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The Contribution of Tunneling to Secondary Isotope Effects*

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Tunneling has long been recognized as a potential contributor to rates and isotope effects in hydrogen-transfer processes, and there is by now a substantial body of experimental evidence as well. By contrast, little has been said until relatively recently about possible contributions of tunneling when the isotopically-substituted hydrogen is not transferred in the rate-determining step. Over the last ten years evidence has accumulated that tunneling by the non-transferred hydrogen attached to a carbon atom from which hydrogen is transferred is a plausible explanation of abnormal temperature dependences of isotope effects and of the non-additivity of isotope effects from multiple isotopic substitution. This paper reviews that evidence, and discusses the scope and limitations of tunneling contributions to secondary isotope effects.

INTRODUCTION

The idea that tunneling can contribute to rates and isotope effects in chemical reactions goes back almost to the beginning of quantum theory, and the theory of tunneling as a factor in proton transfer processes was developed by Bell more than 30 years ago.¹ Since then he and others have further developed the theory and accumulated evidence that tunneling is indeed a common occurrence in proton transfer processes.²⁻⁴ This is a very well known story, and it is not the purpose of this paper to review it in any detail. Nonetheless, the expected consequences of tunneling will be described very briefly as background for the discussion of its role in secondary isotope effects.

Theory points out three major factors expected to promote tunneling: (1) Low mass, which makes tunneling particularly likely when hydrogen is the moving particle, and makes tunneling more likely for protium than for deuterium or tritium, (2) Low temperature; as the temperature is raised, tunneling becomes progressively less important and disappears at the high-temperature limit, (3) A narrow barrier to a chemical

* Dedicated to Professor Dionis E. Sunko on the occasion of his seventieth birthday.

reaction. Because tunneling is more important the lighter the isotope, a clear prediction is that deuterium or tritium isotope effects should be larger than they would otherwise be if tunneling were not a factor. Unfortunately there are few cases where isotope effects are so large that tunneling must be invoked.⁴ On the other hand, semiclassical isotope effects⁵ are so variable that it is entirely possible that a significant tunnel correction would still not give an overall isotope effect that would be too large to account for without invoking tunneling. For this reason, the temperature dependence of the isotope effect is a much more reliable test than the simple magnitude of the effect at a single temperature.

The temperature dependence criterion works as follows. In the absence of tunneling, the temperature dependence should follow the Arrhenius equation (equation 1).

$$\ln k_{\text{obs}} = -\frac{E_a}{RT} + \ln A \quad (1)$$

In the presence of tunneling, the rate at low temperatures will be greater than predicted by equation (1), resulting in curvature of the Arrhenius plot, but this curvature will usually be too slight to be apparent over the limited temperature range (*ca.* 30–40 °C) covered by most rate studies in solution. But since the curvature has the effect of reducing the apparent slope, linear extrapolation to $1/T = 0$ will result in a value of $\ln A$ which is smaller than the true value. Because tunneling is more important for protium than for deuterium or tritium, A_H will be underestimated more seriously than A_D or A_T . Thus tunneling will lead to A_H/A_D and $A_H/A_T < 1$. In the absence of tunneling the ratios of Arrhenius preexponential factors should be very close to unity. The absolute minimum values at ordinary temperatures are $A_H/A_D = 0.5$ and $A_H/A_T = 0.33$, but these are based on an unrealistic model in which bending vibrations of the transition state disappear.^{3,4} More plausible values for the lower limits would be in the range 0.7–0.8. Many values below this range are to be found in the literature.⁴

Another criterion for tunneling was based on the idea that the relation between deuterium and tritium isotope effects derived from semiclassical considerations alone (equation 2)^{6,7} should be violated if there is tunneling. Subsequent experiments⁸ and

$$k_H/k_T = (k_H/k_D)^{1.44} \quad (2)$$

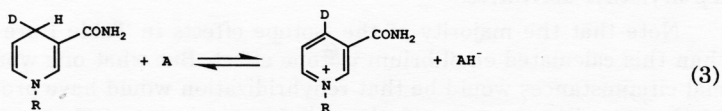
calculations⁹ have revealed, however, that any deviation will normally be too small to detect. We will see below that a variant of this criterion is indeed useful when secondary isotope effects are involved.

EXPERIMENTAL EVIDENCE ON SECONDARY ISOTOPE EFFECTS

For most of this review, we shall be concerned only with secondary isotope effects on hydrogen transfer processes in which the secondary (non-transferred) hydrogen is on the same carbon atom as the hydrogen being transferred. In order to distinguish these two types of hydrogens, the convention used will be that the primary (transferred) hydrogen will be represented by a subscript and the secondary hydrogen by a superscript. Thus, k_H^H/k_H^T represents a secondary tritium isotope effect when the atom

transferred is protium. The same convention is used for the Arrhenius parameters A and E_a .

The earliest evidence that something unexpected was occurring was a report that hydride transfer from nicotine adenine dinucleotide (NADH, equation 3) gave second-



dary kinetic isotope effects of 1.14–1.16, values that were much larger than the corresponding equilibrium isotope effects (1.01–1.03).¹⁰ Since the equilibrium isotope effects represent complete transfer of the hydride, one would normally expect the kinetic isotope effect to be *smaller* than the equilibrium effect.

These results were soon followed by evidence that β -secondary tritium isotope effects in elimination reactions of β -arylethyl derivatives were unusually large.^{11–14} These data are summarized in Table I, which also includes one example of an α -phenylethyl derivative.¹⁴ In this case it is not possible to measure the equilibrium isotope effect because the elimination is irreversible. It is, however, possible to get a reliable estimate of the equilibrium isotope effect by using the fractionation factors of Hartshorn and Shiner.^{15,16} These are equilibrium constants for isotope exchange reactions calculated from force fields consistent with spectroscopic data for small molecules. The relevant ones in this particular case are for equations (4) and (5), which can be combined to give equation (6).

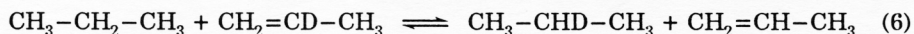
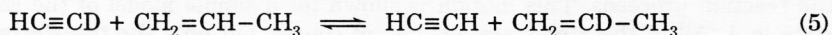
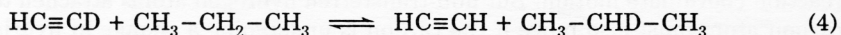


TABLE I

Secondary Isotope Effects for $\text{PhCHTCH}_2\text{X} + \text{RO}^-$ at 50 °C

X	Base/Solvent	$(k_{\text{H}}/k_{\text{T}})_{\text{sec}}$	$(k_{\text{H}}/k_{\text{D}})_{\text{sec}}^{\text{d}}$
NMe ₃	EtO ⁻ /EtOH	1.165±0.009	1.11
NMe ₃ ^a	EtO ⁻ /EtOH	1.267±0.012	1.18
NMe ₃	OH ⁻ /30% DMSO	1.235±0.016	1.16
NMe ₃	OH ⁻ /40% DMSO	1.250±0.023	1.17
NMe ₃	OH ⁻ /50% DMSO	1.243±0.031	1.16
SMe ₂	OH ⁻ /30% DMSO	1.119±0.023	1.08
SMe ₂	OH ⁻ /40% DMSO	1.144±0.026	1.10
SMe ₂	OH ⁻ /50% DMSO	1.134±0.026	1.09
OTs	<i>t</i> -BuO ⁻ / <i>t</i> -BuOH	1.239±0.023	1.16
OTs ^b	<i>t</i> -BuO ⁻ / <i>t</i> -BuOH	1.191±0.012	1.13
Br	<i>t</i> -BuO ⁻ / <i>t</i> -BuOH	1.270±0.010	1.18
NMe ₃ ^c	EtO ⁻ /EtOH	1.224±0.006	1.15

^a*p*-CF₃Ph; ^b*p*-ClPh;

^c α -Phenylethyl derivative at 54.5 °C;

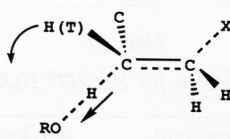
^dCalculated from equation (2).

Thus $K_6 = K_4/K_5 = 1.501/1.336 = 1.1235$ at 25 °C. Assuming exponential temperature dependence, K_6 becomes 1.11 at 50 °C. From equation (2), the corresponding tritium effect is 1.17. This reaction represents the isotope effect for conversion of an sp^3 C-H bond to sp^2 , where the C is attached to two other C atoms. It thus should be a very good model for the unknown equilibrium isotope effect for the elimination from a β -arylethyl derivative.

Note that the majority of the isotope effects in Table I are as large as or larger than this calculated equilibrium isotope effect. But what one would expect under normal circumstances would be that rehybridization would have proceeded only part way in the transition state, and that all kinetic isotope effects would be significantly *smaller* than the equilibrium effect. It thus appears that some factor absent from the equilibrium effect is contributing to the kinetic effect. Tunneling is a logical choice, for it can affect only rates, not equilibria.

THEORY AND PREDICTIONS

To strengthen the case for tunneling as a cause of the discrepancy it is necessary to show that reasonable assumptions predict effects of the same magnitude as those observed, and that theory makes further predictions than can be tested. The application of isotope-effect theory to the hydride transfer was made by Huskey and Schwen,¹⁵ and to the elimination reactions by Saunders.^{16,17} In order for an isotopically-substituted atom to affect the contribution of tunneling to a reaction, the mass of that atom must contribute to the *effective mass along the reaction coordinate*. The only way it can do that is if it is moving as the system progresses along the reaction coordinate from reactants to products. For a proton transfer, it is obvious that the atom being transferred meets this requirement, for its motion constitutes the major part of the reaction coordinate motion. But non-transferred hydrogen atoms attached to the same carbon atom must also move if the carbon is undergoing a change in hybridization as the reaction proceeds. This motion is shown for a simple model of the E2 transition state in **1**. All of the atoms are moving, of course, but only the transferred and non-



transferred hydrogen motions are shown for the sake of clarity. The non-transferred hydrogen is moving because it must shift from the position it occupies in the sp^3 hybridized reactant to that it occupies in the sp^2 hybridized product. Although the effective mass along the reaction coordinate is still determined mainly by the transferred hydrogen, it is modified by a contribution from the motion of the non-transferred hydrogen. If the latter is replaced by deuterium or tritium, the effective mass along the reaction coordinate will increase even if the transferred hydrogen remains the same in both cases.

These qualitative considerations can be incorporated in a quantitative treatment by the BEBOVIB-IV program¹⁸ as follows. The fundamental vibrational frequencies of

reactant and transition state models are calculated from the geometry of the molecule, the atomic masses, and the force constants governing vibrational motions of the atoms. These force constants can be estimated from values obtained by vibrational analysis of simple molecules. The geometries, masses, and frequencies are in turn used to calculate the partition functions of the isotopic reactants and transition states, from which the isotope effects can be calculated.

In order to obtain a realistic transition state model in which all atoms are moving in such a way as to convert reactants to products, it is necessary to introduce off-diagonal force constant matrix elements which constrain the relevant motions to occur in proper phase with one another. In **1**, for example, the RO-H bond must contract, the H-C bond stretch, the C-C bond contract, and C-X bond stretch at the same time to fulfill this requirement. In order to ensure that the non-transferred hydrogen is contributing to the reaction coordinate motion, additional off-diagonal elements must be used to couple its bending motions with the stretch of the transferred atom. When that is done, entirely reasonable values of the force constants predict substantial tunneling contributions to the secondary isotope effect.

The reader is referred to the original literature¹⁷ for a complete tabulation of the results of the model calculations. For present purposes a few specific examples will suffice. A model without the stretch-bend coupling gives only negligible tunnel effects: $k_{\text{H}}^{\text{H}}/k_{\text{H}}^{\text{T}}$ for model **1** with the proton half transferred is 1.067 without and 1.074 with the tunnel correction. When the coupling is introduced to an appropriate extent, these figures become 1.073 and 1.283, respectively. In other words, the overall effect owes more to tunneling than it does to the semiclassical isotope effect, and only by introducing the coupling is it possible to achieve an overall effect that approximates the experimentally observed effects.

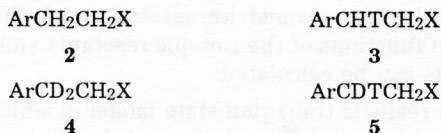
The calculations thus pass the first test of agreeing with established experimental results. Even more significant, however, is that they make predictions that can be tested by further experiments. As noted in the Introduction, a general test for tunneling with respect to primary isotope effects is that $A_{\text{H}}/A_{\text{D}}$ and $A_{\text{H}}/A_{\text{T}}$ should be substantially less than unity. The model calculations show that analogous behavior is to be expected for secondary isotope effects. In the absence of coupling, $A_{\text{H}}^{\text{H}}/A_{\text{H}}^{\text{T}}$ remains above 0.95; in its presence, $A_{\text{H}}^{\text{H}}/A_{\text{H}}^{\text{T}}$ can be substantially lower. The model that gives $k_{\text{H}}^{\text{H}}/k_{\text{H}}^{\text{T}}$ of 1.283 gives $A_{\text{H}}^{\text{H}}/A_{\text{H}}^{\text{T}}$ of 0.58.

A second prediction is that changing the transferred atom from protium to deuterium should diminish the extent of tunneling by increasing the effective mass along the reaction coordinate. Thus the tunnel correction to the secondary isotope effect should also be diminished. How to test this prediction is a little less obvious, for it would be a formidable if not impossible experimental job to measure $k_{\text{D}}^{\text{H}}/k_{\text{D}}^{\text{T}}$ with sufficient precision to distinguish it from $k_{\text{H}}^{\text{H}}/k_{\text{H}}^{\text{T}}$. It is, however, possible to make an indirect test by using equation (7), which is the source of equation (2) and which also gives, with appropriate m values, equation (8).^{4,17} The experimental $k_{\text{H}}^{\text{H}}/k_{\text{H}}^{\text{T}}$ values

$$\frac{\ln(k_1/k_2)}{\ln(k_1/k_3)} = \frac{1 - (m_1/m_2)^{0.5}}{1 - (m_1/m_3)^{0.5}} \quad (7)$$

$$k_{\text{H}}/k_{\text{T}} = (k_{\text{D}}/k_{\text{T}})^{3.26} \quad (8)$$

were obtained by measuring isotope fractionation in E2 reactions of a mixture of **2** and **3**. Similarly, a mixture of **4** and **5** provides the means for measuring k_D^D/k_D^T . The



transferred atom is the same for both k_D^D and k_D^T , so k_D^D/k_D^T and k_H^D/k_H^T should be the same provided multiple isotopic substituents in a molecule exert their effects independently. That they do so was predicted many years ago by Bigeleisen,¹⁹ and his prediction, called *The Rule of the Geometric Mean*, has been confirmed repeatedly. Thus, application of equation (8) to k_D^D/k_D^T should give k_H^H/k_H^T . But the model calculations (see above) predict that the tunnel correction to k_D^D/k_D^T should be less than that to k_H^H/k_H^T , leading to the relationship when tunneling is significant.

$$k_H^H/k_H^T > (k_D^D/k_D^T)^{3.26}$$

EXPERIMENTAL TEMPERATURE DEPENDENCES OF THE ISOTOPE EFFECTS

The Arrhenius parameters for five secondary tritium isotope effects on E2 reactions are shown in Table II.^{13,14} The subscript a denotes an experimental (apparent) value so as to distinguish between observed (A_a) and calculated (A) preexponential factors. Three of the A_{aH}^H/A_{aH}^T values are clearly indicative of tunneling, and support conclusions from the magnitudes of the isotope effects. The second and fifth entries do not permit such a clear-cut conclusion. Although both A_{aH}^H/A_{aH}^T values are significantly below unity, they certainly do not demand tunneling. Nonetheless, both reactions give k_H^H/k_H^T values (Table I) that are too large to be easily explained without invoking tunneling. We have argued that these apparently inconsistent observations can be reconciled if one takes account of the results of model calculations.¹³ They show that $A_{aH}^H/A_{aH}^T \approx 0.9$ can be consistent with an important tunnel correction: a model that gives $k_H^H/k_H^T = 1.25$ at 25 °C gives $A_H^H/A_H^T = 0.87$ and $(k_H^H/k_H^T)_{sc} = 1.08$. The major part of the overall isotope effect is still due to tunneling, even though the temperature dependence is only slightly abnormal. While a low ratio of Arrhenius preex-

TABLE II
Arrhenius Parameters of Secondary Isotope Effects in E2 Reactions

Substrate	Base/solvent	$E_{aH}^T - E_{aH}^H$, kcal mol ⁻¹	A_{aH}^H/A_{aH}^T
PhCHTCH ₂ NMe ₃ ⁺	EtO ⁻ /EtOH	0.326 ± 0.022	0.705 ± 0.024
PhCHTCH ₂ Br	<i>t</i> -BuO ⁻ / <i>t</i> -BuOH	0.200 ± 0.028	0.927 ± 0.040
<i>p</i> -ClPhCHTCH ₂ OTs	<i>t</i> -BuO ⁻ / <i>t</i> -BuOH	0.340 ± 0.021	0.704 ± 0.023
<i>p</i> -CF ₃ PhCHTCH ₂ NMe ₃ ⁺	EtO ⁻ /EtOH	0.478 ± 0.028	0.602 ± 0.026
PhCH(CH ₂ T)NMe ₃ ⁺	EtO ⁻ /EtOH	0.203 ± 0.015	0.898 ± 0.020

ponential factors is strong evidence for tunneling, a near normal ratio cannot decisively exclude it. Only if the isotope effect itself is too small to be consistent with a significant tunnel correction can tunneling be ruled out.

This argument is important in considering another example of secondary isotope effects in hydrogen transfer, the bovine serum amine oxidase catalyzed oxidation of benzylamine.¹⁹ In this case $A_{\text{aH}}^{\text{H}}/A_{\text{aH}}^{\text{T}}$ was reported to be 0.81 ± 0.05 and $A_{\text{aD}}^{\text{D}}/A_{\text{aD}}^{\text{T}}$ to be 1.02 ± 0.06 , values that were taken to offer no support for tunneling. But $k_{\text{H}}^{\text{H}}/k_{\text{H}}^{\text{T}}$ at 25 °C was 1.195 ± 0.016 , which is at the upper limit expected in the absence of tunneling. The point was made above (see p. 507) that only a very product-like transition state should give a semiclassical effect even approaching the upper limit, for only then would rehybridization be nearly complete in the transition state. While the temperature dependence of the isotope effect in the benzylamine oxidation can hardly be regarded as providing unequivocal support for tunneling, neither can it exclude tunneling. That $A_{\text{aD}}^{\text{D}}/A_{\text{aD}}^{\text{T}} > A_{\text{aH}}^{\text{H}}/A_{\text{aH}}^{\text{T}}$ is fully in accord with model calculations,¹⁷ because any tunneling that occurs will contribute less to the former than to the latter. If tunneling were contributing in neither case, both values would be expected to be near unity and very close to each other.

EXPERIMENTAL EVIDENCE ON THE ADDITIVITY OF SECONDARY ISOTOPE EFFECTS

The first evidence for a breakdown of the rule of the geometric mean in a non-enzymatic reaction was reported by Kreevoy's group for hydride transfers similar to that of equation (3).²¹ They found the secondary deuterium isotope effect was diminished when deuterium was the transferred atom. Nonadditivity of isotope effects has also been reported in enzymatic hydride transfers.^{22,23}

Evidence from our group on the relation between H/T and D/T secondary isotope effects is collected in Table III.^{13,14} In all cases $k_{\text{D}}^{\text{D}}/k_{\text{D}}^{\text{T}}$ is much less than $k_{\text{H}}^{\text{H}}/k_{\text{H}}^{\text{T}}$, and remains decisively smaller when converted to $(k_{\text{H}}^{\text{H}}/k_{\text{H}}^{\text{T}})_{\text{calc}}$ by the application of equation (8). To make $(k_{\text{H}}^{\text{H}}/k_{\text{H}}^{\text{T}})_{\text{calc}}$ as large as $k_{\text{H}}^{\text{H}}/k_{\text{H}}^{\text{T}}$ would require an exponent of 6 or more, a value well beyond anything that could be ascribed to the approximations employed in the derivation of equations (7) and (8). These results constitute perhaps the single most convincing line of evidence for the role of tunneling in secondary isotope effects in elimination reactions.

TABLE III

Comparison of Secondary H/T and D/T Isotope Effects in E2 Reactions at 50 °C

Substrate	Base/solvent	L	$k_{\text{L}}^{\text{L}}/k_{\text{L}}^{\text{T}}$, 50 °C	$(k_{\text{H}}^{\text{H}}/k_{\text{H}}^{\text{T}})_{\text{calc}}^{\text{b}}$
PhCHTCH ₂ NMe ₃ ⁺	EtO ⁻ /EtOH	H	1.204 ± 0.015	
PhCDTCH ₂ NMe ₃ ⁺	EtO ⁻ /EtOH	D	1.031 ± 0.010	1.105
<i>p</i> -ClPhCHTCH ₂ OTs	<i>t</i> -BuO ⁻ / <i>t</i> -BuOH	H	1.191 ± 0.012	
<i>p</i> -ClPhCDTCH ₂ OTs	<i>t</i> -BuO ⁻ / <i>t</i> -BuOH	D	1.027 ± 0.008	1.091
<i>p</i> -CF ₃ PhCHTCH ₂ NMe ₃ ⁺	EtO ⁻ /EtOH	H	1.267 ± 0.012	
<i>p</i> -CF ₃ PhCDTCH ₂ NMe ₃ ⁺	EtO ⁻ /EtOH	D	1.032 ± 0.003	1.108
PhCH(CH ₂ T)NMe ₃ ⁺	EtO ⁻ /EtPH	H	1.224 ± 0.006 ^a	
PhCH(CD ₂ T)NMe ₃ ⁺	EtO ⁻ /EtOH	D	1.029 ± 0.003 ^a	1.098

^a at 54.5 °C; ^b From equation (8) and the figures in column 4

The decisive character of results on the secondary effects encouraged us to believe that the relation between $k_{\text{H}}^{\text{H}}/k_{\text{T}}^{\text{H}}$ and $k_{\text{D}}^{\text{D}}/k_{\text{T}}^{\text{D}}$, the primary isotope effects, might be an additional useful criterion of tunneling. Unfortunately, the observed and calculated values of $k_{\text{H}}^{\text{H}}/k_{\text{T}}^{\text{H}}$ were within experimental error of each other.¹³ The experimental procedures for determining the primary effect are more complex and more subject to error than those for the secondary effect, and slight contamination of the deuterated species by protium causes much more serious errors in the large primary than in the small secondary effects. In addition, the calculated isotope effect is more sensitive to the precise value of the exponent, the exact magnitude of which depends on the model used to derive it. Our own model calculations show that primary semiclassical isotope effects in elimination reactions require exponents ranging from 3.18 to 3.34 to satisfy equation (8).²⁴ The comparable range for secondary effects greater than 1.10 is 3.19 to 3.72. There is thus no doubt that the calculated range is violated by the secondary effects, but systematic errors of 10% or less can make the difference between a fit and a violation for the primary effects. In any event, it is clear from model calculations that deviation from the rule of the geometric mean due to tunneling for the secondary effect should be accompanied by a comparable deviation for the primary effect.^{13,25} While tunneling can contribute to the primary but not to the secondary effect if the non-transferred hydrogen is not moving in the reaction coordinate motion,¹⁷ the converse situation is hard to imagine.

Further evidence that the problem is simply a matter of insufficient experimental accuracy and/or precision is found in the successful application of the criterion for both the primary and secondary effects to the oxidation of benzyl alcohol catalyzed by yeast alcohol dehydrogenase.²⁶ At 25 °C the secondary effects are $k_{\text{H}}^{\text{H}}/k_{\text{H}}^{\text{T}} = 1.35 \pm 0.015$, $k_{\text{D}}^{\text{D}}/k_{\text{D}}^{\text{T}} = 1.03 \pm 0.006$, and $(k_{\text{H}}^{\text{H}}/k_{\text{H}}^{\text{T}})_{\text{calc}} = 1.11$. The primary effects are $k_{\text{H}}^{\text{H}}/k_{\text{T}}^{\text{H}} = 7.13 \pm 0.07$, $k_{\text{D}}^{\text{D}}/k_{\text{T}}^{\text{D}} = 1.73 \pm 0.02$, and $(k_{\text{H}}^{\text{H}}/k_{\text{T}}^{\text{H}})_{\text{calc}} = 5.91$. The excellent precision of both the secondary and primary effects leaves no doubt that the observed effects are larger than the calculated. A less clear-cut case is the oxidation of benzylamine catalyzed by bovine serum amine oxidase.²⁰ The observed $k_{\text{H}}^{\text{H}}/k_{\text{H}}^{\text{T}}$ is now 1.195 ± 0.016 and $k_{\text{D}}^{\text{D}}/k_{\text{D}}^{\text{T}}$ is 1.051 ± 0.011 , which yields $(k_{\text{H}}^{\text{H}}/k_{\text{H}}^{\text{T}})_{\text{calc}} = 1.176 \pm 0.040$. Although the calculated value is a little below the observed, they are now within experimental error of each other.

The benzylamine oxidation is discussed in the previous section where the evidence from the temperature dependence of the secondary isotope effect is likewise not decisive for tunneling. It was noted then that the magnitude of the isotope effect was difficult to explain without invoking at least moderate tunneling. The temperature dependences of the primary isotope effects in this reaction are $A_{\text{aH}}^{\text{H}}/A_{\text{aH}}^{\text{T}} = 0.12 \pm 0.04$, and $A_{\text{aD}}^{\text{D}}/A_{\text{aD}}^{\text{T}} = 0.51 \pm 0.10$, which argue strongly for tunneling. But comparison of the different primary isotope effects gives $k_{\text{H}}^{\text{H}}/k_{\text{T}}^{\text{H}} = 35.2 \pm 0.8$, $k_{\text{D}}^{\text{D}}/k_{\text{T}}^{\text{D}} = 3.07 \pm 0.07$, and $(k_{\text{H}}^{\text{H}}/k_{\text{T}}^{\text{H}})_{\text{calc}} = 38.7 \pm 2.9$, a result that argues against tunneling. It has been pointed out that incomplete rate control by the hydride transfer in a multistep enzyme mechanism is expected to have an effect opposite to that from tunneling, with $(k_{\text{D}}/k_{\text{T}})^{3.26} > k_{\text{H}}/k_{\text{T}}$.²⁴ A small contribution from this source might just counterbalance a small tunnel correction, but such an effect should also make the temperature dependence more normal, and the temperature dependences of the primary effects are well outside the normal range. Much of the evidence either supports or is consistent with tunneling, but the inconsistencies make the evidence less than compelling.

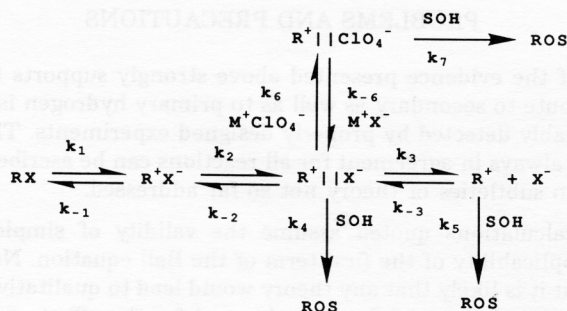
PROBLEMS AND PRECAUTIONS

The weight of the evidence presented above strongly supports the idea that tunneling can contribute to secondary as well as to primary hydrogen isotope effects, and that it can be reliably detected by properly designed experiments. That all criteria for tunneling are not always in agreement for all reactions can be ascribed to experimental uncertainties or to subtleties of theory not so far addressed.

The model calculations quoted assume the validity of simple transition state theory and the applicability of the first term of the Bell equation. Neither assumption is unassailable, but it is likely that any theory would lead to qualitatively similar results for the Arrhenius preexponential factor ratios and for the effect of increased mass of the transferred atom on the tunneling contribution to the secondary isotope effect. The calculations of Huskey and Schowen¹⁵ carry this latter point to its logical conclusion: what is to be expected if the transferred atom is not an isotope of hydrogen but a much heavier atom? The found that a transferred atom of mass 16 led to no violation of the rule of the geometric mean. Thus it seems unlikely that tunneling would contribute to secondary isotope effects in displacements and solvolyses.

A recent study of the solvolysis of ferrocenylmethyl benzoate at first sight seemed to offer evidence that tunneling could contribute to the secondary isotope effect.²⁷ The α -deuterium isotope effects ($\text{FcCH}_2\text{OCOPh}$ vs. $\text{FcCD}_2\text{OCOPh}$) are large, 1.53 for acetolysis and 1.48 for formolysis at 25 °C in the presence of lithium perchlorate. In addition, the $A_{\text{aH}}/A_{\text{aD}}$ ratios are abnormal, running 0.49 in acetolysis and 0.38 in formolysis. Even more striking, the ratios become 0.02 in both solvents in the absence of lithium perchlorate. These figures are low enough that tunneling would be strongly supported if this were a hydrogen transfer process. In the present case, however, they are so low as to excite suspicion, for none of the $A_{\text{aH}}^{\text{H}}/A_{\text{aH}}^{\text{T}}$ ratios reported in Table II for secondary isotope effects are as low as 0.5, and the corresponding $A_{\text{aH}}^{\text{H}}/A_{\text{aH}}^{\text{D}}$ ratios should show even less deviation from unity.

There is, however, an alternative to tunneling that can account for the abnormal temperature dependence of the isotope effect. We must keep in mind that solvolysis is not a simple process in which a free carbocation is generated in the first step and then rapidly reacts with solvent in a second step. Instead, several different kinds of ion pairs can be involved along the way, with the formation or reaction of any one of the ion pairs or of the free ions being potentially rate determining. The possibilities in terms of the Winstein²⁸ solvolysis mechanism are outlined in Scheme 1. A key observation is that in the absence of lithium perchlorate, added benzoate ion depresses the rate in a manner that is strongly temperature dependent: pronounced at 40 °C, negligible at 20 °C. This suggests that the rate-determining step is changing from k_5 at the highest temperature to an earlier step at the lowest. This is probably the k_2 step, which is rate-determining in the presence of lithium perchlorate because the solvent-separated ion pair then reacts rapidly via the k_6 and k_7 steps. Now k_2 is expected to display a maximal isotope effect because there is no covalent bonding left between the carbocation and the leaving group, while k_5 should display a smaller effect because a covalent bond has started to form between the carbocation and the solvent. Thus the apparent isotope effect declines sharply as the temperature is raised because of both the normal tendency to decrease with increasing temperature and the added factor of a change to a rate-determining step with a smaller intrinsic isotope effect. The less pronounced abnormality of the temperature dependence of the isotope effect in the



Scheme 1

presence of lithium perchlorate may result from k_2 not being wholly rate determining even under these conditions. Tunneling cannot be totally excluded as a cause, but does not seem very likely.

The lesson to be drawn from this last investigation is that the criteria for tunneling described in earlier sections can be applied with confidence only to reactions with single, well-defined rate determining steps. Mechanistic complexity can mimic a variety of deviations from normal behavior, and must be excluded or its effects taken into account before abnormalities can be ascribed to fundamental causes such as tunneling.

REFERENCES

1. R. P. Bell, *The Proton in Chemistry* Cornell University Press, Ithaca, New York, 1959, Chap. 11.
2. R. P. Bell, *The Proton in Chemistry* 2nd edition, Cornell University Press, Ithaca, New York, 1973, Chap. 12.
3. R. P. Bell, *The Tunnel Effect in Chemistry*, Chapman and Hall, London and New York, 1980.
4. L. Melander and W. H. Saunders, Jr., *Reaction Rates of Isotopic Molecules*, Wiley-Interscience, New York, 1980, Chaps. 2, 3, and 5.
5. The term *semiclassical isotope effect* refers to all factors that influence the isotope effect other than tunneling. For hydrogen transfer, the major such factor is zero point energy.
6. Ref. 4, pp. 28-29, 143-144.
7. C. G. Swain, E. C. Stivers, J. F. Reuwer Jr., and L. J. Schaad, *J. Amer. Chem. Soc.* **80** (1958) 5885.
8. E. S. Lewis and J. K. Robinson, *J. Amer. Chem. Soc.* **90** (1968) 4337.
9. M. J. Stern and R. E. Weston, Jr., *J. Chem. Phys.* **60** (1974) 2815.
10. L. C. Kurz and C. Frieden, *J. Amer. Chem. Soc.* **102** (1980) 4198.
11. Rm. Subramanian and W. H. Saunders, Jr., *J. Amer. Chem. Soc.* **85** (1981) 1099.
12. Rm. Subramanian and W. H. Saunders, Jr., *J. Amer. Chem. Soc.* **106** (1984) 7887.
13. Md. Amin, R. C. Price, and W. H. Saunders, Jr., *J. Amer. Chem. Soc.* **112** (1990) 4467.
14. S. Lin, unpublished results in these laboratories,
15. W. P. Huskey and R. L. Schowen, *J. Amer. Chem. Soc.* **105** (1983) 5704.
16. W. H. Saunders, Jr., *J. Amer. Chem. Soc.* **106** (1984) 2223. See also *J. Amer. Chem. Soc.* **108** (1986) 5041.
17. W. H. Saunders, Jr., *J. Amer. Chem. Soc.* **107** (1985) 164. See also *J. Amer. Chem. Soc.* **108** (1986) 5041.

18. L. B. Sims, G. Burton, and D. E. Lewis, Bebovib IV, Quantum Chemistry Program Exchange, Department of Chemistry, Indiana University, Bloomington, Indiana 47401, Program N. 337. See also L. B. Sims and D. E. Lewis in E. Buncler and C. C. Lee, Eds., *Isotopes in Organic Chemistry*, Elsevier, Amsterdam, 1984, Vol. 6, Chap. 4.
19. J. Bigeleisen, *J. Chem. Phys.* **23** (1955) 2264.
20. K. L. Grant and J. P. Klinman, *Biochemistry* **28** (1989) 6597.
21. D. Ostovic, R. M. G. Roberts, and M. M. Kreevoy, *J. Amer. Chem. Soc.* **105** (1983) 7629.
22. P. F. Cook, N. J. Oppenheimer, and W. W. Cleland, *Biochemistry* **20** (1981) 1817.
23. R. Srinivasan and H. F. Fisher, *J. Amer. Chem. Soc.* **107** (1985) 4301.
24. Unpublished results.
25. W. P. Huskey, *J. Phys. Org. Chem.* **4** (1991) 361.
26. Y. Cha, C. J. Murray, and J. P. Klinman, *Science* **243** (1989) 1325.
27. S. Ašperger, Z. Kukrić, W. H. Saunders Jr., and D. Šutić, *J. Chem. Soc., Perkin Trans. 2*, (1992) 275.
28. S. Winstein and G. C. Robinson, *J. Amer. Chem. Soc.* **85** (1958) 169.

SAŽETAK

Doprinos tuneliranja sekundarnim izotopnim efektima

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Prezentirani su pokazatelji doprinosa tuneliranja sekundarnim izotopnim efektima. Posebna je pažnja posvećena utjecaju tuneliranja na temperaturnu ovisnost sekundarnoga izotopnog efekta i neaditivnosti izotopnih efekata u slučaju višestruke izotopne supstitucije.