.19×10^{-1}	
34.5	3.82×10^{-1}	ln $A = 32.8\ (\pm 0.4)$
39.0	6.15×10^{-1}	$E_a = 86.4\ (\pm 0.9)$ kJ mol^{-1}
25.0[c]	$1.33(\pm 0.03) \times 10^{-1}$	
3(X = H, L = D) in H_2O; [NaOH] = 0.100 M		
14.1	4.28×10^{-3}	$\Delta H^{\ddagger} = 90.8\ (\pm 0.4)$ kJ mol^{-1}
20.8	9.91×10^{-3}	$\Delta S^{\ddagger} = +25.8\ (\pm 1.3)$ J K^{-1} mol^{-1}
24.8	1.65×10^{-2}	$\Delta G^{\ddagger} = 83.1(\pm 0.8)$ kJ mol^{-1}
28.8	2.82×10^{-2}	
36.3	6.82×10^{-2}	ln $A = 33.6\ (\pm 0.2)$
41.0	1.15×10^{-1}	$E_a = 93.3\ (\pm 0.4)$ kJ mol^{-1}
47.4	2.35×10^{-1}	
25.0[c]	$1.72\ (\pm 0.05) \times 10^{-2}$	

[a] [NaOH] = 0.100 M.
[b] Rate constants are means of at least two separate determinations whose values agreed to within 2%.
[c] Interpolated values.

Table 7. Rates for deprotonations of 1-(2-hydroxy-5-nitrophenyl)-2-nitropropane, 3 (X = NO_2, L = H or D)

T (°C)	[b]k_{obs} (s^{-1})	Activation parameters
3(X = NO_2, L = H) in H_2O[a]		
30.0	8.80×10^{-3}	$\Delta H^{\ddagger} = 81.3\ (\pm 0.3)$ kJ mol^{-1}
40.0	2.47×10^{-2}	$\Delta S^{\ddagger} = -15.3\ (\pm 0.8)$ J K^{-1} mol^{-1}
45.0	4.00×10^{-2}	$\Delta G^{\ddagger} = 85.9\ (\pm 0.5)$ kJ mol^{-1}
55.0	1.03×10^{-1}	ln $A = 27.53\ (\pm 0.09)$
		$E_a = 81.3\ (\pm 0.3)$ kJ mol^{-1}
25.0[c]	$5.07\ (\pm 0.15) \times 10^{-3}$	
3(X = NO_2, L = D) in H_2O[a]		
30.0	9.06×10^{-4}	$\Delta H^{\ddagger} = 99.1\ (\pm 0.1)$ kJ mol^{-1}
40.0	3.16×10^{-3}	$\Delta S^{\ddagger} = 24.2\ (\pm 0.3)$ J K^{-1} mol^{-1}
45.0	5.80×10^{-3}	$\Delta G^{\ddagger} = 91.9\ (\pm 0.2)$ kJ mol^{-1}
55.0	1.81×10^{-2}	ln $A = 32.31\ (\pm 0.03)$
		$E_a = 99.1\ (\pm 0.1)$ kJ mol^{-1}
25.0[c]	$4.75\ (\pm 0.13) \times 10^{-4}$	

[a] Carbonate buffer ay pH 10.2.
[b] Rate constants are means of at least two separate determinations whose values agreed to within 2%.
[c] Extrapolated values.

Table 8. Summary of rates, primary kinetic isotope effects (25 °C) and associated activation parameters

Compounds	k^H	k^H/k^D	Activation parameters
7(X = H, X = H and D)	$3.53 \times 10^{-1}\ M^{-1}\ s^{-1}$	7.7(±0.7)	$E_a^D - E_a^H = 3.2$ (±1.8) kJ mol^{-1} $A^H/A^D = 0.5$ (±0.3)
7(X = NO_2, X = H and D)	$2.59 \times 10^{0}\ M^{-1}\ s^{-1}$	7.8(±0.7)	$E_a^D - E_a^H = 4.3$ (±4.9) kJ mol^{-1} $A^H/A^D = 1.2$ (±1.4)
3(X = H, X = H and D)	$1.33 \times 10^{-1}\ s^{-1}$	7.8(±0.4)	$E_a^D - E_a^H = 6.9$ (±0.8) kJ mol^{-1} $A^H/A^D = 0.5$ (±0.8)
3(X = NO_2, X = H and D)	$5.07 \times 10^{-3}\ s^{-1}$	10.7(±0.6)	$E_a^D - E_a^H = 17.8$ (±0.4) kJ mol^{-1} $A^H/A^D = 0.008$ (±0.004)

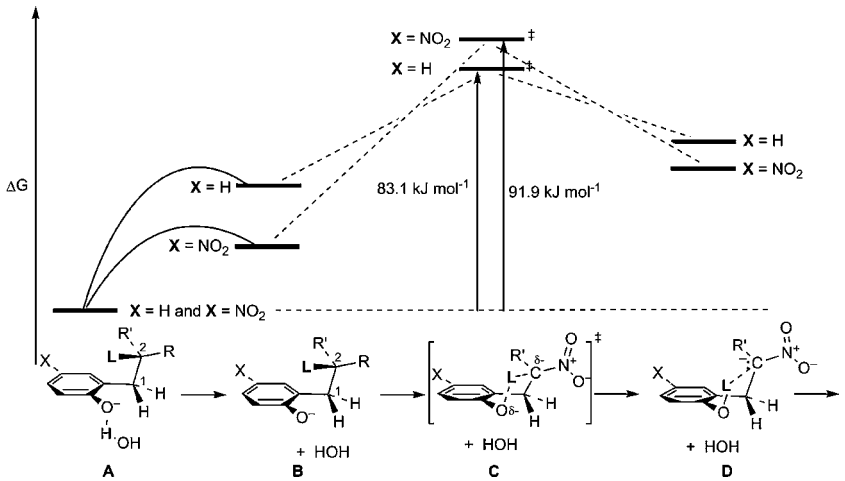

Figure 5. Diagramme of possible barrier relationships to account for the enhanced tunnel contribution in the reactions of **3**(X = NO_2)

No similar problems with solubility were experienced for the phenols **3**(X = H) and **3**(X = NO_2. In the case of **3**(X = H, L = H and D), rates were determined in aqueous 0.1 M sodium hydroxide and for **3**(X = NO_2, L = H and D), in the same aqueous sodium carbonate buffer (pH = 10.2) used earlier. As noted earlier, these are conditions under which reactivity is dominated by the intramolecular deprotonation.

Rate constants at range of temperatures, and calculated activation parameters for **3**(X = H, L = H and D) are presented in Table 6, and compared in Table 8. For this intramolecular reaction, entropies of activation are now positive and comparable (19.6 and 25.8 J K^{-1} mol^{-1}, respectively), but the kie, $k^H/k^D = 7.8$ (±0.4) (Table 8) is not dissimilar to those found for intermolecular deprotonations by hydroxide and, again, arises from the difference in activation energies with closely comparable pre-exponential factors.

The situation for the isotopomers **3**(X = NO_2, L = H and D) is less simple (Tables 7 and 8). While Eyring treatment of the temperature dependence of rates for the D-isotopomer **3**(X = NO_2, L = D), yields a positive entropy of activation (24.2 J K^{-1} mol^{-1}) closely comparable to those found for **3**(X = H, L and D), and a similar pre-exponential factor, the dependences for the H-isotopomer, **3**(X = NO_2, L = H) reveal a negative entropy of activation (−15.3 J K^{-1} mol^{-1}), and a significantly reduced pre-exponential factor. The result is an elevated kie, $k^H/k^D = 10.9$(±0.6), at 25 °C, associated with an exaggerated difference in activation energies, $E_a^D - E_a^H = 17.8$ (±0.4) kJ mol^{-1}, and much reduced ratio of pre-exponential factors, $A^H/A^D = 0.008$ (±0.001), reflecting, we suggest, anomalous behaviour of **3**(X = NO_2, L = H).

CONCLUSIONS

The data presented here have no resemblance to the extreme tunnelling situations encountered in the interesting enzyme-catalysed reactions mentioned earlier.[7] However, the possibility that tunnelling contributes to reactivity in all the compounds studied must not be excluded. Kreevoy[45] has commented that shallow tunnelling is likely to be wide spread, and points out that it is as intrinsic to quantum mechanisms as zero-point energy differentials. There is probably no completely unambiguous way to demonstrate (or exclude) the phenomenon for reactions around 300°K. The pattern we have found is consistent with a small but measurable additional tunnelling contribution to the reactivity of **3**(X = NO_2, L = H) only. Comparison of the behaviours of the two isotopomeric pairs of phenolic nitroalkanes suggests that its reactivity is enhanced by a factor of *ca* 1.5 by this additional tunnelling contribution. Bell's[46] truncated correction

for tunnelling through an inverted parabolic barrier then yields $\nu^{\ddagger} = 600i\,cm^{-1}$ for the imaginary frequency.

The behaviour found in the intramolecular deprotonations might usefully be compared to those in intermolecular deprotonations of 2-nitropropane by alkyl pyridine bases in water or aqueous alcoholic mixtures[47–49] which, in contrast to deprotonations by hydroxide described in this work and elsewhere, also exhibit elevated kies associated with exaggerated activation energy differences and small ratios of pre-exponential factors. These effects are most pronounced[44] when the pyridines carry alkyl substituents at 2- and 6-positions. The acidities of the pyridinium ions ($6 < pK_a < 7$) are not badly mismatched to that of 2-nitropropane. The reactions are at least 10^6-fold slower ($\Delta\Delta G^{\ddagger} \sim 34\,kJ\,mol^{-1}$) than those with hydroxide, ($k < 6.7 \times 10^{-7}\,M^{-1}\,s^{-1}$), reflecting both the basicity change and steric hindrance to approach of the basic nitrogen lone pair to the nitroalkane hydrogen. The effects of steric hindrance remain a matter of debate,[50] but enhanced light atom tunnelling has been associated with these high symmetrical barriers, and pressure dependences also suggest that exclusion of solvent from the reaction volume contributes to the tunnelling, possibly by reducing the mass of the transferring particle.[51]

In our two intramolecular reactions, change of the remote substituent from X = H to $X = NO_2$ induces only a 35-fold rate reduction (for the D-isotopomers) corresponding to an increase in free energy of activation of 8.8 kJ mol^{-1}, an amount which, in comparison to the behaviour described above, does seem to be large enough to account for the observed tunnelling in **3**($X = NO_2$). A more detailed consideration of the course of the intramolecular reactions, however, suggests an explanation (Fig. 5).

We have already pointed out that the likely ground state conformation of the reactants (A in Fig. 5) is one in which only minor and energetically undemanding adjustments in dihedral angles are necessary to bring the anionic oxygen within reacting distance of the acidic C–H bond. Additionally, desolvation of the anionic oxygen must precede proton abstraction and, if the pK_a shifts on moving from water to DMSO (10.1–18.1 for phenol and 7.2–10.8 for *p*-nitrophenol)[52] are taken as indicative, this step (A → B in Fig. 5) may cost as much as 45.6 kJ mol$^{(1}$ in the case of **3**(X = H) and 20.5 kJ mol$^{(1}$ in the case of **3**($X = NO_2$). Comparison with the experimentally determined free energies of activation for barriers for the deuteriated isotopomers (83.1 and 91.9 kJ mol^{-1}) then suggests that the remaining parts of the free energies of activation might differ by as much as 33.9 kJ mol^{-1}, similar to the differences in activation energy found in the intermolecular deprotonations we have cited above. These are the parts of the reaction associated with the actual bonding changes at the migrating hydron, taking B *via* transition state C to D, a carbanion in which charge remains largely localised[53] on carbon, but which is hydrogen bonded to the phenolic hydroxyl group. The process is then completed by charge and solvent reorganisation (not shown) to yield a fully delocalised nitronate. This raising of barrier is expected to be effective in promoting tunnelling if it is also associated with a narrowing of the barrier and we suggest that, because of the intramolecular nature of the process under consideration and the mode of operation of the substituent, the width of the barrier for the process in which bonding changes occur at the migrating hydron must be the same in **3**(X = H and **3**($X = NO_2$). On the reactant side (A or B), the remote nitro group should have no effect on conformational preferences at the reacting group of atoms. Similar geometry considerations are applicable on the product side. Additionally, because of the higher acidity of the phenolic hydroxyl group in **3**($X = NO_2$), the internal hydrogen bonding in D may be more favourable than with **3**(X = H), and although we cannot accurately place D on the energy axis, we place D(X = H) above D($X = NO_2$) in our diagramme.

These are qualitative arguments, but we believe that they have some weight, and the point we wish to make in Fig. 5 is, that irrespective of details, simple trigonometry demands a narrowing of the barrier for the transfer in **3**($X = NO_2$). Computational studies are in progress and these are expected to yield detail of the barrier shape required to account for the experimental result that an enhanced tunnelling contribution occurs in **3**($X = NO_2$, L = H) but not in **3**($X = NO_2$, L = D).

EXPERIMENTAL SECTION

General methods

NMR spectra were recorded on Brüker 300, 400 or 500 AMX spectrometers. Chemical shifts are parts per million (ppm) downfield from tetramethylsilane. Signal splittings are quoted in Hz. Signals are listed as: singlet (s), doublet (d), triplet (t), quartet (q), and multiplet (m) with width (W) to outside lines. Infrared spectra were recorded on a Perkin-Elmer Spectrum FTIR and were run as liquid films or as films evaporated from deuteriated chloroform. UV–Vis spectra were recorded on a Cary 50 UV-visible spectrophotometer. Mass spectra were recorded on a Kratos MS25, Fisons VG Trio 2000 or on a Micromass platform. Modes of ionisation are electron impact (EI), positive chemical ionisation (+CI) using ammonia and fast atom bombardment (FAB), positive electrospray (+ES), and negative electrospray (−ES). Melting points were recorded on a Kofler heated stage microscope and are uncorrected. Thin layer chromatography (TLC) was carried out on Polygram Sil G/UV_{254} 0.25 mm silica gel plates with solvent systems as indicated. Analytical gas chromatography was carried out using: Perkin-Elmer capillary gas chromatography model 8310 with flame ionisation detection (FID). Analytical HPLC was carried out using: Waters 510 HPLC pump, Bondclone C18 100 × 8 mm column, Perkin-Elmer LC480 Diode Array System with detection at 255 nm and 285 nm premixed degassed solvent systems 75:25 MeOH: H_2O or as stated in the text, flow rate 2 ml/min.

The compounds

1-(2-Methoxyphenyl)-2-nitropropene: 2-Methoxybenzaldehyde (13.5 g, 0.1 mol) and ammonium acetate (2.0 g) were dissolved in nitroethane (100 ml), in an RB flask. The mixture was heated to reflux overnight and monitoring by TLC then indicated full conversion of reactant to a new product. Most of the nitroethane was then removed by distillation at atmospheric pressure before cooling and dilution with ethyl acetate. This organic mixture was then washed with dilute aq. HCl, then with aq. sodium bicarbonate solution and finally with saturated sodium sulphate solution before drying over anhydrous magnesium sulphate. Filtration and evaporation yielded an orange oil (16.2 g, 84%) whose NMR spectrum indicated that it was the anticipated alkene. A portion was recrystallised from methanol; mp 51–53 °C (lit., 53[22]). δH (500 MHz, $CDCl_3$) 8.15 (1H, s), 7.28 (1H, t, $J = 10.1$), 7.16 (1H, d, $J = 10.1$), 6.89 (1H, t, $J = 10.1$), 6.82 (1H, d, $J = 10.1$), 3.75(3H, s), and 2.25(3H,s); δC (75 MHz, $CDCl_3$) 158.6, 147.9, 132.2, 130.4, 130.2, 121.8, 120.8, 111.2, 55.9, 14.4.

1-(2-Methoxyphenyl)-2-nitropropane, **7**(X = H, L = H): Sodium hydroxide pellets (1.02 g) and sodium borohydride (1.02 g) were dissolved in absolute ethanol (30 ml). In a separate flask, 1-(2-methoxyphenyl)-2-nitropropene (0.84 g) was dissolved in absolute ethanol (20 ml) in a stirred cooled flask. Aliquots (*ca* 100 μl) of the sodium borohydride solution were then added, and the reaction was monitored a few minutes after each addition by loss of the broad absorption at 348 nm in the UV–Vis spectrum of the mixture (5 μl of the mixture diluted in 5 mls of ethanol). Reaction was complete after addition of 1.8 ml of borohydride solution and 1 h at 0 °C. Any excess sodium borohydride was destroyed by addition of acetone (2 ml). After stirring for 10 min, solid carbon dioxide was added, followed by a few drops of aqueous HCl to adjust the solution to pH 6 as judged by spotting on wide-range pH paper. Saturated aqueous NaCl solution (40 ml) was then added and the mixture was left undisturbed for 1 h before extraction with ether. The combined ether layers were dried over anhydrous Na_2SO_4, evaporated, and the resulting yellow oil was subjected to bulb-to-bulb distillation (145–150 °C at 1 mm Hg) to yield 1-(2-Methoxyphenyl)-2-nitropropane, as a light yellow oil (0.61 g, 72%) which was a single component by GLC and HPLC analysis. δH (500 MHz, $CDCl_3$) 7.29 (1H, t, $J = 8.0$), 7.11 (1H, d, $J = 7.8$), 6.91 (2H, m), 4.95(1H, 6 lines, W = 34.1), 3.87(3H, s), 3.30(1H, dd, $J = 13.6$ and 7.4), 3.09(1H, dd, $J = 13.6$ and 6.7 Hz); 1.56(3H, d, $J = 6.6$); δC (75 MHz, $CDCl_3$) 157.9, 131.4, 129.3, 124.4, 121.0, 110.7, 83.4, 55.5, 37.4, 19.8; ν_{max}/cm^{-1}, 3064, 2936, 1539, 1439, 1238, 1124, 1021, 747; *m/z* (EI) 195(28%, $M^{+\cdot}$, found 195.0898, calcd. for $C_{10}H_{13}O_3N$, 195.0980), 151(69%), 148(100%), 120(82%), 115(57%), 91(100%), 84(44%), 77(39%), 49(81%).

2-Deuterio-1-(2-Methoxyphenyl)-2-nitropropane, **7**(X = H, L = D): 1-(2-Methoxyphenyl)-2-nitropropane, **7**(X = H, L = H), (1.02 g) was dissolved in methanol-OD (5 ml) and pyridine (1 ml) added. The reaction mixture was refluxed under nitrogen atmosphere for 35 h, and the exchange was followed by ^{1}H-NMR spectroscopy. The solvent and pyridine were then removed under reduced pressure and the residue was taken up in fresh methanol-OD (2 ml) and pyridine (0.2 ml) added. The mixture was refluxed for further 48 h before the solvent and pyridine were removed under reduced pressure to leave a light yellow oil, purified by distillation under vacuum. δH (300 MHz, $CDCl_3$) 7.80 (1H, t, $J = 8.0$), 7.11 (1H, d, $J = 7.8$), 6.91 (2H, m), 3.87(3H, s), 3.30(1H, d, $J = 13.6$); 3.09(1H, d, $J = 13.6$); 1.57(3H, s); δC (75 MHz, $CDCl_3$) 157.7, 131.2, 130.1, 124.2, 120.9, 110.6, 83.2, 55.5, 36.8, 19.2; ν_{max}/cm^{-1}, 3064, 2939, 1602, 1575, 1495; *m/z* (EI) 196(26%, $M^{+\cdot}$), 152(63%), 149(100%), 121(80%), 115(57%), 91(100%). Integration of the H-NMR spectrum over the signal region for the exchangeable site (δ4.95) indicated deuterium incorporation in excess of 97%.

1-(2-Hydroxyphenyl)-2-nitropropane, **3** (X = H, L = H and D): 1-(2-Methoxyphenyl)-2-nitropropane(X = H or D) (0.81 g, 4.1 mmol) was dissolved in chloroform (5.0 ml), in a round bottom flask fitted for inert atmosphere. The solution was cooled to −78 °C and stirred under nitrogen. Boron tribromide (0.5 ml) was then added to the solution by syringe, and the temperature of the reaction mixture was allowed to rise to 20 °C and then to left undisturbed for 1 h. The temperature was then reduced again to −80 °C and the reaction was quenched by pouring the reaction mixture into cold methanol (10.0 ml). The temperature was then allowed to rise to room temperature, and the solvent was removed by evaporation under reduced pressure. The residue was taken up in fresh methanol (10 ml) and the solvent was removed again under reduced pressure. This process was repeated, and tlc analysis then indicated the presence of a single major product. Final purification was by column chromatography (silica, eluting with ether: petrol 50:50 (v/v), containing 0.05% of formic acid) to yield a near colourless oil (0.61 g, 89%).

For **3** (X = H, L = H), δH (500 MHz, $CDCl_3$) 7.16 (1H, t, $J = 7.4$), 7.09 (1H, d, $J = 7.4$), 6.89 (1H, t, $J = 7.4$), 6,76 (1H, d, $J = 7.4$), 5.2(1H, bs), 5.03(1H, 6 lines, W = 34.2), 3.31(1H, dd, $J = 13.8$ and 7.8); 3.11(1H, dd, $J = 13.8$ and 6.3), 1.59(3H, d, $J = 6.6$); δC (75 MHz, $CDCl_3$) 154.2, 131.9, 129.2, 122.6, 121.4, 115.8, 83.4, 36.7, 19.7; ν_{max}/cm^{-1} 3468, 2932, 1595, 1447, 1504; *m/z*(Cl,NH_3) 180(M-1), 146, 164, 131; (EI) 181, 134, 107; (ES −ve) 180 (100%, M-H, found 180.0661, calcd. for $C_9H_{10}O_3N$, 180.0661)

For **3** (X = H, L = D), δH (500 MHz, $CDCl_3$) 7.16 (1H, t, $J = 7.4$), 7.09 (1H, d, $J = 7.4$), 6.89 (1H, t, $J = 7.4$), 6,76 (1H, d, $J = 7.4$), 5.8(1H, bs), 3.31(1H, d, $J = 13.8$); 3.11(1H, d, $J = 13.8$), 1.59(3H, s). Integration of the H-NMR spectrum over the signal region (δ5.03) for the exchangeable site indicated deuterium incorporation in excess of 97%.

1-(2-methoxy-5-nitrophenyl)-2-nitropropane, **7** (X = NO_2, L = H or D): 1-(2-Methoxyphenyl)-2-nitropropane (L = H or D) (0.41 g, 2.1 mmol) was dissolved in glacial acetic acid (2 ml) and the stirred solution cooled to 5 °C. A mixture of concentrated (70%) nitric acid and acetic acid (2 ml dissolved in) was then added over a period of 10 min, and the reaction was followed by tlc, which indicated the formation of two new compounds. The solution was allowed to warm to 20 °C and stirred for 4 h when it was poured into ice-water (20 ml) and extracted with three portions (5 ml each) of dichloromethane. The combined extracts were dried over anhydrous magnesium sulfate and evaporated to yield an oil containing residual acetic acid, which was pumped off under high vacuum at 35 °C. Analysis of the resulting brown oil by HPLC indicated the presence of two major components in *ca* 6:4 ratio and the major component was isolated by chromatography on silica, eluting with 30:70 v/v ether: petrol containing 0.05% of formic acid, to yield a light yellow oil (0.18 g, 0.79 mmol, 38%).

For **7** (X = NO_2, L = H), δH (300 MHz, $CDCl_3$) 8.10 (1H, dd, $J = 9.3$ and 2.9), 7.92 (1H, d, $J = 2.9$), 6.88 (1H, d, $J = 9.3$), 4.85 (1H, 6 lines, W = 34.1), 3.89(3H, s), 3.22(1H, dd, $J = 13.8$ and 8.5), 3.05(1H, dd, $J = 13.8$ and 5.8), 1.51(3H, d, $J = 6.6$); δC (75 MHz, $CDCl_3$) 162.5, 141.2, 126.5, 125.4, 125.2, 110.3, 82.2, 56.4, 36.1, 19.3; ν_{max}/cm^{-1}, 2942, 1546, 1512, 1336, 1260, 1100, and 1029; *m/z*(Cl,NH_3) 258(100%, M + NH_4), 193(71%); (EI) 240(8%, M^+, found 240.0739, calcd. for $C_{10}H_{12}O_5N_2$, 240.0741), 193 (100%) 166 (44%), 115(19%), 77(31%).

For **7** (X = NO_2, L = D), δH (300 MHz, $CDCl_3$) 8.10 (1H, dd, $J = 9.3$ and 2.9), 7.92 (1H, d, $J = 2.9$), 6.88 (1H, d, $J = 9.3$), 3.89(3H, s), 3.21(1H, d, $J = 13.8$), 3.04(1H, d, $J = 13.8$), 1.50(3H, s). Integration over of the H-NMR spectrum over the signal region (δ4.85) for the exchangeable site indicated deuterium incorporation in excess of 97%.

1-(2-Hydroxy-5-nitrophenyl)-2-nitropropane, **3** (X = NO_2, L = H and D): The methyl ethers were dissolved in chloroform (*ca* 30 mgs in 0.5 ml of chloroform) in a small RB flask with a well fitting stopper. At room temperature, the reagent (BF_3: SMe_2, 0.5 ml) was added by a syringe in a single portion and the flask stoppered and swirled to mix. The stoppered flask was then was left undisturbed at 20 °C for 24 h with occasional swirling. A deep red oil was deposited, which could be redissolved with a little heating. After warming to ensure homogeneity, the liquid was transferred by pipette to about 50 ml of methanol in an ice-cooled RB flask. The flask was then placed on the rotavap and the volume was reduced to about 3 ml of red liquid. This was taken up in chloroform (20 ml) and partitioned with water. The

water layer became deep red and the chloroform layer lost much of its colour. The chloroform layer was separated, and shaken with a second wash with water (about 5 ml) before being separated again, and then dried over anhydrous magnesium sulphate. The sample was applied to a short silica wad, and filtered by washing with ether with a little formic acid (2 drops in 10 ml). Much of the residual dark red colour was retained on the silica. Evaporation of the eluate yielded an oil, which solidified slowly. Preparative TLC on silica, eluting with $CHCl_3$; MeOH; HCOOH 97.0; 2.8:0.2, by volume, then recrystallisation from ether: hexane gave off-white crystals as needles, mp 107–108 °C (17 mgs).

For **3** (X = NO_2, L = H), δH (300 MHz, $CDCl_3$) 7.99 (1H, dd, J = 8.7 and 2.8), 7.96 (1H, d, J = 2.8), 6.83 (1H, d, J = 8.7), 6.79(1H,bs), 4.94 (1H, 6 lines, W = 34.2); 3.25(1H, dd, J = 14.2 and 8.5 Hz); 3.07(1H, dd, J = 14.2 and 5.7); 1.55(3H, d, J = 6.6); δC (75 MHz, $CDCl_3$) 159.9, 141.3, 127.2, 125.2, 123.4, 115.6, 82.3, 35.9, 19.4; ν_{max}/cm^{-1} 3380, 3094, 2987, 1594, 1514, 1333, 1265; *m/z* (CI) 244(88%, M + $NH_4^{+\cdot}$), 227(9%, M + H^+), 211(100%), 194(91%), 177(32%), 148(41%); *m/z* (ES −ve) 225 (100%, M-H, found 225.0506, calcd. for $C_9H_9O_5N_2$, 225.0511).

For For **3** (X = NO_2, L = D), δH (300 MHz, $CDCl_3$) 8.00 (1H, dd, J = 8.7 and 2.8), 7.96 (1H, d, J = 2.8), 6.82 (1H, d, J = 8.7), 4.05(1H, bs), 3.25(1H, d, J = 14.2); 3.07(1H, d, J = 14.2); 1.55(3H, s). Integration over of the H-NMR spectrum over the signal region (δ4.94) for the exchangeable site indicated deuterium incorporation in excess of 97%.

The Nef chemistry: 1-(2-Hydroxyphenyl)-2-nitropropane, **3** (X = H, L = H) (0.052 g) was dissolved in a mixture of methanol and water (5 ml of 1:1 v/v). Sodium hydroxide solution was added (1 ml of 1 M) and the solution was left undisturbed for 5 min. Air was then bubbled through the basic solution and dilute hydrochloric acid to make pH = 0. The aerated solution was then stirred for 5 min before extraction into chloroform and drying over anhydrous magnesium sulfate. Examination by tlc on silica, eluting with ether: petrol (1:1 v/v) showed the absence of the recovered nitroalkane and a single major new material, more polar than the nitroalkane. This with was isolated by preparative TLC on silica as a colourless oil which crystallised on standing, identified as *2-hydroxyphenylacetone*, **10**(X = H), (lit., mp 63–64[26,27]). δH (400 MHz, $CDCl_3$) 7.11 (1H, td, J = 7.4 and 1.4), 7.02 (1H, dd, J = 7.4 and 1.2), 6.83 (1H, t, J = 7.5), 6,80 (1H, dd, J = 7.3 and 1.2), 6.2(1H, bs), 3.71 (2H, s), 2.28 (3H, s); δC (75 MHz, $CDCl_3$) 210.4, 155.1, 131.0, 129.1, 121.0, 120.9, 117.5, 46.5, and 29.9; ν_{max}/cm^{-1} 3380, 3094, 2987, 1711; *m/z* (ES −ve) 149 (100%, M-H), 127 (6%).

Reaction kinetics

Solutions: Water was distilled in an all-glass apparatus and deoxygenated with nitrogen. Dimethoxyethane was stirred over calcium hydride and then distilled under nitrogen from calcium hydride. The mixed solvents (DME: water) were prepared by weight.

Stock solutions of aqueous solutions of NaOH in water were by dilution of certified 1N concentrates (Fisher Chemical Company). Solutions of NaOD in D_2O were made up by dilution of 40% NaOD in D_2O (Aldrich) in D_2O and molarities determined by titration against standard hydrochloric acid. Stock solutions of NaOH in mixed solvents were made up by weight using the tabulated densities of NaOH and NaOD solutions and molarities checked by titration against standard hydrochloric acid. Stock solutions of nitroalkanes were made up and stored prior to use in glassware that had, after cleaning, been given a final rinse with a dilute solution (0.01 M) of formic acid in water prior to drying and use. In the absence of this precaution, solutions of deuteriated materials could slowly lose the deuterium content. The carbonate buffer solutions were prepared by dissolving sodium carbonate (2.293 g) and sodium hydrogen carbonate (1.477 g) in water (1000 ml). Solution pH was measured at 25 °C using a EDT pH meter and FisherBrand glass electrode was calibrated against standard buffers at pH 4 and pH 10 (Hydrion buffer capsules).

UV–Vis spectroscopy: UV–Vis investigations were carried out on a Cary-50 BIO spectrometer fitted with a thermostatted block. Temperatures of cells in the block were measured using a platinum resistance thermometer dipping into a specially constructed cell. In a typical experiment, the basic solvent, 2.5 ml, was pipetted into cell under nitrogen flow. The cell was then stoppered and allowed to equilibrate to the set temperature. Reaction was initiated by addition of 10 μl of a solution of the nitroalkane to ethanol (*ca* 0.3 M) and changes at the appropriate wavelength (see text) were monitored, collecting data for at least five half-lives. Final absorbances were less than 1.5 and typically absorbance changes were between 0.2 and 0.4 units. For the reaction kinetics, at least 50 points were collected over at least four half-lives and data transferred to Microsoft Excel™ for treatment. Rate constants for H-isotopomers were extracted by non-linear least squares fitting of $A_{calcd} = A_{inf} - \Delta A e^{-kt}$ to the observed absorbances using A_{inf}, ΔA and k as adjustable parameters using the Solver add-in. Uncertainties and statistics associated with fitting were generated using the *SolvStat* macro of Billo,[54] and correlation coefficients were >0.999 in all cases and in most cases > 0.9999. For runs with deuteriated materials, initial points showed deviation from first order behaviour, ascribed to reactions of small residual amounts of undeuteriated material. Omission of points from the first 5% of reaction again yielded excellent fits and rate constants for the deuteriated isotopomers. Fitting to a sum of two exponentials (five adjustable parameters) over the whole range yielded rates for both isotopomers and rate constants obtained in this way were consistent with those obtained by fitting to single exponentials with allowance for residual undeuteriated material, but with large uncertainties for the minor component. For *1-(2-methoxyphenyl)-2-nitropropane* and *1-(2-hydroxyphenyl)-2-nitropropane*, deprotonation rates were measured using a using a Hi-Tech SF 61 stopped-flow spectrofluorimeter, mixing equal volumes of solutions of the nitroalkane(*ca* 5×10^{-4} M) and the appropriate aqueous base.

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