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ORIGIN OF APPARENT SWAIN–SCHAAD DEVIATIONS IN CRITERIA FOR TUNNELING

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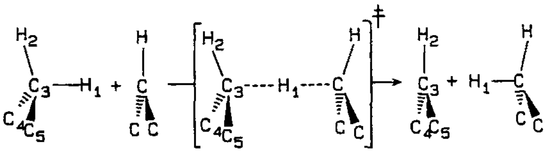
Vibrational analysis calculations have been conducted in an effort to understand the origins of apparently anomalous relationships reported between k_H/k_T and k_D/k_T kinetic isotope effects. The actual isotopic substitutions used in previous work are more complex than a simple comparison between H/T and D/T isotope effects. The relationships between the actual isotope effects determined in these studies amount to tests of two standards of conventional isotope effect theory, the rule of the geometric mean (or the lack of isotope effects on isotope effects) and the Swain–Schaad rule. Model calculations illustrate the importance of violations of the rule of the geometric mean (over Swain–Schaad deviations) arising in models that incorporate both explicit reaction-coordinate coupling of two isotopic sites and reaction-coordinate tunneling. Implications for experimental studies of tunneling using apparent Swain–Schaad exponents are discussed.

INTRODUCTION

Comparisons between kinetic isotope effects arising from novel isotopic substitutions in reactants have been used recently to detect tunneling contributions to reaction rates.[1] Ostensibly, these studies center around the relationship between the isotope effects k_H/k_T and k_D/k_T. The Swain–Schaad model,[2] which includes no treatment of tunneling, predicts that a ratio of the logarithm of the respective isotope effects should be 3·3 (3·26–3·34 depending on the choice of masses used in this simple treatment[3]). Deviations from the Swain–Schaad prediction are said to be diagnostic of tunneling. The use of Swain–Schaad deviations to detect tunneling was explored a number of years ago using the relationship between the isotope effects k_H/k_D and k_H/k_T. Computational efforts[4] and experimental results[5] were used to justify the conclusion that there was no correlation between the magnitude of the exponent relating H/D and H/T isotope effects and the extent of tunneling. Recent computational and experimental observations of deviations in studies maintained to be tests of the Swain–Schaad relationship between a different pair of isotope effects (k_H/k_T and k_D/k_T) appear to contradict the conclusions of the older work.

An essential point not given adequate consideration in some of the recent studies is the significance of the actual isotopic substitutions used in both the experimental[1] and computational work.[3] A careful analysis of the isotopic substitutions reveals two potential components to an apparent Swain–Schaad breakdown. The isotopic substitutions used in the previous work can be specified with reference to the model reaction in equation (1):



If a rate constant for a particular isotope is identified by k_{ij}, where i and j designate the hydrogen isotope at the H-1 and H-2 sites, respectively, true tests of the Swain–Schaad rule for the primary and secondary isotope effects are the determination of the exponents r_1 and r_2 expressed by

$$k_{HH}/k_{TH} = (k_{DH}/k_{TH})^{r_1};\ k_{HH}/k_{HT} = (k_{HD}/k_{HT})^{r_2} \quad (2)$$

[throughout this paper, subscripts refer to quantities derived from primary (1) or secondary (2) isotope effects]. Out of experimental necessity, recent studies[1,6] have included an extra isotopic substitution among the rate constants. For comparisons with experimental work, previous computational work[3] has also included the extra isotopic substitution. The actual exponents, S_1 and S_2, determined in these studies are defined by

$$k_{HH}/k_{TH} = (k_{DD}/k_{TD})^{S_1};\ k_{HH}/k_{HT} = (k_{DD}/k_{DT})^{S_2} \quad (3)$$

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The exponents S_1 and S_2 will be simple tests of the validity of the Swain–Schaad relationship only in the case where the extra isotopic substitution has no effect.

The extra isotopic substitution in S_1 and S_2 has the form of a test of the rule of the geometric mean (RGM).[6,7] One way of stating this rule as it applies to isotope effects is that there are no isotope effects on isotope effects. In another context, violations of the RGM are equivalent to the 'non-additivity' of multiple isotope effects.[8] A convenient expression for a test of the RGM for primary and secondary isotope effects on the reaction of equation (1) is provided in the equation

$$k_{DH}/k_{TH} = (k_{DD}/k_{TD})^{v_1};\; k_{HD}/k_{HT} = (k_{DD}/k_{DT})^{v_2} \qquad (4)$$

If the D/T isotope effects are unaffected by the extra isotopic substitution, then the RGM is said to hold and v_1 and v_2 are unity. If the extra isotopic substitution changes the D/T isotope effects, then the RGM is violated and S_1 and S_2 are no longer simple measures of the Swain–Schaad relationship. Recent studies involving measurements of the exponents S_1 and/or S_2 amount to tests of both the RGM and the Swain–Schaad relationship.

It is informative to rewrite S_1 and S_2 to reveal explicitly the dual-test nature of these exponents. Using the definitions of appropriate RGM tests [v_1 and v_2 of equation (4)] and the definitions for the true Swain–Schaad tests [r_1 and r_2 of equation (2)], the exponents S_1 and S_2 can be rewritten in terms of two components as is shown in the equation

$$S_1 = r_1 v_1;\; S_2 = r_2 v_2 \qquad (5)$$

One component contributes to S_1 or S_2 when the RGM is violated (v_1 or $v_2 \neq 1$), and the other component is a true test of the Swain–Schaad rule ($r_1$or r_2). Because the original report[3] of calculations does not include all of the isotopic substitutions necessary for testing the relative contributions of Swain–Schaad and RGM violations to S_1 and S_2, reported here are appropriate vibrational-analysis calculations on a generic hydrogen transfer model.

COMPUTATION RESULTS

The model used for the vibrational analysis corresponds to the reaction in equation (1). Force fields and geometries for models of isotopic reactants and symmetrical transition states were generated as outlined under Vibrational Models and Computational Method. One type of reaction coordinate ('H-2 coupling') used for a transition-state model included explicit force-field coupling of certain bending motions, sensitive to the H-2 mass, with the stretching coordinates about H-1. A second type of reaction coordinate ('no H-2 coupling') was generated by simple force-field coupling of the C–H-1 stretches with no force-field coupling to bending coordinates. Tunneling terms were calculated from isotopic reaction-coordinate frequencies (generated from the models) using the truncated Bell tunnel correction.[9,10]

Figures 1–4 display the results of the calculations expressed in terms of exponents[*] as functions of

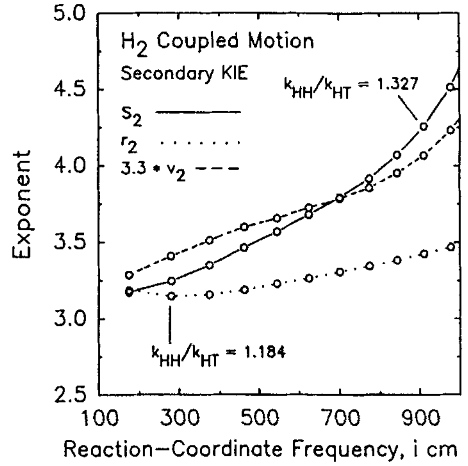

Figure 1. Exponents calculated for secondary kinetic isotope effects on a vibration model in which motions of the secondary isotopic site are coupled to stretches about the primary hydrogen site to generate a reaction coordinate. For definitions of symbols, see text

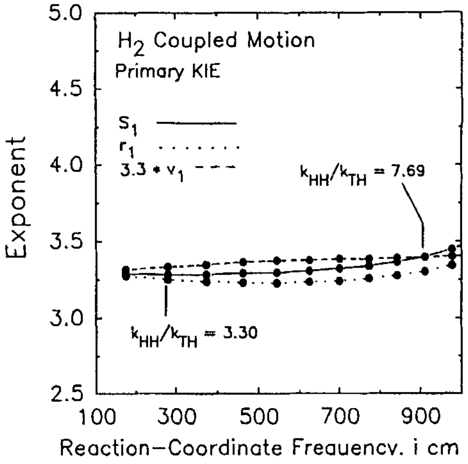

Figure 2. Exponents calculated for primary kinetic isotope effects on the same vibrational model used for Figure 1

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[*] Note that the difference in the relative influence of changes in exponents of typical primary and secondary isotope effects is considerable. For example, a change in r [equation (2)] from 3·3 to 3·5 will increase k_H/k_D by only 0·9% if $k_D/k_T = 1·05$, whereas k_H/k_D will increase by 25% if $k_D/k_T = 3·0$.

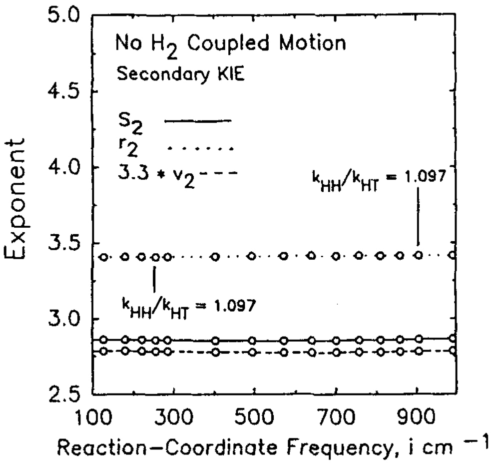

Figure 3. Exponents calculated for secondary kinetic isotope effects on a vibrational model with a simple stretch–stretch coupling scheme to generate a reaction coordinate. In this model there is no explicit force-field coupling of internal coordinates involving the secondary hydrogen site to coordinates used to generate the reaction coordinate. For definitions of symbols, see text

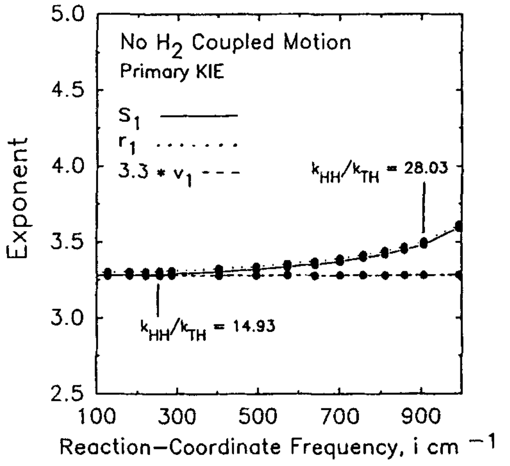

Figure 4. Exponents calculated for primary kinetic isotope effects on the same vibrational model used for Figure 3

reaction-coordinate frequency. As the reaction-coordinate frequency increases, estimates of tunneling contributions to rate constants increase. Three curves are shown on each of the figures. One curve (solid lines) is the exponent S_1 or S_2 computed using isotope effects calculated with the appropriate isotopic substitutions shown in equation (3). A second curve (dotted lines) shows the pure Swain–Schaad test, r_1 or r_2, defined in equation (2). The third curve (dashed lines) shows RGM violations, as defined in equation (4), multiplied by the reference exponent of 3·3. Each of the figures displays the relative contribution of pure Swain–Schaad tests and RGM violations to S_1 and S_2, the exponents of concern in recent studies.

With reference to equation (5), S_1 and S_2 become identical with pure Swain–Schaad exponents (r_1 and r_2) in the limit of no RGM violation ($v_1 = v_2 = 1$). In the limit of no deviation of pure Swain–Schaad exponents from the reference value of 3·3, all deviations in S_1 and S_2 originate from RGM violations, and the exponents become $3{\cdot}3\,v_1$ and $3{\cdot}3\,v_2$. The degree to which the points on either dotted or dashed lines coincide with the points on the solid lines and different from 3·3 represents the relative importance of pure Swain–Schaad deviations (from 3·3) and RGM violations to deviations (from 3·3) in S_1 and S_2.

DISCUSSION

Role of RGM violations

In agreement with the vibrational models reported by Saunders,[3] exceptionally large exponents S were computationally observed only for secondary isotope effects using models with force-field coupling of internal coordinates involved in the motions of H-1 and H-2, the sites of isotoic substitution. The curves in Figure 1 illustrate the dominant role that the RGM violation plays in determining the deviation of S_2 from 3·3. Deviations in the pure Swain–Schaad exponent, r_2, are small and are insignificant in comparison with the contributions from RGM violations. Large exponents S_2 are therefore a consequence of RGM violations and not Swain–Schaad deviations on these vibrational models. The extra isotopic substitution used in recent measurements is thus an essential feature of the experimental design according to these models.

The origin of these RGM violations on vibrational models has been attributed to the influence of extra isotopic substitution on the reduced mass of the reaction coordinate in hydrogen transfer reactions where tunneling may be significant.[11,12] Vibrational models that demonstrate RGM violations include force-field coupling of the two isotopic sites in the scheme used to generate a reaction coordinate, and the reaction-coordinate frequency must be large enough to require consideration of tunneling. For the purpose of constructing the figures, it was convenient to define the RGM violation as an exponent [equation (5)]. To explain the origins of the RGM violations, it is more convenient to define the violation in terms of the ratios g_1 and g_2.

$$g_1 = \frac{k_{DH}/k_{TH}}{k_{DD}/k_{TD}};\quad g_2 = \frac{k_{HD}/k_{HT}}{k_{DD}/k_{DT}} \tag{6}$$

It is now straightforward to separate the semi-classical (SC) and tunneling (Q) components of the RGM violation:

$$g_1 = \frac{(k_{DH}/k_{TH})_{SC}}{(k_{DD}/k_{TD})_{SC}} \times \frac{Q_{DH}/Q_{TH}}{Q_{DD}/Q_{TD}};$$

$$g_2 = \frac{(k_{HD}/k_{HT})_{SC}}{(k_{DD}/k_{DT})_{SC}} \times \frac{Q_{HD}/Q_{HT}}{Q_{DD}/Q_{DT}} \qquad (7)$$

For the points shown in Figures 1 and 2 at the 906 i cm^{-1} reaction coordinate frequency, $g_1 = 1\cdot 0175$ and $g_2 = 1\cdot 0163$. For both the primary and secondary effects, the RGM violation originates almost entirely from the tunnelling terms in equation (7) $[Q_{DH}/Q_{TH})/(Q_{DD}/_{TD}) = 1\cdot 0186$ and $(Q_{HD}/Q_{HT})/(Q_{DD}/Q_{DT}) = 1\cdot 0195]$.

The vibrational models predict that the RGM violations defined as in equation (6) are nearly identical for the primary and secondary kinetic isotope effects. The influence of extra isotopic substitution at the primary site on tunneling contributions to secondary isotope effects is roughly the same as the influence of isotopic substitution at the secondary site on the tunneling contribution to the primary isotope effect. Given that for these vibrational models $g_1 \approx g_2$, the absence of deviant exponents, S_1, for primary isotope effects on models showing large values for S_2 is expected. The following equation shows these exponents redefined in terms of the RGM violations g_1 and g_2:

$$S_1 = r_1\left[1 - \frac{\ln(g_1)}{\ln(k_{HH}/k_{TH})}\right]^{-1};$$

$$S_2 = r_2\left[1 - \frac{\ln(g_2)}{\ln(k_{HH}/k_{HT})}\right]^{-1} \qquad (8)$$

These equations show that the influence of the RGM violation on the S exponents depends on the magnitude of the primary or secondary isotope effects. Since the primary effect (k_{HH}/k_{TH}) is large, the RGM effect is much smaller on S_1 than on S_2.

Observations of large RGM violations may have origins different from the coupled-motion/reaction-coordinate tunneling mechanism described here. Any scheme that will account for different effective initial and/or final states on isotopic substitution (without violating the Born–Oppenheimer assumption concerning the separation of electronic and nuclear motion) is a potential source of an RGM violation on an isotope effect. The effects of reaction-coordinate tunneling could be considered as generating different transition-state 'structures' for different isotopes. Additionally, variational transition-state theory may generate different structures at the free-energy bottleneck[13,14] for different isotopes. Effective structures may also appear different for different isotopes in cases of multiple rate-limiting steps or multiple reaction pathways where the effective or virtual[15] transition-state structure changes on isotopic substitution. In a similar way, recent NMR and computational studies of the 2,3-dimethyl-2-butyl cation have revealed apparent RGM violations that have their origins in different conformational preferences for different isotopes.[8] The effective structure of the cation, considered to be an average of various conformational states, is changed as isotopes are introduced.

Models without complex reaction-coordinate motions

For simple schemes to generate reaction-coordinate motions in the absence of stretch–bend coupling, S_1 and S_2 do not become exceptionally large. S_2 does, however, become significantly smaller than the reference value of 3·3. Figure 3 shows that the small exponent derives from an RGM violation so small that under other circumstances the isotope effects would be classified as following the RGM (in Figures 3 and 4 at the 905 i cm^{-1} point, $g_1 = 0\cdot 9947$ and $g_2 = 0\cdot 9949$). Because the exponent S_2 is very sensitive to the RGM violation, a value much lower than the reference of 3·3 is calculated.

In the absence of H-2 coupling (Figures 3 and 4), S_1 and S_2 never become exceptionally large, although it could be argued that S_1 begins to show a significant deviation from 3·3 at high values of the reaction-coordinate frequency. High confidence should not be attributed to these small deviations in S_1 predicted by the model calculations, because even the presence of the deviations may be dependent on the procedure used to account for tunneling. Unusually large values of S_1 in the absence of RGM violations require that the tunnel corrections for H/T and D/T isotope effects be related by an exponent greater than 3·3. The presence of deviations in S_1 will therefore depend on the precise nature of the tunnel correction. The Bell correction used here and in previous work[3] gives only a crude estimation of the influence of tunneling,[16] particularly at the high reaction-coordinate frequencies where the small deviations begin to appear.

In contrast, the presence of deviations in S_2 predicted by model calculations with H-2 coupling and tunneling is not likely to show a strong dependence on the procedure used to account for tunneling because the deviations arise from RGM violations. The RGM violations originate from the greater tunnel effects seen for H transfer than are seen for D transfer, a consequence of tunneling that is expected to be reproduced in all schemes used to account for tunneling.

Implications for experimental studies of tunneling

Recent observations[1] of apparent Swain–Schaad deviations in enzymatic hydrogen transfer reactions remain consistent with interpretations involving tunneling. The experiments included the extra isotopic substitution required for the determination of S_1 or S_2 as opposed to true Swain–Schaad exponents, r_1 or r_2. Researchers intent on similar studies of tunneling should take note of the actual isotopic substitutions used in the previous work, and the critical role of RGM violations as opposed to true Swain–Schaad deviations in vibrational models of the type presented here.

VIBRATIONAL MODELS AND COMPUTATIONAL METHOD

Most parameters used to build transition-state models were selected by taking weighted averages[17] of appropriate reactant and product force constants and geometric parameters. A modeling scheme was developed for exploration of a wide range of reaction-coordinate motions and transition-state structures, originally for purposes other than the calculations reported here. The force fields and reaction-coordinate generation are more elaborate than is necessary for the purpose of this paper. The details of the models are reported here for the sake of completeness. Additional descriptions including justifications for the modeling scheme for this vibrational model (called HHIE3) and related models are available.[11,18]

Because all calculations reported in this paper used a single transition-state model (weighting factors of 0·5 for both product and reactant parameters), it is convenient merely to list the force constants and geometric parameters for the reactant-state and transition-state models. Refer to the reaction and numbering scheme of equation (1), and note that the transition-state model is symmetric about the H-1 atom. Force constants have units of mdyne Å^{-1} for stretching coordinates and mdyne Å rad^{-2} for other coordinate types. All bond lengths are listed in Å. With the exception of the coupling force constants introduced to generate reaction coordinates, all force fields are the fully-redundant, simple-valence type. Reactant (coordinate, force constant, geometry): H-1—C-3, 4·70, 1·10; C-4—C-3, 4·35, 1·53; H-1—C-3—H-2, 0·55, 109·47122; C-4—C-3—C-5, 1·00, 109·47122; H-1—C-3—C-4, 0·60, 109·47122. Transition state: H-2—C-3, 4·70, 1·10; H-1—C-3, 2·35, 1·307944; C-4—C-3, 4·35, 1·53; H-1—C-3—H-2, 0·275, 99·735611; C-4—C-3—C-5, 1·00; 117·20057; H-2—C-3—C-4, 0·60, 117·20057; H-1—C-3—C-4, 0·30, 99·735611. Force constants for the torsional motion about C—H-1—C were set to 0·0 and the linear bend force constants (about H-1) were estimated using method proposed by Burton *et al.*[19] (the value used was 0·1 mdyn Å rad^{-2}). As part of a modeling scheme designed to vary transition-state structures smoothly from reactants to products it was necessary to introduce non-linear out-of-plane bending coordinates[20] about C-3 in the transition state.* In keeping with the fully redundant nature of the force field, three of these coordinates were added, each with a force constant of 0·125/3 mdyne Å rad^{-2}.

The curvature parameter method[22] was used to guide the generation of reaction coordinates. For guaranteed success with this method, all force-field redundancies among coordinates to be coupled must be removed before the scheme is applied. Because stretch–bend interactions were used in the scheme to generate reaction coordinates, and the bends were part of a redundant set of coordinates, redundant valence-angle bends and non-planar out-of-plane bends were removed according to standard methods to transform the force-constant matrix to a non-redundant form. This form of the force-constant matrix was then used only for the purpose of ensuring that for a given curvature parameter, stretch–bend and stretch–stretch coupling constants of a specified magnitude would generate a reaction coordinate. For the H-2-coupled reaction coordinates, all non-planar out-of-plane coordinates about a single carbon atom were coupled to the corresponding C–H-1 stretch, and the two C–H-1 stretches were also coupled. For reaction coordinates without H-2 coupling, only the two C–H-1 stretches were coupled.

Isotopic frequencies and isotope effects were calculated using the vibrational analysis sections of the program BEBOVIB[21] using the Bigeleisen–Wolfsberg[23] formulation of isotope effects. All calculations are for 25 °C.

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* For nonplanar out-of-plane bending coordinates, subroutine XCORD in BEBOVIB[21] incorrectly calculates the out-of-plane angle. The error has no influence on frequencies calculated because the angle calculation is only carried out as a check on the geometry. Our local version of the program was modified to calculate the angle correctly.

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