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Communication

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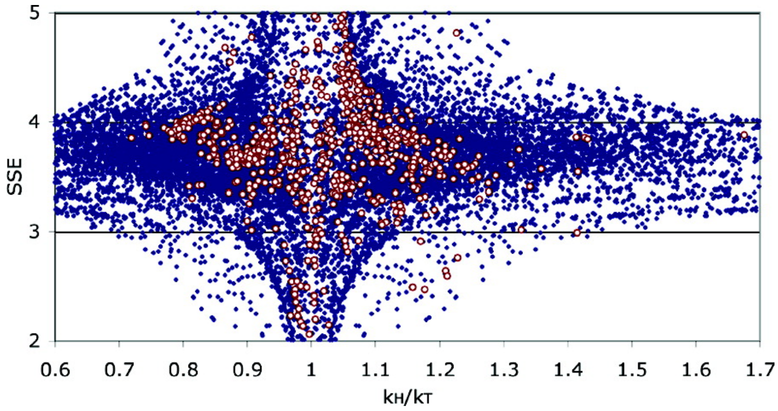

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COMMUNICATIONS

The Normal Range for Secondary Swain−Schaad Exponents without Tunneling or Kinetic Complexity

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Quantum mechanical tunneling affects the rates of barrier crossings in all chemical reactions, and there has been considerable interest in identifying reactions where the impact of tunneling is large. Experimental probes for tunneling most often involve kinetic isotope effects (KIEs), and tunneling has been inferred from unusually large KIEs or large differences in Arrhenius factors for isotopomers.[1] Another important probe for tunneling involves the measurement of relative rates for protium versus deuterium versus tritium and comparison of these rates with semiclassical[2] predictions. Most often, an approximate treatment first described by Swain and Schaad is used as the measure of semiclassical expectations.[3] For example, experimental KIEs would be expected to fit eq 1 with a Swain−Schaad exponent (SSE) of roughly 3.34 in the absence of tunneling.[4] A larger SSE might be taken as evidence for substantial tunneling.[5] Assuming semiclassical behavior, eqs 1 and 2 are often used to extrapolate KIEs to different isotopes (e.g., estimation of k_H/k_T from k_H/k_D).[6] SSEs are also often used to assess intrinsic KIEs and kinetic complexity in mechanisms.[1i,j,7]

$$\left(\frac{k_H}{k_T}\right) = \left(\frac{k_D}{k_T}\right)^{SSE} \tag{1}$$

$$\left(\frac{k_H}{k_T}\right) = \left(\frac{k_H}{k_D}\right)^{SSE'} \tag{2}$$

The determination of SSEs for hydrogen atoms being transferred (1° SSEs) has been carried out for diverse reactions over the last 40 years.[8] A fair summary is that 1° SSEs are usually close to semiclassical expectations, even for reactions in which other observations suggest extensive tunneling. More recently, SSEs for hydrogen atoms not being transferred (2° SSEs) have become an often-used probe for tunneling, particularly in enzymatic reactions.[1i,j,9] The 2° SSEs vary from the Swain−Schaad expectation much more often than 1° SSEs, and thus they are considered to be a more sensitive probe for tunneling.

The Swain−Schaad treatment involves greatly simplifying assumptions versus the full semiclassical theory of isotope effects, due to Bigeleisen and Mayer.[10] More than 30 years ago, Stern and Vogel analyzed in detail the range of possible SSEs within the full theory.[11] They found that, for small KIEs, SSEs can in fact vary from negative infinity to positive infinity. Their results also show clearly that there is no reliable expectation for the value of an SSE for a small or inverse isotope effect. Even for “reasonably large” isotope effects (defined as having $k_H/k_D > 2.7$), the SSEs can fall in a broad range ($SSE' = 1.33$ to 1.58 for eq 2), and it was expected that deviations from this range should not be rare.

Given these conclusions, it may seem rather surprising that the Swain−Schaad relationship is used so commonly, or that it is used at all with small isotope effects, or that the modern literature contains consideration of a “semiclassical limit” for SSEs.[12] However, Stern and Vogel had demonstrated only theoretical possibilities for the range of SSEs and not the likelihood of unusual SSEs. In fact, they emphasize that the Swain−Schaad relationship should work well for large isotope effects. In addition, the expected SSE of about 3.34 for eq 1 has been often observed for large KIEs.[8] For real reactions, it is quite uncertain how often the theoretical possibilities for deviation from the Swain−Schaad relationship will materialize.

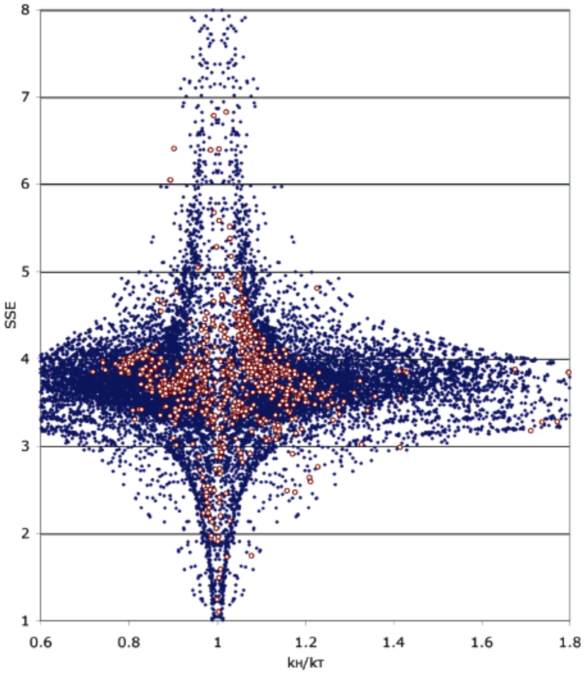

Figure 1. Distribution of SSEs for eq 1 vs k_H/k_T based on exact harmonic semiclassical isotope effects. The blue dots are based on 15 996 sets of EIEs, and the red open circles are based on 954 sets of KIEs. The limited domain and range were chosen for clarity; the full distribution is shown in Supporting Information.

We describe here an analysis of the range of 2° SSEs that may be realistically expected at 25 °C in the absence of tunneling or kinetic complexity. The results define when a 2° SSE may be considered to implicate tunneling or kinetic complexity, revise the SSEs for extrapolation of 2° KIEs, and serve as a guide to the uncertainty in such extrapolations.

To evaluate the range of 2° SSEs to be expected semiclassically, 15 996 sets of *exact* harmonic semiclassical equilibrium isotope effects (EIEs) were calculated for simple C−H/D/T exchange reactions and 954 sets of exact harmonic semiclassical 2° H/D/T KIEs were calculated for C−H positions in simple organic reactions.[13] This was accomplished by first optimizing diverse ground-state and transition structures in B3LYP/6-31G* calculations, then calculating the isotope effects at 25 °C from the harmonic frequencies.[10] SSEs were then calculated for each set of isotope effects. The results are summarized in Figure 1.

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The B3LYP/6-31G* calculations here have previously led to accurate predictions of experimental KIEs.[14] Limited studies at other theoretical levels (HF/6-31G* and B3LYP/6-311+G**) gave a similar distribution of SSEs.

KIEs are harder than EIEs to calculate in large numbers, and therefore we have far fewer 2° SSEs based on KIEs. Within semiclassical theory, 2° EIEs and 2° KIEs are quite similar: EIEs are derived from the 3N-6 vibrational frequencies, while KIEs are derived from 3N-7 vibrations plus a temperature-independent contribution from the imaginary frequency. This imaginary frequency factor is usually a minor contributor to significant 2° H/D/T KIEs, and its effect of the average of SSEs for $k_H/k_T > 1.1$ and $k_H/k_T < 0.9$ was <0.01. From this and the similarity of distributions for 2° SSEs based on KIEs versus EIEs, we expect that the distribution of 2° SSEs based on EIEs should adequately represent semiclassical 2° KIEs.

For the purpose of analysis, we will assume that the results of Figure 1 are statistically representative of the universe of organic reactions. This assumption leads to three conclusions: (1) In the range $0.9 < k_H/k_T < 1.1$, the Swain−Schaad relationship is of no value. SSEs as low as −296 and as high as 2100 were observed in this range. There is no semiclassical limit for SSEs without the context of the magnitude of the isotope effect. (2) For $k_H/k_T < 0.9$ and $k_H/k_T > 1.1$, the mean and median 2° SSE is 3.72. This corresponds to 1.368 for SSE′ in eq 2 [$\mathrm{SSE}' = \mathrm{SSE}/(\mathrm{SSE} - 1)$]. The use of the conventional values for SSE and SSE′ to extrapolate 2° KIEs should be discontinued, and conclusions based on these values may need to be reevaluated. The original values came from reduced masses for C−H stretching frequencies,[4] ignoring bending vibrations, and it should not be surprising that they do not apply to 2° KIEs. (3) For $k_H/k_T > 1.1$, an approximate 95% confidence interval is defined by the lines $\mathrm{Max} = 3.66 + 0.24/(k_H/k_T - 1)$ and $\mathrm{Min} = 3.40 - 0.13/(k_H/k_T - 1)$. For $k_H/k_T < 0.9$, the approximate 95% confidence lines are: $\mathrm{Max} = 3.55 + 0.2/(1 - k_H/k_T)$ and $\mathrm{Min} = 3.52 - 0.12/(1 - k_H/k_T)$. Experimental 2° SSEs outside of this range may be sufficiently unusual to be considered as evidence for nonsemiclassical behavior or kinetic complexity, but SSEs inside this range are not. Extrapolations of 2° KIEs should take into account the uncertainty.

Stern and Vogel warned of the variability of SSEs.[11] The results here amplify that warning, while providing a framework for the interpretation of 2° SSEs and the extrapolation of KIEs with regard to the possible error. Ultimately, however, it should be recognized that the Swain−Schaad treatment is an approximation that should be applied only with proper caution. In many cases, a detailed theoretical analysis of the SSEs to be expected for the particular system of interest would be most appropriate.

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Supporting Information Available: Details of all calculations, lists of reactions studied, and an expanded view of the SSE distribution. This material is available free of charge via the Internet at http://pubs.acs.org.

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(13) EIEs were calculated for all possible C−H/D/T single-position exchange reactions for methane, ethene, ethyne, ethane, methanimine, ethanol, formaldehyde, HCN, methanol, methylamine, acetone, acetaldehyde, propyne, and 26 additional neutral molecules, H_3CO^-, $H_2C{=}CHO^-$, $H_2C{=}CHCH_2O^-$, $H_2C{=}OH^+$, $H_3CCH{=}OH^+$, allyl cation, 2-propyl cation, $H_3C\bullet$, $ClH_2C\bullet$, $FH_2C\bullet$, $H_2C{=}CHO\bullet$, and nine additional reactive intermediates, with a total of 127 substitution positions. KIEs were based on single-position isotopic substitutions in 20 ene reactions, 9 diimide reductions, 11 hydride transfer reactions, 24 radical reactions, 5 carbene reactions, 12 electrocyclic reactions, a sigmatropic reaction, a Diels−Alder reaction, 8 S_N2 reactions and the retro-reactions for all nonsymmetrical cases. Complete reaction lists are given in Supporting Information. Calculations used the program QUIVER (Saunders, M.; Laidig, K. E.; Wolfsberg, M. *J. Am. Chem. Soc.* **1989**, *111*, 8989−8994). Frequencies were scaled by 0.9614.

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