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Reaction Branching and Extreme Kinetic Isotope Effects in the Study of Reaction Mechanisms

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1 Introduction

Isotopes are of immense importance in the elucidation of reaction mechanisms as tracers and through their influence on reaction rates.[1] Kinetic isotope effects are used for determining the degree of bond cleavage/formation in the transition state of the reaction. However, the interpretation of kinetic isotope effects are often complicated by short-lived intermediates. As will be discussed in this review, reaction branching may, under certain conditions, give rise to both unusually small and unusually large isotope effects. Extreme isotope effects of this origin are sometimes accompanied by anomalous temperature effects. These unusually large isotope effects and anomalous temperature effects from reaction branching may mimic those caused by tunnelling.

The occurrence of reaction branching, inferred from measured extreme isotope effects, has been employed as evidence of short-lived intermediates. Accordingly, amplified and attenuated isotope effects have been used as probes of hydrogen-bonded carbanions in hydron-transfer reactions as well as probes of carbocations and ion pairs in solvolysis. The method has the potential to probe also other types of intermediates, *i.e.* free radicals.

Below, effects from branching from a common intermediate, branching directly from the substrate, miscellaneous large isotope effects, and temperature effects that mimic tunnelling will be discussed together with some examples.

2 Branching from a Common Intermediate

Let us consider the following simple type of reaction branching, where I denotes a short-lived intermediate:[2]

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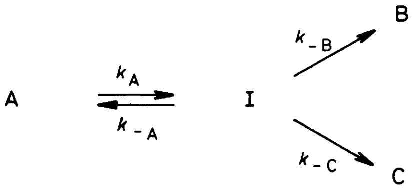
[1] See for example, (*a*) L. Melander and W. H. Saunders, Jr., 'Reaction Rates of Isotopic Molecules', Wiley-Interscience, New York, 1980; (*b*) 'Proton-Transfer Reactions', ed. E. Caldin and V. Gold, Chapman and Hall, London, 1975; (*c*) R. P. Bell, 'The Proton in Chemistry', 2nd Edn., Chapman and Hall, London, 1973; (*d*) R. P. Bell, 'The Tunnel Effect', Chapman and Hall, New York, 1980.

[2] (*a*) P. Ahlberg and S. Bengtsson, *Chem. Scr.*, 1974, **6**, 45; (*b*) A. Thibblin, S. Bengtsson, and P. Ahlberg, *J. Chem. Soc., Perkin Trans. 2*, 1977, 1569; (*c*) A. Thibblin and P. Ahlberg, *J. Am. Chem. Soc.*, 1979, **101**, 7311; (*d*) A. Thibblin, *Chem. Scr.*, 1983, **22**, 182; (*e*) M. Ölwegård, I. McEwen, A. Thibblin, and P. Ahlberg, *J. Am. Chem. Soc.*, 1985, **107**, 7494; (*f*) P. Ahlberg and A. Thibblin, 'Synthesis and Applications of Isotopically Labeled Compounds', 1985, Proceedings of the Second International Symposium, Kansas City, MO, USA, Elsevier Science Publishers B.V., Amsterdam, 1986, p.p. 89—94, and references therein; (*g*) A. Thibblin, *J. Phys. Org. Chem.*, 1988, **1**, 161.



(1)

The steady-state approximation applied to equation 1 yields the following relationships between the phenomenological and microscopic rate constants (k_{AB} and k_{AC} are the rate constants for reaction of A to B and C, respectively):

$$k_{AB} = k_A \times k_{-B}/(k_{-A} + k_{-B} + k_{-C}) \tag{2}$$

$$k_{AC} = k_A \times k_{-C}/(k_{-A} + k_{-B} + k_{-C}) \tag{3}$$

Accordingly, the following expressions for the kinetic isotope effects are obtained (the prime denotes the heavy isotope):

$$k_{AB}/k_{AB'} = (k_A/k_{A'})(k_{-B}/k_{-B'})(k_{-A'} + k_{-B'} + k_{-C'})/(k_{-A} + k_{-B} + k_{-C}) \tag{4}$$

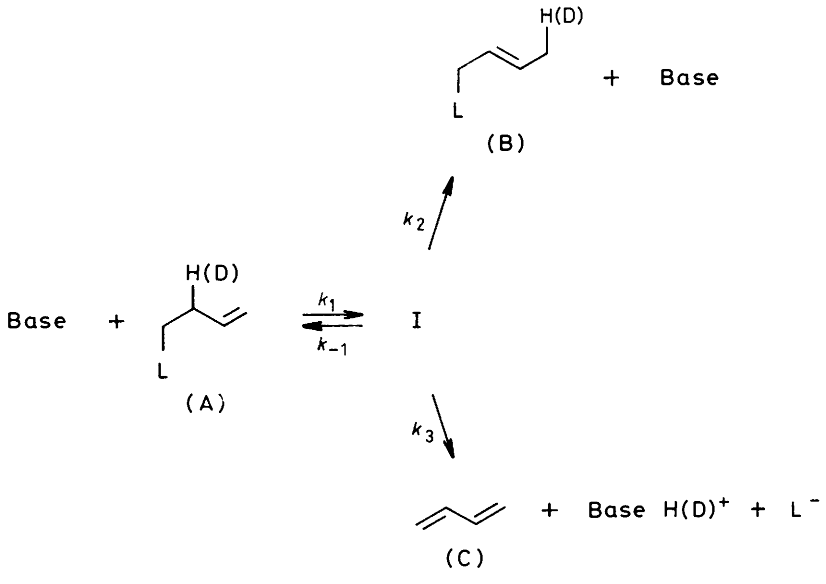
$$k_{AC}/k_{AC'} = (k_A/k_{A'})(k_{-C}/k_{-C'})(k_{-A'} + k_{-B'} + k_{-C'})/(k_{-A} + k_{-B} + k_{-C}) \tag{5}$$

Thus, for example, the observed isotope effect on the reaction A to B is a product of two isotope effects, $k_A/k_{A'}$ and $k_{-B}/k_{-B'}$, and a third factor. This latter factor depends on the relative magnitude of k_{-B} and k_{-C} and their isotope effects. If $k_{-B}/k_{-B'} > k_C/k_{-C'}$, the following expression is valid:

$$k_{AB}/k_{AB'} > k_A/k_{A'} > k_{AC}/k_{AC'} \tag{6}$$

Thus we conclude:[2c–g] *Competition between two processes, which have different kinetic isotope effects and which follow a common (rate-limiting) step sensitive to isotopic substitution, results in an amplified observed isotope effect for the overall reaction which proceeds* via *the competing step with the largest isotope effect. The other overall reaction will show an attenuated isotope effect. If the isotope effect on the first step is substantial, the amplification may yield an unusually large overall isotope effect.*

A. Carbanionic Reactions.—The generalization may be exemplified in the following way using Scheme 1. Let the substrate be a carbon acid which is dehydronated by a base to give a hydrogen-bonded carbanion with a kinetic deuterium isotope effect of 7. For simplicity, we assume that internal return is not significant ($k_{-1} \ll k_2,k_3$). In addition, let us assume that the intermediate gives



I = Base H$^+$, tightly hydrogen-bonded carbanion

Scheme 1

two products, a rearrangement product formed by intramolecular rehydronation of the carbanion, also showing a kinetic isotope effect of 7, and another product formed *via* a reaction step that is insensitive to isotopic substitution.

Accordingly, the substrate disappears with a primary kinetic isotope effect of $(k^{\mathrm{H}}_{\mathrm{AB}} + k^{\mathrm{H}}_{\mathrm{AC}})/(k^{\mathrm{D}}_{\mathrm{AB}} + k^{\mathrm{D}}_{\mathrm{AC}}) = 7$. However, the measured kinetic isotope effect on the rate of formation of the product B is enlarged owing to the competition, while the kinetic isotope effect on the rate of formation of C is decreased. The magnitude of the amplification and attenuation depends on the relative amounts of the two products. Let us assume, for example, that they are formed in equal amounts, *i.e.* $k_2 = k_3$. This implies that the measured isotope effects for the formation of the two products are $k^{\mathrm{H}}_{\mathrm{AB}}/k^{\mathrm{D}}_{\mathrm{AB}} = 7 \times 7 \times [(1 + 1)/(7 + 1)] = 12$ and $k^{\mathrm{H}}_{\mathrm{AC}}/k^{\mathrm{D}}_{\mathrm{AC}} = 7 \times 1 \times [(1 + 1)/(7 + 1)] = 1.8$. If C is the dominant product, *i.e.* $k_2 \ll k_3$, the measured isotope effects are much larger, $\sim 7 \times 7 = 49$ and $\sim 7 \times 1 = 7$, respectively.

Competition from a common tightly hydrogen-bonded allylic carbanion as the cause of enlarged and attenuated kinetic isotope effects has been thoroughly investigated in our laboratories.[2–4] The experimental results presented in these papers are accommodated in a mechanism in which a hydron is initially

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[3] A. Thibblin and P. Ahlberg, *J. Am. Chem. Soc.*, 1977, **99**, 7926.

[4] (*a*) A. Thibblin, *Chem. Scr.*, 1983, **22**, 70; (*b*) A. Thibblin, *J. Am. Chem. Soc.*, 1983, **105**, 853.

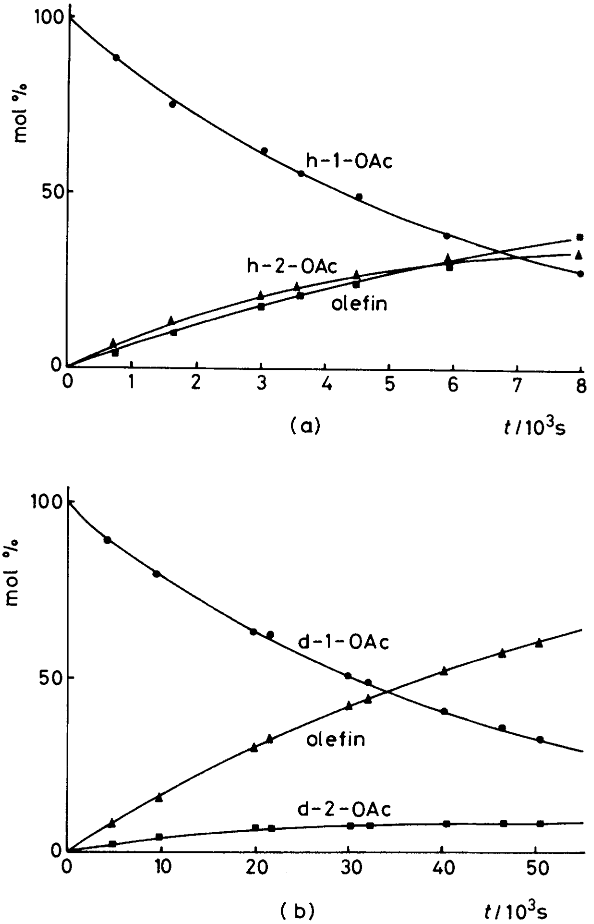

Figure 1 *The time dependence of substrate and products in the reaction of* 1-(2-*acetoxy*-2-*propyl*)*indene* (**h-1-OAc**) *and* 1,3-($^2H_2$)-1-(2-*acetoxy*-2-*propyl*)*indene* (**d-1-OAc**), *respectively, with quinuclidine in methanol at* 20.00 °C [2b]

abstracted from the substrate to form a tightly hydrogen-bonded intermediate involving the carbanion and the conjugated acid of the hydron-abstracting base. In the next step, the carbanion is either rehydronated to form a tautomer or undergoes loss of a leaving group to form an olefin. Thus, enlarged and attenuated primary kinetic isotope effects have been used as a probe of a common tightly hydrogen-bonded intermediate in base-catalysed 1,3-hydron transfer competing with base-promoted 1,2-elimination reactions (Scheme 1 and Figure 1). Independent evidence in favour of an intermediate common to rearrangement and elimination has been also presented.[3]

This mechanistic scheme implies an increase in the overall rearrangement isotope effect while the overall elimination isotope effect is decreased relative to the ionization isotope effect (*cf.* equation 6). Reversibility of the ionization step, *i.e.* $k_{-1} \gg k_2,k_3$, decreases the observed isotope effects. Accordingly, the isotope effects for the rearrangement and elimination as well as for the disappearance of the substrate are lowered. The largest isotope effect that we have measured for this type of system is a rearrangement $k^{\mathrm{H}}/k^{\mathrm{D}}$ of *ca.* 90[4] and the smallest is an elimination $k^{\mathrm{H}}/k^{\mathrm{D}}$ of *ca.* 1 (the value is very small owing to both substantial internal return and a large product ratio tautomer/olefin).[2b]

There is controversy over the borderline between *E*2 and *E*1cB reactions.[5] What is the dependence of the mechanism on structure? Do base-promoted elimination reactions make use of both types of mechanisms in parallel or is there an exclusive switch of mechanism on crossing the borderline, *i.e.* do the mechanisms merge on the borderline? Is a stepwise mechanism possible for substrates with such an efficient leaving group as chlorine?

We have studied the reaction system shown in Scheme 2 in which the substrate 1-Cl is reacted with pyridine in methanol. The base-catalysed 1,3-hydron transfer, *i.e.* the formation of 2-Cl shows an unusually large primary kinetic deuterium isotope effect, 14.6 ± 1.0 at 30 °C. The extreme isotope effect is proposed to originate from reaction branching in accord with Scheme 1, *i.e.* the base-promoted elimination and base-catalysed rearrangement of 1-Cl make use of at least one common hydrogen-bonded carbanion intermediate.[2e]

The above generalization based upon equation 1 also implies that not only intramolecular rearrangement but also internal return to starting material may exhibit an amplified kinetic isotope effect when competing with a process from the intermediate that is less sensitive to isotopic substitution. Such a process may be exchange. Cram *et al.* concluded that the imine (3) ionizes with a kinetic isotope effect of *ca.* 3 at 75 °C to a potassium-ion–carbanion ion pair (Scheme 3).[6] Approximate isotope effects of intramolecular return to starting material and collapse to rearranged imine (3′) were calculated as 34 ± 19 and 27, respectively. The results were discussed using a mechanistic model (Scheme 3) with azaallylic ion pairs as intermediates. It was concluded that these isotope effects are composite and represent combinations of large numbers of individual rate constants.[2c] However, the results are conveniently explained by the competition model (equation 1). The ion-pair collapses ($k_{-\mathrm{a}}$ and $k_{-\mathrm{b}}$), having substantial isotope effects, compete with exchange (k_{e}) with a small isotope effect.

Large isotope effects, originally attributed to tunnelling, have been measured by Caldin and co-workers in hydron-transfer reactions of (4-nitrophenyl)nitromethane with bases containing the imine group in non-polar solvents.[7] For example (equation 7), an isotope effect of $k^{\mathrm{H}}/k^{\mathrm{D}} = 45$ was measured in toluene with tetramethylguanidine (BH).[7a]

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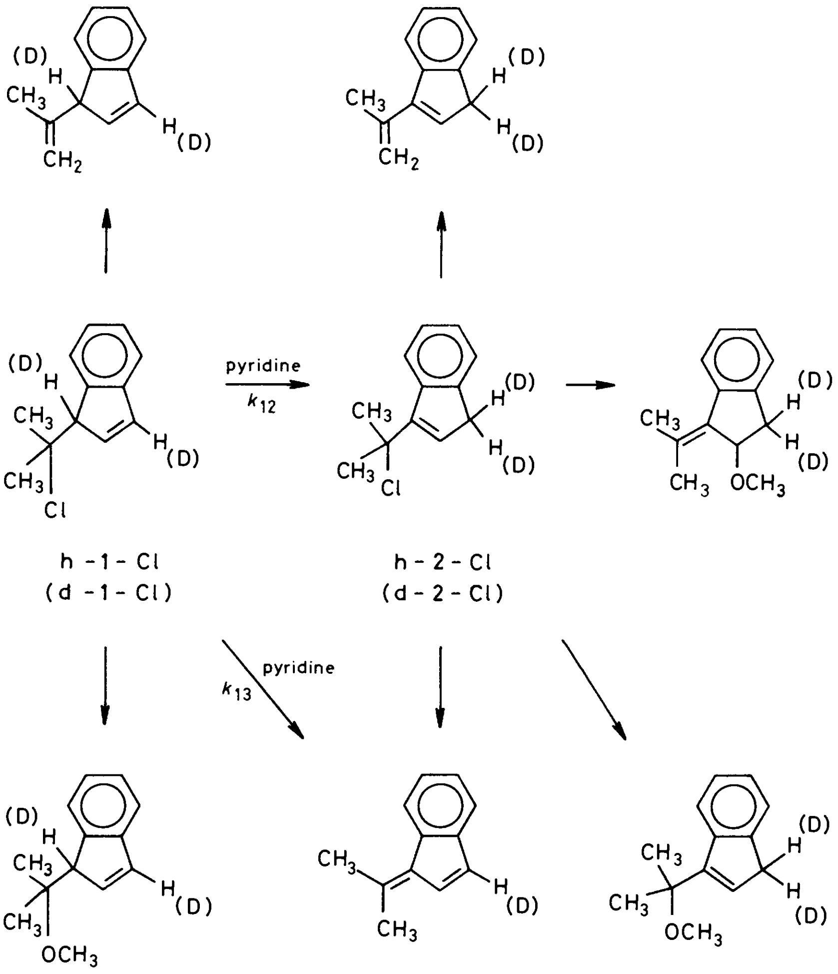
[5] See, for example, A. Thibblin, *J. Am. Chem. Soc.*, 1988, **110**, 4582, and references therein.

[6] R. D. Guthrie, D. A. Jaeger, W. Meister, and D. J. Cram, *J. Am. Chem. Soc.*, 1971, **93**, 5137.

[7] (*a*) E. F. Caldin and S. Mateo, *J. Chem. Soc., Chem. Commun.*, 1973, 854; (*b*) E. F. Caldin and S. Mateo, *J. Chem. Soc., Faraday Trans. 1*, 1975, **71**, 1876; (*c*) *ibid.*, 1976, **72**, 112.



h-1-Cl
(d-1-Cl)

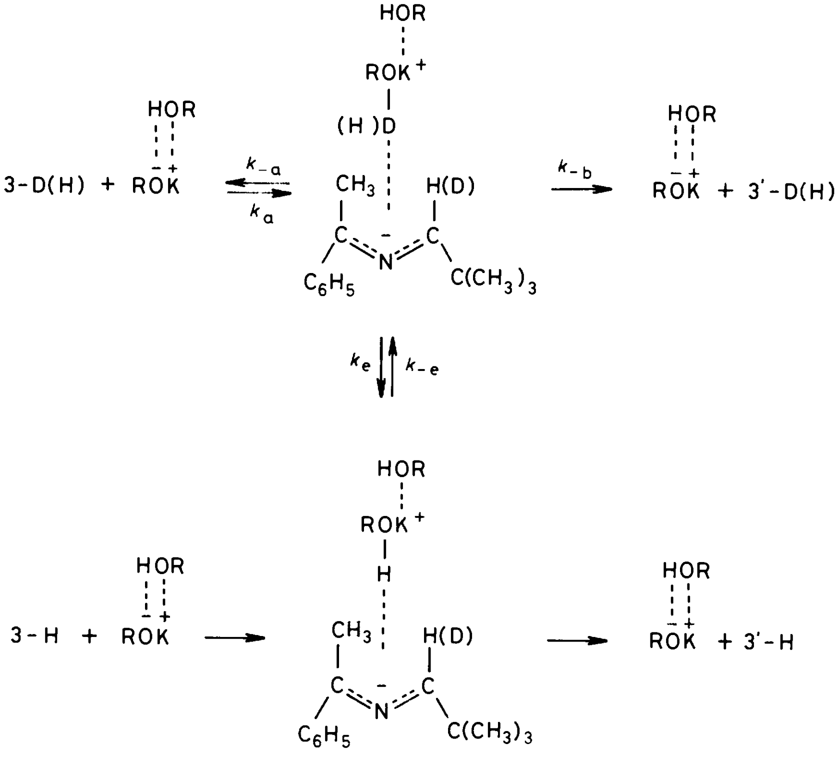
h-2-Cl
(d-2-Cl)

Scheme 2

$$ArCD_2NO_2 + BH \longrightarrow ArCDNO_2^- \cdots DBH^+ \qquad (7)$$

However, it has been pointed out that the kinetics are complex since the ion pair initially formed from the deuterium substrate gives several other ion pairs as a result of isotopic scrambling; these also return to the substrate.[2c,8] If these factors are not taken into consideration, an overestimation of the magnitude of the isotope effect will result since protonation competes favourably with deuteration of the anion in the ion pair. Kresge and Powell have measured a

[8] (*a*) O. Rogne, *J. Chem. Soc., Chem. Commun.*, 1977, 695; (*b*) O. Rogne, *Acta Chem. Scan., Ser. A*, 1978, **32**, 559; (*c*) O. Rogne, *J. Chem. Soc., Faraday Trans. 1*, 1978, **74**, 1254.



Scheme 3

tritium isotope effect of 46 for the T–H exchange in the same system, corresponding to $k^H/k^D = 14$.[9]

A common intermediate has also been demonstrated for acid-catalysed H–D exchange and bromination of the bicyclic amidine in Scheme 4. The common intermediate in this case is not a carbanion but a ketene aminal formed by proton transfer from carbon in an amidinium ion to an amidine nitrogen.[10]

B. Solvolysis.—Many solvolysis reactions involve branching of the type presented by equation 1. Accordingly, an initial rate-limiting ionization is followed by partitioning of the carbocationic intermediate, ion or ion pair, to give substitution and elimination products, sometimes accompanied by internal return (equation 8).

If the return occurs from a free carbocation (external return), the concentration of X^- is involved in the rate constant and isotope-effect expressions (equations

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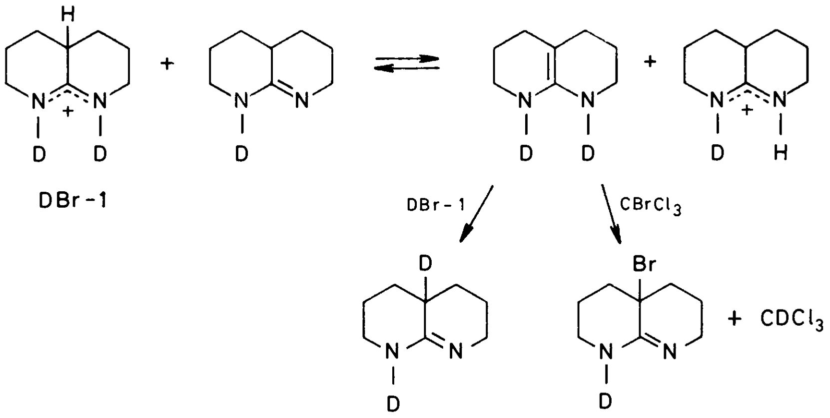
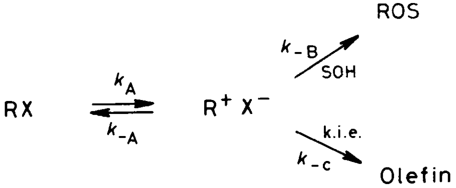
[9] A. J. Kresge and M. F. Powell, *J. Am. Chem. Soc.*, 1981, **103**, 201.

[10] S. Löfås and P. Ahlberg, *J. Am. Chem. Soc.*, 1985, **107**, 7534.



Scheme 4



(8)

2—6). The following discussion holds also for a mechanism with a free carbocation as intermediate.

If the substrate RX is isotopically substituted in the β-position, the ionization ($k_{\rm A}$) is slowed down owing to a secondary isotope effect. The dehydronation ($k_{-\rm C}$) of the ion pair, on the other hand, shows a primary isotope effect. The nucleophilic substitution (by the solvent or other nucleophile) is expected to show only a small inverse secondary isotope effect. The value should be close to unity since the transition state for the attack of the nucleophile is expected to have a structure very similar to the high-energy carbocationic intermediate. The same is valid for the return process.

For the sake of simplicity, let us assume that internal return is not significant, *i.e.* $k_{-\rm A} \ll k_{-\rm B}, k_{-\rm C}$ (equation 8). The isotope effect on the disappearance of the substrate is then equal to the ionization isotope effect $k^{\rm H}_{\rm A}/k^{\rm D}_{\rm A}$. However, equations 4 and 5 yield an isotope effect on the overall substitution reaction that is attenuated relative to $k^{\rm H}_{\rm A}/k^{\rm D}_{\rm A}$; the overall elimination isotope effect $k^{\rm H}_{\rm AC}/k^{\rm D}_{\rm AC}$ is enlarged. If the substitution reaction is much faster than the elimination reaction, a maximum overall elimination isotope effect $k^{\rm H}_{\rm AC}/k^{\rm D}_{\rm AC} = (k^{\rm H}_{\rm A}/k^{\rm D}_{\rm A})(k^{\rm H}_{-\rm C}/k^{\rm D}_{-\rm C})$, *i.e.* a product of a secondary and a primary isotope effect, is obtained.[11–13]

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[11] A. Thibblin, *J. Chem. Soc., Perkin Trans. 2*, 1986, 320.
[12] A. Thibblin, *J. Am. Chem. Soc.*, 1987, **109**, 2071.
[13] A. Thibblin, *J. Phys. Org. Chem.*, 1989, 2, 15.

The measured isotope effects for the solvolysis of 9-(2-chloro-2-propyl)fluorene and its $^2H_6$-analogue in 25 vol% acetonitrile in water (Scheme 5) were analysed in accord with the competition model.[12] The protium compound was found to give a product ratio olefin/alcohol of 1.67. The ionization isotope effect was as large as $k_1^H/k_1^D = 2.2$, a value close to the expected maximum for a $^2H_6$-compound. The overall elimination isotope effect was found to be relatively large for a solvolytic elimination reaction, $k_{46}^H/k_{46}^D = 3.7$. It was concluded that this isotope effect was composed of the ionization isotope effect, $k_1^H/k_1^D = 2.2$, the dehydronation isotope effect, $k^H_{-4}/k^D_{-4} = 2.8$, and the isotope effect for the nucleophilic attack of water on the intermediate, $k^H_{-2}/k^D_{-2} \sim 1$:

$$k_{46}^H/k_{46}^D = (k_1^H/k_1^D)(k^H_{-4}/k^D_{-4})(k^D_{-2} + k^D_{-4})/(k^H_{-2} + k^H_{-4}) \qquad (9)$$

Moreover, quite in agreement with the proposed mechanistic model (Scheme 5), a drastic decrease in the solvent polarity decreases the amount of alcohol product and the overall elimination isotope effect decreases to 2.8; no change in the isotope effect (2.2) for the disappearance of the substrate occurs.

An isotope effect as large as $k^H/k^{D_6} = 5.7$ at 25 °C has been measured for the acid-catalysed dehydration of 2-phenyl-2-propanol in 25 vol% acetonitrile in water.[13] The isotope effect is large owing to the competition between slow dehydronation of the intermediate and a fast nucleophilic attack of solvent water. The corresponding reaction of the methyl ether shows similar behaviour.[13]

A solvolytic system that is not accompanied by substitution but by external or internal return may also exhibit an enlarged overall elimination isotope effect owing to the competition between return (with a secondary isotope effect close to unity) and dehydronation of the carbocation intermediate (with a primary isotope effect) that follows an ionization with a substantial isotope effect.[11–16] Accordingly, Fry has simulated the observed isotope effect for an *E*1 reaction as a function of the amount of return.[15]

C. Oxidation–Reduction Reactions.—Unusually large hydrogen isotope effects in oxidation reactions may arise from the following type of mechanism. An initially formed radical reacts with oxygen to give the product. A by-product is formed by a competing reaction of the radical with an inhibitor (equation 10).

Both k_1 and k_2 involve abstraction of a hydrogen and are expected to show substantial isotope effects. The formation of the byproduct (k_3), on the other hand, is not likely to be sensitive to isotopic substitution. Thus, more by-product

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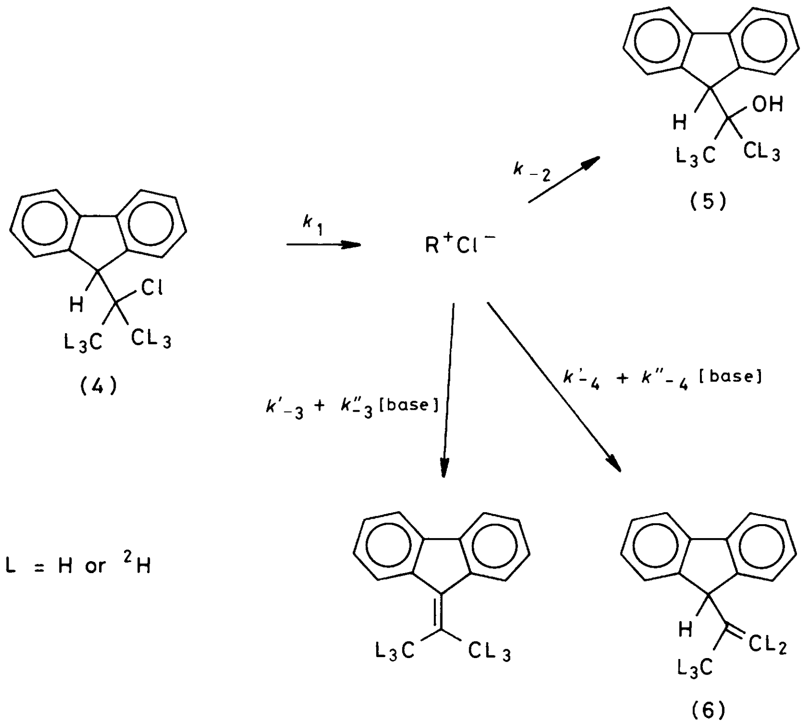
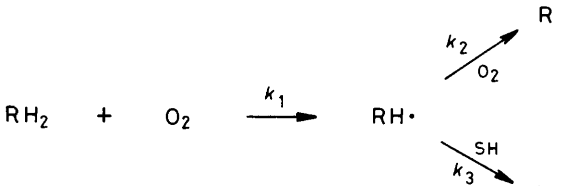
[14] A. Thibblin, *J. Am. Chem. Soc.*, in press.

[15] A. Fry, *Chem. Soc. Rev.*, 1972, **1**, 163.

[16] (*a*) S. G. Smith and D. J. W. Goon, *J. Org. Chem.*, 1969, 3127; (*b*) V. J. Shiner, Jr., W. Dowd, R. D. Fischer, S. R. Hartshorn, M. A. Kessick, L. Milakofsky, and M. W. Rapp, *J. Am. Chem. Soc.*, 1969, **91**, 4838; (*c*) M. P. Jansen, M. K. Koshy, N. N. Mangru, and T. T. Tidwell, *J. Am. Chem. Soc.*, 1981, **103**, 3863; (*d*) X. Creary, C. C. Geiger, and K. Hilton, *J. Am. Chem. Soc.*, 1983, **105**, 2851; (*e*) X. Creary, *J. Am. Chem. Soc.*, 1984, **106**, 5568.



Scheme 5



(10)

is formed from the deuterated substrate. Accordingly, an unusually large kinetic isotope effect on the formation of the product results (*cf.* equation 4).

A primary adsorptive isotope effect has been postulated as an explanation for the large isotope effect, $k^H/k^D = 14.2 \pm 0.9$, observed in the oxidation of benzyl alcohol by manganese dioxide.[17] The proposed reaction mechanism may be summarized as in equation 11.

This rationalization of the unusually large isotope effect is valid *only* if the

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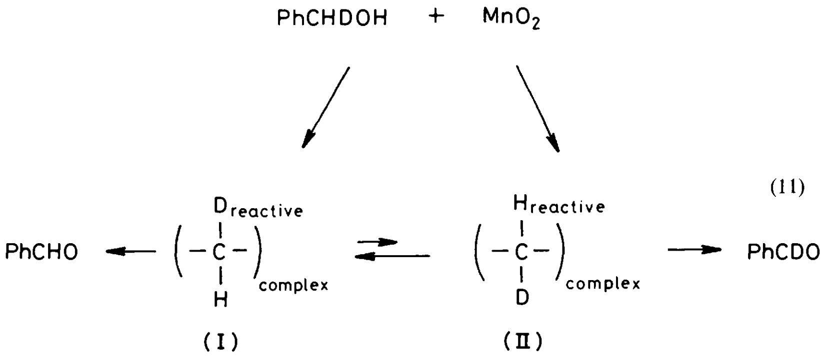
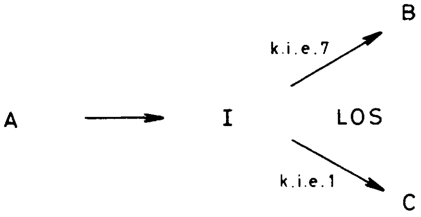
[17] I. M. Goldman, *J. Org. Chem.*, 1969, **34**, 3289.



(11)



(12)

adsorption complexes (I) and (II) are thermodynamically *more* stable than non-adsorbed benzyl alcohol.

Oxidation reactions are usually mechanistically complex. It is plausible that the unusually large hydrogen isotope effects measured in some reactions of this type,[18] *e.g.* the oxidation of formate ion by $[(bpy)_2(py)Ru^{IV}(O)]^{2+}$ (bpy is 2,2′-bipyridine and py is pyridine) exhibits an isotope effect of $k_{HCOO^-}/k_{DCOO^-} = 19$ at 25 °C,[18a] are caused by branching.

D. Solvent Isotope Effects.—The reaction branching shown in equation 1 may also yield a large inverse solvent isotope effect. For example, let I be an intermediate formed irreversibly from A; I may either be hydronated by the solvent LOS (or by buffer acid) (L = H or D) to give B or react to give product C. A substantial isotope effect on the hydronation step and a negligible isotope effect on the other product-forming step result in an inverse solvent isotope effect for the reaction A to C. Accordingly, equations 4 and 5 and the values in equation 12 yield $k_{AB}^{DOS}/k_{AB}^{HOS} < 1$ and $k_{AC}^{DOS}/k_{AC}^{HOS} < 7$; the extreme values are attained when B is the dominant product.

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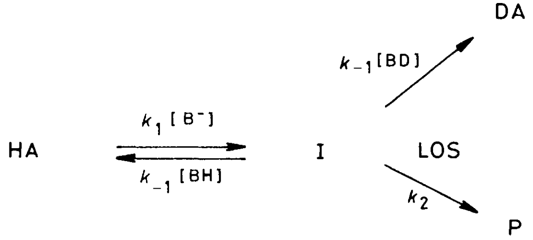
[18] (*a*) L. Roecker and T. J. Meyer, *J. Am. Chem. Soc.*, 1985, **108**, 4066; (*b*) D. Bethell and V. D. Parker, *J. Chem. Soc., Perkin Trans 2*, 1982, 841; (*c*) J. A. Gilbert, S. W. Gersten, and T. J. Meyer, *J. Am. Chem. Soc.*, 1982, **104**, 6872; (*d*) R. A. Binstead, B. A. Moyer, G. J. Samuels, and T. J. Meyer, *J. Am. Chem. Soc.*, 1981, **103**, 2897; (*e*) R. Stewart and R. Van der Linden, *Tetrahedron Lett.*, 1960, 28; (*f*) L. Roecker and T. J. Meyer, *J. Am. Chem. Soc.*, 1987, **109**, 746.



(13)

Another example is afforded by the dehydronation of a substrate in a fast pre-equilibrium step to give a solvent-equilibrated carbanion intermediate (or a BH–carbanion complex that undergoes rapid hydrogen exchange), which is either rehydronated by the solvent LOS or another general acid, or reacts to product (equation 13), when a large inverse solvent isotope effect may result. This special case of branching as the cause of a large inverse solvent isotope effect has been discussed by Keeffe and Jencks.[19]

The mechanism shown in equation 13 accounts for large inverse isotope effects on the initial rate constant for formation of P in the following way (for simplicity, the formation of P from the intermediate is assumed to be insensitive to isotopic substitution). At the first part of reaction, before significant exchange with the solvent LOS has occurred, the reaction is retarded by the reversal of the first step, *i.e.* $k_{-1}[\mathrm{BH}]$ competes with k_2. The reaction is retarded more in HOS than in DOS owing to a primary deuterium isotope effect on rehydronation, $k_{-1}^{\mathrm{HOS}}[\mathrm{BH}] > k_{-1}^{\mathrm{DOS}}[\mathrm{BD}]$. This retardation is responsible for the enlarged inverse solvent isotope effect.

Application of the steady-state approximation to equation 13 yields the following expressions for the rate constant and the solvent isotope effect:

$$k_{\mathrm{obs}}^{\mathrm{LOS}} = k_1[\mathrm{B}^-]k_2/(k_{-1}[\mathrm{BL}] + k_2) \tag{14}$$

$$k_{\mathrm{obs}}^{\mathrm{DOS}}/k_{\mathrm{obs}}^{\mathrm{HOS}} = (k_1^{\mathrm{DOS}}/k_1^{\mathrm{HOS}})\{(k_{-1}^{\mathrm{HOS}}[\mathrm{BH}] + k_2)/(k_{-1}^{\mathrm{DOS}}[\mathrm{BD}] + k_2)\} \tag{15}$$

The second factor of equation 15 may have a substantial value. The magnitude depends principally on the ratio $k_{-1}^{\mathrm{HOS}}/k_{-1}^{\mathrm{DOS}}$ and the magnitude of k_2 relative to $k_{-1}^{\mathrm{LOS}}[\mathrm{BL}]$. The inverse isotope effect increases from a minimum value at zero buffer concentration to a maximum value at high buffer concentration.

When the first step is not rate-limiting and $[\mathrm{BH}] = [\mathrm{BD}]$ the observed isotope effect is given by

$$k_{\mathrm{obs}}^{\mathrm{DOS}}/k_{\mathrm{obs}}^{\mathrm{HOS}} = (k_1^{\mathrm{DOS}}/k_1^{\mathrm{HOS}})(k_{-1}^{\mathrm{HOS}}/k_{-1}^{\mathrm{DOS}}) \tag{16}$$

Accordingly, it is possible to observe a very large inverse isotope effect since

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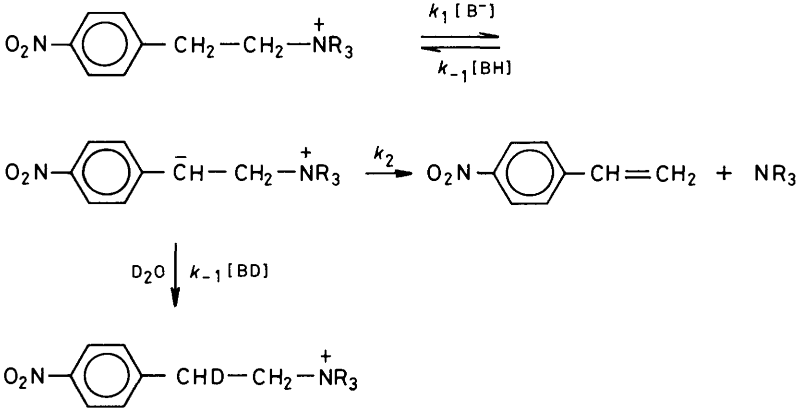
[19] J. R. Keeffe and W. P. Jencks, *J. Am. Chem. Soc.*, 1981, **103**, 2457.



Scheme 6

the measured value is the product of a primary deuterium isotope effect (second factor) multiplied by the inverse solvent isotope effect on the ionization step which may attain a value of < 2.[20]

Keeffe and Jencks have measured an inverse solvent deuterium isotope effect of 7.7 on the initial rate of the reversible *E*1cB reaction presented in Scheme 6.[19] The hydronation of the carbanion in this system is much more effective with added buffer acid than with water. Accordingly, the measured isotope effect increases with enhanced concentration of acid (*cf.* equation 15).

The data by More O'Ferrall and Slae[21] for the dehydration of 9-fluorenylmethanol in aqueous sodium hydroxide have also been analysed in a similar way;[19] an isotope effect $k_{\mathrm{obs}}^{\mathrm{D_2O}}/k_{\mathrm{obs}}^{\mathrm{H_2O}} = 7.9$ was obtained. Large inverse isotope effects have been measured in acid solution for the initial rate of cyclohexanone oxidation.[22] Another large inverse solvent isotope effect, $k_{\mathrm{D_2O}}/k_{\mathrm{H_2O}} = 3.5$, measured for the glucokinase reaction,[23] may also be caused by branching. A very large inverse solvent isotope effect has been reported for a photochemically induced double bond migration in a 2,3-unsaturated ester.[24]

3 Branching Directly from the Substrate

Equation 17 constitutes another type of branching in which the substrate A reacts reversibly to compound B in competition with the reaction to the final product C.

This type of branching may result in an apparently large isotope effect on k_{AC} since, if there is an isotope effect on k_{AC} but not on k_{AB}, the isotopically substituted substrate yields a different amount of B than the unsubstituted; and, if only the

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[20] D. A. Winey and E. R. Thornton, *J. Am. Chem. Soc.*, 1975, **97**, 3102.

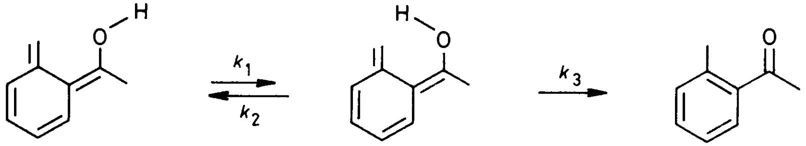
[21] R. A. More O'Ferrall and S. Slae, *J. Chem. Soc. B*, 1970, 260.

[22] J. S. Littler, G. R. Quick, and D. Wozniak, *J. Chem. Soc., Perkin Trans. 2*, 1980, 657.

[23] D. Pollar-Knight and A. Cornish-Bowden, *Eur. J. Biochem.*, 1984, **141**, 157.

[24] M. J. Jorgensen, *J. Am. Chem. Soc.*, 1969, **91**, 198.

$$\begin{tikzcd} A \arrow[r, shift left, "k_{AB}"] \arrow[d, "k_{AC}"'] & B \arrow[l, shift left, "k_{BA}"] \\ C & \end{tikzcd} \qquad (17)$$



(7a) (7b)

Scheme 7

formation of the product C is recorded, an unusually large value for the kinetic isotope effect may result. An example: $k^{\mathrm{H}}_{\mathrm{AC}} = 100\ \mathrm{s}^{-1}$, $k_{\mathrm{AB}} = 10\ \mathrm{s}^{-1}$, $k_{\mathrm{BA}} = 0.1\ \mathrm{s}^{-1}$, and $k^{\mathrm{D}}_{\mathrm{AC}} = 10\ \mathrm{s}^{-1}$ result in an apparent isotope $(k^{\mathrm{H}}_{\mathrm{AC}}/k^{\mathrm{D}}_{\mathrm{AC}})_{\mathrm{obs}}$ that depends on the time interval which is used. Let us assume that the times for formation of 60.65 mol% C from unsubstituted and isotopically substituted substrate (0.0100 s and 4.9 s, respectively) are used for calculation of the isotope effect. The measured value is then $(k^{\mathrm{H}}_{\mathrm{AC}}/k^{\mathrm{D}}_{\mathrm{AC}})_{\mathrm{obs}} = 490$.[25]

Bordwell and co-workers have measured an unusually large kinetic isotope effect that is caused by this type of branching. They measured $k^{\mathrm{H}}/k^{\mathrm{D}} = 340$ for the dehydronation of 2-phenyl-1-nitrocyclopentene with sodium methoxide in methanol.[26] However, after careful analysis of the kinetic data they concluded that methoxide anion was added rapidly to the substrate and that the addition product slowly gave back the substrate; the latter underwent slow dehydronation to give product with a 'normal' isotope effect of *ca.* 5.

Another example of this type of branching is probably the following reaction system. The reketonization of (7) (generated by flash photolysis of the ketone) in a mixture of ether, isopentane, and ethanol has been asssumed to react by 1,5-hydrogen shift of sigmatropic type (Scheme 7).[27] It was concluded that (7a) was the more stable of the two conformers; reaction occurs only from (7b) according to the rate expression given by equation 18.

$$k_{\mathrm{obs}} = k_1 k_3/(k_2 + k_3) \qquad (18)$$

Deuterated enol reacts more slowly; $k^{\mathrm{H}}_{\mathrm{obs}}/k^{\mathrm{D}}_{\mathrm{obs}}$ was measured as 3 at 300 K and

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[25] Obtained by computer simulation of the integrated rate expressions corresponding to equation 17.

[26] F. G. Bordwell, K. C. Yee, and A. C. Knipe, *J. Am. Chem. Soc.*, 1970, **92**, 5945.

[27] (*a*) K.-H. Grellmann, H. Weller, and E. Tauer, *Chem. Phys. Lett.*, 1983, **95**, 195; (*b*) U. Baron, G. Bartelt, A. Eychmuller, K.-H. Grellmann, U. Schmitt, E. Tauer, and H. Weller, *J. Photochem.*, 1985, **28**, 187.

180 at 140 K (corresponding to about 11 at 300 K). These isotope effects arise from a substantial isotope effect on k_3; k_1 and k_2 are not expected to show any significant isotope effects. The change in isotope effect with temperature was attributed to tunnelling since k_2 was assumed to be much larger than k_3 in the whole temperature interval.[27]

However, the results may be explained in the following way without invoking any tunnelling. A fast interconversion of the conformers at 300 K is reasonable but it is possible that the equilibrium is 'frozen' at low temperature, *i.e.* (7a) is formed from (7b) but (7a) returns very slowly to (7b). Thus, the system is similar to that described in connection with equation 17.

A trivial cause of unusually large kinetic isotope effects is that the reaction is accompanied by the formation of a by-product by branching directly from the substrate (equation 17, $k_{BA} = 0$). Thus, if the rate of the side reaction is not sensitive to isotopic substitution, more of the by-product is formed from the more slowly reacting isotopically substituted compound. If this is not considered, a very small apparent rate constant for formation of the main product from the 'heavy' substrate may result which gives an 'enlarged' kinetic isotope effect. Thus, the rate constants given in connection with equation 17 and $k_{BA} = 0$, and assuming that the times for the formation of 40 mol% C are employed for calculation of the isotope effect yield $(k^{H}_{AC}/k^{D}_{AC})_{obs} = 15$.[25] On the other hand, if the rate of disappearance of A is measured (with rate constant $k_{obs} = k_{AB} + k_{AC}$), an attenuated isotope effect k^{H}_{obs}/k^{D}_{obs} is obtained.

4 Miscellaneous Large Isotope Effects

Other unusually large isotope effects in the literature include the following examples. There is no specific reason to invoke branching, but it should be of interest to reconsider these reactions with that possibility in mind.

An unusually large isotope effect, $k^{H}/k^{D} \sim 27$ at 0 °C, has been measured for the complex reaction of acid-catalysed *cis–trans* isomerization of a diene–iron tricarbonyl complex.[28] Hydrogen atom abstraction from phenols by polyvinyl acetate radicals has been found to exhibit a deuterium isotope effect of 57 ± 23 at 50 °C.[29] Another example of an unusually large isotope effect for a hydrogen abstraction has been reported for the 2-hydroxyphenoxyl radical, $k^{H}/k^{D} \sim 104$ at 25 °C.[30] A kinetic deuterium isotope effect of 25 at 65 °C has been measured for hydrogen atom abstraction from cyclohexene.[31] The thermal oxidation of 4a,4b-dihydrophenanthrene and the analogous ($^{2}H_{12}$)-compound by oxygen exhibits $k^{H}/k^{D} = 95$ at -31 °C (corresponding to about 40 at 25 °C).[32]

An unusually large primary hydrogen isotope effect has been measured for the

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[28] T. H. Whitesides and J. P. Neilan, *J. Am. Chem. Soc.*, 1975, **97**, 907.

[29] J. Kardos, I. Fitos, J. Szammer, and M. Simonyi, *J. Chem. Soc., Perkin Trans. 2*, 1978, 405.

[30] K. Loth, F. Graf, and H. H. Gunthard, *Chem. Phys.*, 1976, **13**, 95.

[31] P. S. Engel, W.-K. Chae, S. A. Baughman, G. E. Marschke, E. S. Lewis, J. W. Timberlake, and A. E. Luedtke, *J. Am. Chem. Soc.*, 1983, **105**, 5030.

[32] (*a*) A. Bromberg, K. A. Muszkat, and E. Fischer, *J. Chem. Soc., Chem. Commun.*, 1968, 1352; (*b*) A. Bromberg, K. A. Muszkat, E. Fischer, and F. S. Klein, *J. Chem. Soc., Perkin Trans. 2*, 1972, 588 and references therein.

ionization of 2-nitropropane with 2,4,6-trimethylpyridine.[33] However, it has been concluded that the value $k^{H}/k^{D} = 24$ measured in t-butyl alcohol–water is too large since it is measured in the presence of oxygen.[34] When the reaction was carried out under nitrogen, the rates were faster and the isotope effect was lower, $k^{H}/k^{D} = 16$.[34] High pressure (3000 bar) was found to decrease the isotope effect down towards 7. Also, Jarczewski and co-workers have measured unusually large isotope effects in hydron transfer from substrates activated by a nitro-group.[35]

5 Temperature Effects that Mimic Tunnelling

The unusually large kinetic isotope effects which have been reported in the literature have almost exclusively been concluded to be caused by tunnelling.[1] In some of these systems, the tunnelling hypothesis is also supported by studies of activation parameters.[1,27] However, it has been shown by simulation that temperature effects on activation parameters for branched reactions may mimic those that are expected to arise from tunnelling.[2g,36] Accordingly, it has been concluded that *both* unusually large primary kinetic isotope effects and ratios of Arrhenius pre-exponential factors considerably smaller than unity may result from branching (equation 1) if the rate of the reaction under study increases more with temperature than the competing side reaction. The latter can be slower than the main reaction by a factor of ten and still give rise to this anomalous temperature effect.[2g] It has also been concluded that branched reactions may result in constant or even increased isotope effect with temperature.[2g]

Acknowledgment. The Swedish Natural Science Research Council has provided financial support for this work.

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[33] (*a*) E. S. Lewis and J. D. Allen, *J. Am. Chem. Soc.*, 1964, **86**, 2022; (*b*) E. S. Lewis and L. H. Funderburk, *J. Am. Chem. Soc.*, 1967, **89**, 2322; (*c*) R. P. Bell, E. S. Lewis, and J. K. Robinson, *J. Am. Chem. Soc.*, 1968, **90**, 4337; (*d*) R. P. Bell and D. M. Goodall, *Proc. Roy. Soc.*, 1966, **A294**, 273.

[34] N. S. Isaacs and K. Jivaid, *J. Chem. Soc., Perkin Trans. 2*, 1979, 1583.

[35] P. Pruszynski and A. Jarczewski, *J. Chem. Soc., Perkin Trans. 2*, 1986, 1117.

[36] The internal-return mechanism may be considered as a special type of branching (one of the competing reactions gives back starting material).[2g] Also, this type of mechanism may give rise to activation parameters which mimic those of reactions with a large tunnel contribution (ref. 37).

[37] H. F. Koch and D. B. Dahlberg, *J. Am. Chem. Soc.*, 1980, **102**, 6102.