Secondary Kinetic Isotope Effects of Diastereotopic Protons in Pericyclic Reactions: A New Mechanistic Probe

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Abstract: The transition structures and secondary kinetic isotope effects for representative pericyclic reactions, obtained by Hartree-Fock (RHF/6-31G*) and density functional theory (B-LYP/6-31G*) calculations, are reported. Isotope effects were calculated with the Bigeleisen–Mayer equation and the Bell tunnel correction. Both methods give similar predictions, but the B-LYP/6-31G* results are closer to the experimental data, where available. The cyclobutene electrocyclic ring opening, the hexatriene and octatetraene electrocyclic ring closures, and the reverse reactions show large differences between isotope effects for diastereotopic hydrogens directed inward (IN) or outward (OUT) on the termini of the transition state. Experimental and prior theoretical results are available for the cyclobutene ring opening and the hexatriene cyclization. For the Cope and Claisen [3,3]-sigmatropic shift reactions, the isotope effects of the axial (IN) and equatorial (OUT) hydrogens are predicted to be different. For the Diels–Alder [4 + 2] cycloaddition, there are large differences between isotope effects for the IN and OUT hydrogens at the diene termini and smaller differences for the *endo* (IN) and *exo* (OUT) hydrogens of the dienophile. These isotope effect patterns are analyzed in terms of steric and electronic interactions in the transition states for concerted pericyclic reactions. The more sterically crowded IN hydrogens have higher bending force constants than the OUT protons. The OUT often have low bending force constants due to diradicaloid character of some of the transition states. The difference between IN and OUT secondary kinetic isotope effects is a sensitive probe of transition state geometry and therefore of mechanism.

Introduction

Kinetic isotope effect (KIE) measurements are one of the few experimental probes for the transition state of the rate-limiting step of a reaction. Consequently, the measurement of KIEs has found widespread use in mechanistic studies of various reaction types.[1] The analysis of primary and secondary isotope effects has been particularly valuable for the investigation of pericyclic reactions.[2] For example, experimental studies of secondary kinetic isotope effects (SKIEs) provide evidence that the Diels–Alder reaction proceeds in a concerted fashion[3] rather than by a stepwise mechanism.[4] Comparisons of theoretical kinetic isotope effects from *ab initio* calculations with experimental data have also been used for the validation of transition structures calculated for various pericyclic processes.[5]

Following an analysis by Streitwieser and co-workers,[6] it is generally accepted that changes in the out-of-plane bending modes of the hydrogen attached to the carbon that undergoes bonding change are largely responsible for the SKIEs. According to this qualitative analysis, the change of a sp^2-hybridized center with a low C–H bending frequency to a sp^3-hybridized center with a high C–H bending frequency leads to an inverse ($k_H/k_D < 1$) kinetic isotope effect because during the reaction, the zero-point energy increases more for the C–H bond than for the C–D bond. For a hybridization change in the opposite direction, a normal SKIE ($k_H/k_D > 1$) is predicted. Hydrogens attached to the same carbon should therefore have identical SKIEs. Within a series of similar reactions, the observed SKIEs at analogous positions should be proportional to the degree of bonding change in the transition state. This qualitative picture has been used to good advantage to describe how transition states change with substitution.[2b] In previous studies from this laboratory, exceptions to this generalization have been predicted from theoretical calculations.[5a] This concept has also been challenged by Truhlar *et al.* on theoretical grounds.[7] A recent theoretical study of E$_2$ elimination reactions[8] suggests that this picture might, at least in certain cases, be oversimplistic. For a series of nucleophiles it was shown that there is no simple relationship between the looseness or tightness of the calculated transition structure geometry and the theoretical

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(6) Streitwieser, A., Jr.; Jagow, R. H.; Fahey, R. C.; Suzuki, S. *J. Am. Chem. Soc.* **1958**, *80*, 2326–2332.

(7) E.g.: (a) Zhao, X. G.; Tucker, S. C.; Truhlar, D. G. *J. Am. Chem. Soc.* **1991**, *113*, 826–832. (b) Wolfe, S.; Kim, C.-K. *J. Am. Chem. Soc.* **1991**, *113*, 8056–8061. (c) Vigganio, A. A.; Pashkewitz, J. S.; Morris, R. A.; Paulson, J. F.; Gonzaloes-Lafont, A.; Truhlar, D. G. *J. Am. Chem. Soc.* **1991**, *113*, 9404–9405.

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KIEs. Gajewski et al.[9] found in a combined SKIE/AM1 study that the equilibrium isotope effect between a sp^2 olefinic carbon and an allyl radical is not unity, as has been assumed earlier.[2] They also showed that upon application of the correct relationship, the extent of bond making and bond breaking deduced from the SKIE varies significantly in certain cases. Clearly a more detailed look at the geometric and electronic structure of the transition state is necessary.

In previous studies, we have shown that the transition structures of a remarkable variety of hydrocarbon pericyclic reactions have many geometrical features in common.[10] This might imply that isotope effects would be quite similar for all of these reactions. The results in this paper suggest that additional environmental effects cause large deviations from this expectation. In the present paper, we report a theoretical study of SKIEs of various typical pericyclic reactions using Hartree—Fock and density functional methods. In studies of several pericyclic reactions, density functional methods have proven to yield excellent results,[11] including the calculation of SKIEs.[11d] We specifically examine theoretical SKIEs for protons attached to the same carbon, but in different environments, termed IN and OUT. The IN position points toward the other part of the rearranging system while the OUT position points away, as shown in Figure 1. The calculated SKIEs for these two positions differ, and the magnitudes of these differences follow patterns that might be useful for mechanistic diagnosis for a variety of reactions.

Computational Methodology

Ab initio quantum mechanical calculations have been performed with the GAUSSIAN92/DFT[12] program. All structures reported are, unless otherwise noted, fully optimized using the RHF/6-31G* and the BLYP/6-31G*P[13] methods. Each stationary point has been characterized by a harmonic frequency analysis and shows the correct number of negative eigenvalues. All energies reported are corrected for zero-point energy (ZPE). The force constants obtained by the frequency calculations have been used to calculate the theoretical SKIEs with the program QUIVER.[14] Based on statistical mechanics and classical transition state theory,[15] QUIVER calculates the reduced partition functions of the various isotopomers from the force constants obtained by *ab initio* calculations using the Bigeleisen—Mayer formalism:[16]

$$\frac{k_H}{k_D} = \frac{\kappa_H \cdot \sigma_H \cdot \sigma^{\ddagger}_H}{\kappa_D \cdot \sigma_D \cdot \sigma^{\ddagger}_D} \text{MMI} \cdot \text{EXC} \cdot \text{ZPE} \tag{1}$$

with κ being the transmission factor and σ the symmetry number, MMI the mass and moment of inertia, EXC the excitation factor, and ZPE the zero-point energy and superscript $\ddagger$ referring to the transition state.

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(12) GAUSSIAN92/DFT Revision G.1; Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Gill, P. M. W.; Johnson, B. G.; Wong, M. W.; Foresman, J. W.; Robb, M. A.; Head-Gordon, M.; Replogle, E. S.; Gomberts, R.; Andres, J. L.; Raghavachari, K.; Binkley, J. S.; Gonzales, C.; Martin, R. L.; Fox, D. J.; Defrees, D. J.; Baker, J.; Stewart, J. J. P.; Pople, J. A.; Gaussian Inc.: Pittsburgh, PA, 1993.

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(16) (a) Bigeleisen, J.; Mayer, M. G. *J. Chem. Phys.* **1947**, *15*, 261—267. (b) Wolfsberg, M. *Acc. Chem. Res.* **1972**, *5*, 225—233.

Under the assumption that MMI = 1 and with κ and σ being identical for the various isotopomers,[17] this becomes after application of the Redlich—Teller product rule and subtitution with the explicit terms for the partition functions[1b]

$$\frac{k_H}{k_D} = \frac{\nu^{\ddagger}_H \prod_1^{3N-6} \frac{u_H}{u_D} \prod_1^{3N-6} \frac{[1 - \exp(-u_H)]}{[1 - \exp(-u_D)]} \exp\left(\prod_1^{3N-6} \frac{u_H - u_D}{2}\right)}{\nu^{\ddagger}_D \prod_1^{3N-7} \frac{u^{\ddagger}_H}{u^{\ddagger}_D} \prod_1^{3N-7} \frac{[1 - \exp(-u^{\ddagger}_H)]}{[1 - \exp(-u^{\ddagger}_D)]} \exp\left(\prod_1^{3N-6} \frac{u^{\ddagger}_H - u^{\ddagger}_D}{2}\right)} =$$

$$\frac{\nu^{\ddagger}_H}{\nu^{\ddagger}_D} \cdot \frac{(s_2/s_1)f(2/1)}{(s_2/s_1)f(2/1)^{\ddagger}} \tag{2}$$

with

$$u_i = \frac{h\nu_i}{kT} = = 1.43879 \frac{\nu_i[\text{cm}^{-1}]}{T[\text{K}]} \tag{3}$$

where the last three terms in (2) are the ratios of the Bigeleisen—Mayer functions $(s_2/s_1)f(2/1)$ for the various isotopomers.

To account for the anharmonicity of molecular vibrations, it is common practice to scale the frequencies obtained from *ab initio* calculations by an empirical scaling factor. For the calculation of theoretical KIEs, these scaling factors deserve special attention since the frequencies are exponential factors in eq 2. In a recent study,[18] different scaling factors for the calculation of fundamental frequencies and zero-point energies from HF/6-31G* harmonic frequencies have been proposed. It can be seen from eq 2 that for typical organic molecules ($\nu_i > 600$ cm^{-1}) and temperatures (T < 500 K), ZPE is the predominant factor determining the KIEs. Therefore, a scaling factor of 0.91 has been used for the force constants from RHF/6-31G* calculations. Unfortunately, no equally thorough study is available yet for force constants from DFT calculations, although preliminary results indicate that these frequencies are too low by ~2—5%,[19] whereas zero-point energies are quite accurate.[20] Therefore, we used a scaling factor of 1.00, which gave excellent results in a previous study.[11d] The SKIEs obtained by these calculations were corrected for tunneling effects[21] using the formula proposed by Bell.[22]

$$\left(\frac{k_H}{k_D}\right)_{corr} = \frac{Q_t(H)}{Q_t(D)} \cdot \left(\frac{k_H}{k_D}\right) \quad \text{with} \quad Q_t = \frac{0.5u^{\ddagger}}{\sin 0.5u^{\ddagger}} \tag{4}$$

Results and Discussion

Electrocyclic Reactions. In their study of the electrocyclic ring opening of cyclobutene, Baldwin et al. showed that diastereotopically different hydrogens show different SKIEs.[23] In good agreement with the experimental values, SKIEs of $k_H/k_D(\text{IN}) = 1.05$ and $k_{(H)}/k_{(D)}(\text{OUT}) = 1.15$ have been calculated at the MP2/6-31G* level. The different kinetic isotope effects for diastereotopic protons were attributed by Baldwin et al. to different timings of the sp^3—sp^2 rehybridization process for bonds to the two types of hydrogens. The preference of a deuterium for the IN position was also observed earlier in a

(17) In the case of the Cope rearrangement, it was found that changes in the reactant conformation state affect the theoretical SKIEs insignificantly: ref 5a, footnote 14.

(18) Pople, J. A.; Scott, A. P.; Wong, M. W.; Radom, L. *Isr. J. Chem.* **1993**, *33*, 345—350.

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(22) Bell, R. P. *The Tunnel Effect in Chemistry*; Chapman and Hall: New York, 1980; pp 60—63.

(23) Baldwin, J. E.; Reddy, V. P.; Hess, B. A., Jr.; Schaad, L. *J. Am. Chem. Soc.* **1988**, *110*, 8555—8556.

substituted cyclobutene ring opening.[24] The isotope effect was explained in terms of a "steric deuterium isotope".[25] This steric kinetic isotope effect[1c] was ascribed to a smaller "effective size" of deuterium as compared to hydrogen and was studied experimentally for various hindered biphenyls[25] and other systems.[24,26] This smaller "effective size" is due to different mean bond lengths for hydrogen and deuterium because of anharmonicity and larger amplitudes of vibration for hydrogen. A general quantitative theory of nonbonded repulsive interactions in the transition state has been developed by Bartell.[27] He proposed a model to describe the relative motion of two nongeminal atoms with strong nonbonding interactions. The motion of these atoms is described by two superimposed harmonic oscillators; the frequency of which is altered by isotopic substitution. Using first-order perturbation theory and some assumptions about the nature of the nonbonding interaction potential function, an expression for the difference of the potential energies of isotopic molecules (and therefore the KIE's) as a function of the nonbonded interactions was derived.
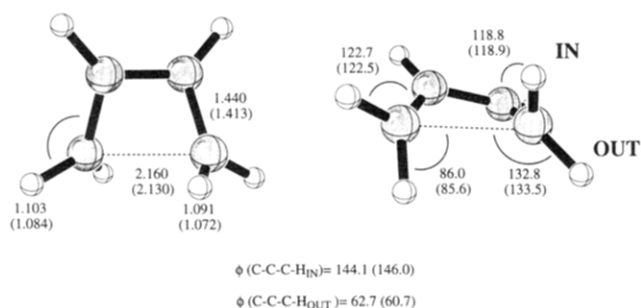

ϕ (C-C-C-H_{IN})= 144.1 (146.0)

ϕ (C-C-C-H_{OUT})= 62.7 (60.7)

Figure 1. Transition structure **2** for the electrocyclic ring opening of cyclobutene. Geometric parameters are BLYP/6-31G* (plain text) and RHF/6-31G* (in parentheses). Bond lengths are in Å, bond angle and dihedrals in deg.

Baldwin *et al.* also studied the electrocyclic ring closure of 1,3,5-hexatriene;[28] they found a k_H/k_{D_2} of 0.88 ± 0.02 for the two IN protons and 1.05 ± 0.03 for the OUT protons. In reasonable agreement with experiment, values of 0.88 and 1.01, respectively, were calculated at the RHF/6-31G* level of theory with inclusion of Bell's tunnel correction. In this transition state, the p-character of the terminal C—H bonding orbitals is very similar in the reactant and the transition structure. The difference in the SKIEs for the IN and the OUT proton in the electrocyclization of hexatriene has been attributed by Baldwin *et al.* to the close proximity of the IN protons in the transition state, resulting in an increase of the force constants due to nonbonding interactions.

Our results for the electrocyclic ring opening of cyclobutene are summarized in Table 1. The BLYP/6-31G* calculations reproduce the experimental activation and reaction energies[29] reasonably well, whereas the RHF/6-31G* energy overestimates the activation energy considerably due to the neglect of

(24) Winter, R. E. K.; Honig, M. L. *J. Am. Chem. Soc.* **1971**, *93*, 4616–4617.

(25) (a) Mislow, K.; Graeve, R.; Gordon, A. J.; Wahl, G. H., Jr. *J. Am. Chem. Soc.* **1964**, *86*, 1733–1741. (b) Melander, L.; Carter, R. E. *Acta Chem. Scand.* **1964**, *18*, 1138–1149.

(26) For an overview on experimental studies of since KIEs see: Carter, R. E.; Melander, L. *Adv. Phys. Org. Chem.*; Gold, V., Ed.; Academic Press, New York: 1973; pp 1–27.

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(28) Baldwin, J. E.; Reddy, V. P.; Hess, B. A., Jr.; Schaad, L. *J. Am. Chem. Soc.* **1988**, *110*, 8554–8555.

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Table 1. Electrocyclic Ring Opening of Cyclobutene (413.15 K)

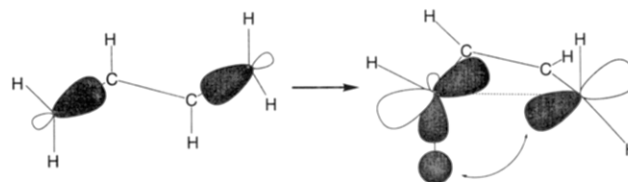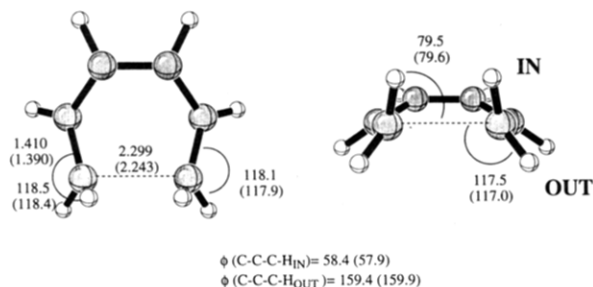|	B-LYP/6-31G*		RHF/6-31G*		
	forward	reverse	forward	reverse	exp forward
E_A [kcal/mol]	29.6	44.7	45.1	58.8	32.5
k_H/k_D(IN)	1.042	0.999	1.054	1.011	1.04 ± 0.03
k_H/k_D(OUT)	1.131	1.094	1.113	1.077	1.15 ± 0.03

Figure 2. Interaction of the C—H bond with the orbitals of the breaking C—C bond in **2**.

correlation energy. The calculated C_2-symmetric transition structures (Figure 1) from both methods are very similar, with the breaking bond somewhat longer in the BLYP/6-31G* calculations. The carbon skeleton is found to be considerably twisted by both methods. It has been noted earlier that similar transition structures are obtained by a wide variety of methods for this reaction.[10,30] For the reverse reaction, the cyclization of 1,3-butadiene **3** to cyclobutene **1**, an inverse SKIE would be expected according to the Streitweiser analysis, since a sp² center is converted into a sp³ center in the reaction. However, the opposite is found! For the IN proton, a k_H/k_D close to unity is calculated whereas a normal SKIE of 8–9% is calculated for the OUT proton. The reduced partition function $(s_2/s_1)f(2/1)$ and the corresponding frequencies of the vibrations for the OUT proton in the transition structure are smaller (4.510) than these functions in either the reactant (4.836) or the product (4.677) at the BLYP/6-31G* level. It is clear that the reaction does not involve the smooth transition of the terminal carbons from sp³ to sp² centers. Instead, the twisting of the carbon backbone in the transition state leads to some radical character at each of the terminal carbons. This produces low force constants for the bending vibrations of the attached hydrogens.[31] For the IN proton, this effect is compensated by steric hindrance resisting the bending motion in the transition state. Specifically, the motion of the IN hydrogens is hindered by the interaction of the occupied C—H bond orbital with the occupied orbitals of the forming C—C bond, as shown in Figure 2. These effects are the same, of course, for the ring opening of cyclobutene. Here, the very large normal isotope effect for the OUT hydrogens arises from the sp³ → radicaloid change in the nature of the C—H bond. The IN hydrogen gives a much smaller normal effect due to the counterbalancing effect of steric hindrance.

A similar picture is obtained for the electrocyclic ring closure of 1,3,5-hexatriene, **4**. The calculated boat-shaped transition structure **5**, shown in Figure 3, is similar by both computational methods. In this disrotatory reaction, the partial C—C bond is less twisted than in the ring opening of cyclobutene. The length of the forming bond calculated at the BLYP/6-31G* level is 0.056 Å longer than that calculated at the RHF/6-31G* level,

(30) Deng, L.; Ziegler, T. *J. Phys. Chem.* **1995**, *99*, 612–618.

(31) The better agreement of the BLYP/6-31G* calculations with the experimental values may be a result of a more balanced description of the diradicaloid character of the transition state.

φ (C-C-C-H_{IN})= 58.4 (57.9)
φ (C-C-C-H_{OUT})= 159.4 (159.9)

Figure 3. Transition structure **5** for the electrocyclic ring closure of 1,3,5-hexatriene. Geometric parameters are BLYP/6-31G* (plain text) and RHF/6-31G* (in parentheses). Bond lengths are in Å, bond angles and dihedrals in deg.

Table 2. Electrocyclic Ring Closure of *cis*-1,3,5-Hexatriene (413.15 K)

	B-LYP/6-31G*		RHF/6-31G*		
	forward	reverse	forward	reverse	exp forward
E_A [kcal/mol]	28.5	36.7	45.8	60.4	29.0
k_H/k_D(IN)	0.855	0.989	0.866	0.983	0.88 ± 0.03
k_H/k_D(OUT)	1.049	1.180	1.019	1.137	1.05 ± 0.03

indicating an even earlier transition state. The BLYP/6-31G* results for the activation energy and exothermicity of the reaction (Table 2) are in good agreement with the experimental results,[32] whereas the RHF/6-31G* method again overestimates the activation energy by more than 16 kcal/mol. The SKIEs calculated by the BLYP/6-31G* method are within experimental error for both positions, whereas the RHF/6-31G* slightly underestimates the SKIEs. For the IN position, the expected inverse SKIE is calculated by both methods. The reduced partition function for the IN proton is larger in the transition state than in either the reactant or the product, because the bending force constants are larger for this proton due to the small H_{IN}−H_{IN} distance of 1.901 Å (BLYP/6-31G*, or 1.858 Å by RHF/6-31G*). Consequently, an inverse isotope effect is also calculated for the reverse reaction. For the OUT proton, there are no strong steric interactions in the transition state, and the force constants are comparable for the transition state and the reactant, which is consistent with the early transition state calculated. The smaller degree of twist of the forming bond results in better overlap between the carbon termini than in the cyclobutene case. Consequently, there is less diradicaloid character in the transition structure of the hexatriene cyclization than in that of the cyclobutene ring opening.

The transition structure calculated for the conrotatory electrocyclic ring closure of *cis,cis*-1,3,5-octatetraene is shown in Figure 4. The forming bond computed by the BLYP/6-31G* method is much longer (0.22 Å) than the one calculated earlier by the RHF/6-31G* method.[33] In agreement with this even earlier transition state obtained by the BLYP/6-31G* method, the pyramidalization of the carbon termini is less advanced in the transition structure. The almost perfect alignment of the carbon termini results in the lack of a twist in the forming C−C bond. The distance between the OUT protons is 2.968 Å, while each IN proton is 2.558 Å from the carbon attached to the other
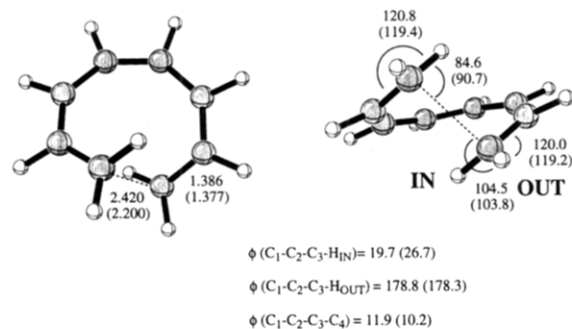
(32) Lewis, K. E.; Steiner, H. *J. Chem. Soc.* **1964**, 3080.

(33) Thomas, B. E., IV; Evanseck, J. D.; Houk, K. N. *Isr. J. Chem.* **1993**, *33*, 287−293.

φ (C_1-C_2-C_3-H_{IN})= 19.7 (26.7)

φ (C_1-C_2-C_3-H_{OUT})= 178.8 (178.3)

φ (C_1-C_2-C_3-C_4)= 11.9 (10.2)

Figure 4. Transition structure **8** for the electrocyclic ring closure of 1,3,5,7-octatetraene. Geometric parameters are BLYP/6-31G* (plain text) and RHF/6-31G* (in parentheses). Bond lengths are in Å, bond angles and dihedrals in deg.

Table 3. Electrocyclic Ring Closure of *cis,cis,cis,cis*-1,3,5,7-Octatetraene (413.15 K)

	B-LYP/6-31G*		RHF/6-31G*		
	forward	reverse	forward	reverse	exp forward
E_A [kcal/mol]	15.6	16.5	33.4	40.9	17.0
k_H/k_D(IN)	0.920	1.015	0.909	0.993	
k_H/k_D(OUT)	1.005	1.112	0.981	1.078	

terminus. The activation energy calculated by the BLYP/6-31G* method (Table 3) is in excellent agreement with the experimental values,[34,35] whereas the RHF method overestimates the exothermicity and the activation energy. The theoretical SKIEs computed reflect the properties of the transition structure. This conrotatory transition structure is less twisted than the one for the ring opening of cyclobutene. It is very reactant-like with little change in the sp^2 hybridization of the carbon termini. Consequently, a SKIE close to unity for the OUT proton is calculated by both methods. For the IN hydrogens, steric repulsion increases the bending force constants and an 8−9% inverse SKIE is predicted.

3,3-Sigmatropic Shift Reactions. The Cope[5a,11d,36] and the Claisen[11d,37] rearrangements have been studied earlier using a variety of theoretical methods. It has been shown that the theoretical KIEs and activation energies from DFT calculations are in excellent agreement with the experimental values.[38,39] Since the transition structures have already been discussed in

(34) Goldfarb, T. D.; Landquist, L. J. *J. Am. Chem. Soc.* **1967**, *89*, 4588.

(35) ΔH_{React} for *trans,cis,cis,trans*-2,4,6,8-decatetraene has been determined as −1 kcal/mol: Huisgen, R.; Dahmen, A.; Huber, H. *Tetrahedron Lett.* **1969**, 1461.

(36) (a) Borden, W. T.; Loncharich, R. J.; Houk, K. N. *Annu. Rev. Phys. Chem.* **1988**, *39*, 213−236. (b) Dewar, M. J. S.; Jie, C. *Acc. Chem. Res.* **1992**, *25*, 537−543. (c) Dupuis, M.; Murray, C.; Davidson, E. R. *J. Am. Chem. Soc.* **1991**, *113*, 9756−9759. (d) Hrovat, D. A.; Morokuma, K.; Borden, W. T. *J. Am. Chem. Soc.* **1994**, *116*, 1072−1076. (e) Jiao, H.; Schleyer, P. v. R. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 334−337. (f) Koszlowski, P. M.; Dupuis, M.; Davidson, E. R. *J. Am. Chem. Soc.* **1995**, *117*, 774−778.

(37) (a) Vance, R. L.; Rodan, N. G.; Houk, K. N.; Jensen, F.; Borden, W. T.; Kormonicki, A.; Wimmer, E. *J. Am. Chem. Soc.* **1988**, *110*, 2314−2315. (b) Dewar, M. J. S.; Jie, C. *J. Am. Chem. Soc.* **1989**, *111*, 511−519.

(38) Doering W. v. E.; Toscano, V. G.; Beasley, G. H. *Tetrahedron* **1971**, *27*, 5299−5306.

(39) (a) Schuler; Murphy *J. Am. Chem. Soc.* **1950**, *89*, 4588. This value has been critized in the literature: (b) Coates, R. M.; Rogers, B. D.; Hobbs, S. J.; Peck, D. R.; Curran, D. P. *J. Am. Chem. Soc.* **1987**, *109*, 1160−1170. (c) ΔH_{react} = −14.8 kcal/mol: Jansen, H. J.; Schmid, H. *Tetrahedron* **1974**, *30*, 1959.

$\phi\,(C_1\text{-}C_2\text{-}C_3\text{-}H_{IN})= -39.1\;(-36.5)$

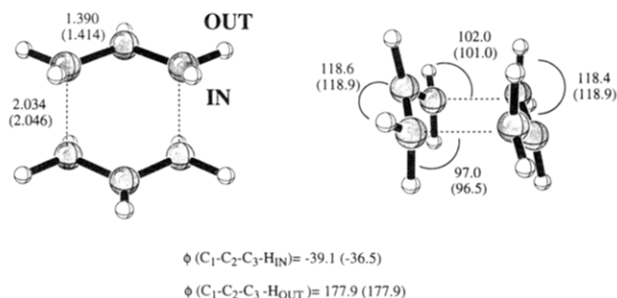$\phi\,(C_1\text{-}C_2\text{-}C_3\text{-}H_{OUT})= 177.9\;(177.9)$

Figure 5. Transition structure **11** for the Cope rearrangement of 1,5-hexadiene. Geometric parameters are BLYP/6-31G* (plain text) and RHF/6-31G* (in parentheses). Bond lengths are in Å, bond angles and dihedrals in deg.

Table 4. Cope Rearrangement of 1,5-Hexadiene (413.15 K)

	B-LYP/6-31G*		RHF/6-31G*		
	forward	reverse	forward	reverse	exp forward
E_A [kcal/mol]	29.7	29.7	56.6	56.6	33.5 ± 0.5
k_H/k_D(IN)	0.949	0.996	0.960	1.001	
k_H/k_D(OUT)	0.960	1.015	0.969	1.029	

previous reports, we will concentrate here on the difference between the SKIEs for hydrogens at the IN and OUT positions.

The C_{2h} (chair) transition structure for the Cope rearrangement is shown in Figure 5. Although the IN hydrogens are pseudo-axial and the OUT protons are pseudo-equatorial, the geometric differences between the IN and OUT positions are much less pronounced than for the electrocyclic reactions. The angles between the C–H bond and the forming/breaking bond differ by only 5° for the two positions. Therefore, there is only a small, but nevertheless significant difference in the SKIEs for the two positions. The inverse SKIE for the IN proton at the 1-position, associated with the sp² → sp³ change, is calculated by both methods to be approximately 1% larger than the SKIE of the corresponding OUT proton. The IN proton has higher force constants for the bending modes due to the smaller angle with the forming C–C bond and 1,3-diaxial (i.e. IN–IN) allyl interactions. These nonbonded interactions lead to a situation similar to the one already discussed for the electrocyclic ring closure of 1,3,5-hexatriene **4** where the reduced partition function for this proton is larger $((s_2/s_1)f(2/1) = 4.966)$ than the one for the sp³-hybridized 3-position $((s_2/s_1)f(2/1) = 4.944)$. The pseudo-equatorial OUT proton in the transition structure has no significant nonbonded interactions; the SKIE for this proton is near unity, indicating that the hybridization at this position is very much like that in the sp²-hybridized reactant. The SKIEs calculated for the 3-position, involving an sp³ → sp² change, equivalent to the reverse reaction of the cases just discussed, confirm this analysis. A very small inverse SKIE is calculated for the IN proton at this position, whereas for the OUT position, involving a more sp²-like environment, a normal SKIE is computed.

The transition structure calculated for the Claisen rearrangement of allyl vinyl ether **12** is shown in Figure 6. The angles between the C–H bond and the forming/breaking bonds are virtually identical for the two protons in the 4-position and are very similar for the 6-position. These angles differ by 18° for the 1-position at the BLYP/6-31G* level (16° at the RHF/6-31G* level). The length of the forming C–C bond differs considerably between the two methods used. This leads to a
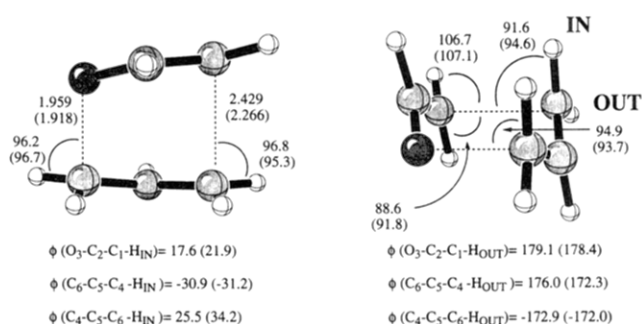

$\phi\,(O_3\text{-}C_2\text{-}C_1\text{-}H_{IN})= 17.6\;(21.9)$ $\phi\,(O_3\text{-}C_2\text{-}C_1\text{-}H_{OUT})= 179.1\;(178.4)$

$\phi\,(C_6\text{-}C_5\text{-}C_4\text{-}H_{IN})= -30.9\;(-31.2)$ $\phi\,(C_6\text{-}C_5\text{-}C_4\text{-}H_{OUT})= 176.0\;(172.3)$

$\phi\,(C_4\text{-}C_5\text{-}C_6\text{-}H_{IN})= 25.5\;(34.2)$ $\phi\,(C_4\text{-}C_5\text{-}C_6\text{-}H_{OUT})= -172.9\;(-172.0)$

Figure 6. Transition structure **13** for the Claisen rearrangement of allyl vinyl ether. Geometric parameters are BLYP/6-31G* (plain text) and RHF/6-31G* (in parentheses). Bond lengths are in Å, bond angles and dihedrals in deg.

Table 5. Claisen Rearrangement of Allyl Vinyl Ether (413.15 K)

	B-LYP/6-31G*		RHF/6-31G*		
	forward	reverse	forward	reverse	exp forward
E_A [kcal/mol]	21.1	38.4	46.5	67.9	30.6
k_H/k_D pos. 1, IN	0.972	1.057	0.977	1.055	
k_H/k_D pos. 1, OUT	1.002	1.042	0.996	1.032	
k_H/k_D pos. 4, IN	1.056	0.933	1.052	0.914	
k_H/k_D pos. 4, OUT	1.049	0.944	1.050	0.930	
k_H/k_D pos. 6, IN	0.970	1.051	0.938	1.020	
k_H/k_D pos. 6, OUT	0.981	1.051	0.964	1.028	

larger out-of-plane displacement of the IN proton in the 4-position and the OUT proton in the 6-position. Accordingly, the SKIEs calculated for the 4- and 6-positions differ only slightly for the IN and OUT protons. At the 1-position, a difference between the SKIEs for the two protons of 3% is computed at the BLYP/6-31G* level.[40] The IN has a smaller angle with the forming bond and has therefore higher bending force constants. The tighter transition structure obtained by the RHF/6-31G* method and the differences in the dihedral angles at the 1- and 6-positions decrease the difference between the SKIEs calculated for the 1-position and increase the difference between the SKIEs at the 6-position.

The Diels–Alder Reaction. The Diels–Alder reaction has been studied previously by many different theoretical methods.[5b,10,25] The present discussion is confined to the SKIEs at different positions.[41] Figure 7 shows the calculated transition structures.

A SKIE close to unity is computed for the 3-position, which remains sp² hybridized throughout the reaction. For the diene, the larger inverse SKIE of the IN proton suggests higher force constants for the out-of-plane bending modes in this position.[42] This arises from bonding interactions with the termini of the approaching dienophile, which results in rotation and pyramidization of the diene termini. This eases the close approach

(40) The small normal SKIE calculated for the OUT hydrogen is due not to a diradicaloid character at this center but to a strong coupling of this hydrogen with the imaginary frequency. This causes the first term in eq 2 to be dominant.

(41) To calculate the SKIEs and to avoid BSSE effects, **15** has been defined as a supermolecule with a fixed distance of 15 Å between the reactants.

(42) It can be deduced form the fact that the vibrational spectra of *cis*- and *trans*-1,3-butadiene are virtually identical that the in-plane bending modes, leading to steric interactions if the two IN protons are negligible: Sverdlov, L. M.; Kovner, M. A.; Krainov, E. P. *Vibrational Spectra of Polyatomic Molecules*; Wiley & Sons: New York, 1974; pp 297–303.
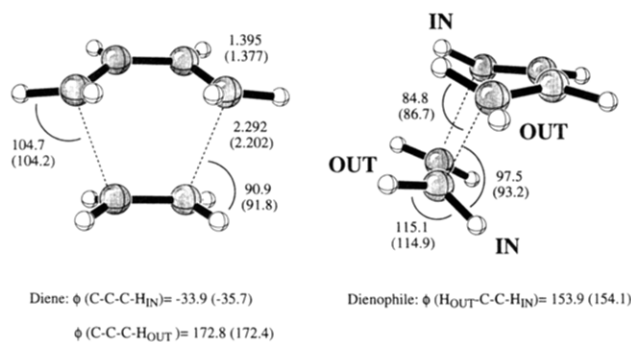
Diene: ϕ (C-C-C-H$_{IN}$)= -33.9 (-35.7)   Dienophile: ϕ (H$_{OUT}$-C-C-H$_{IN}$)= 153.9 (154.1)

ϕ (C-C-C-H$_{OUT}$)= 172.8 (172.4)

Figure 7. Transition structure **16** for the concerted Diels—Alder reaction. Geometric parameters are BLYP/6-31G* (plain text) and RHF/6-31G* (in parentheses). Bond lengths are in Å, bond angles and dihedrals in deg.

Table 6. Diels—Alder Reaction of 1,3-Butadiene and Ethene (373.15 K)

| | B-LYP/6-31G* | | RHF/6-31G* | | |
	forward	reverse	forward	reverse	exp forward
E_A [kcal/mol]	22.8	52.6	47.8	83.9	27.0
k_H/k_D pos. 1, IN	0.933	1.011	0.940	1.024	
k_H/k_D pos. 1, OUT	0.983	1.036	0.975	1.032	
k_H/k_D pos. 2, IN	0.958	1.045	0.954	1.043	
k_H/k_D pos. 2, OUT	0.978	1.077	0.973	1.065	
k_H/k_D pos. 3	0.999	0.981	1.004	0.992	

of the two IN hydrogens of the diene. The dihedral angle of the IN C—H bond at the 1-position is 34° (BLYP/6-31G*) with respect to the diene plane, whereas the OUT C—H bond is bent only 7° out of the diene plane. This OUT proton remains very reactant-like. Therefore, only a small inverse SKIE of 2% is calculated at the BLYP/6-31G* level. For the IN (endo) and OUT (exo) positions of the dienophile, the same effects can be observed, although the difference between the SKIEs of the IN and OUT protons is less pronounced. The interactions of the IN hydrogens with the diene lead to a larger angle of 98° between the C—H$_{IN}$ and the forming C—C bond as compared to the 91° for the corresponding C—H$_{OUT}$ (BLYP/6-31G*). By this tilt, the steric interaction of the IN proton with the diene is decreased, which leads to a smaller SKIE for this proton. Therefore, the difference in the SKIEs is only ~2% for the exo and endo hydrogens of the dienophile.

Conclusion

Diastereotopical protons have different secondary kinetic isotope effects in a variety of concerted pericyclic reactions. The differences follow a pattern that makes it possible to use the IN and OUT protons as probes for the properties of the

transition states. The OUT proton, generally having less nonbonding interactions, reflects the electronic properties of the transition state such as the extent of the rehybridization process or the diradicaloid character of the carbon termini in the transition state. Twisting of the forming or breaking σ-bond, leading to this diradicaloid character, results in lower bending force constants in the transition state than in either the reactant or the product. The SKIEs determined for the OUT hydrogens can therefore not be explained solely by a smooth rehybridization process, as has been proposed earlier.[23,26] The IN proton provides information about the nonbonded interactions on the inside surface of the transition state. These repulsive interactions can be divided into orbital—orbital interactions between the occupied orbital of the C—H$_{IN}$ bond and the occupied orbital of the forming or breaking bonds in the transition state (as shown in Figure 2)[36e,43] and steric repulsion of the IN hydrogens with each other or the carbon termini. They result in an increase in the bending force constants of the IN hydrogens and a preference of deuterium for these positions.

The direct computation of these force constants has several advantages over the more qualitative concepts of rehybridization or steric kinetic isotope effects. It has been shown in the present paper and in earlier studies[11d] that the theoretical SKIEs calculated by nonlocal density functional methods are in excellent agreement with the available experimental data. The thorough analysis of the reduced partition functions obtained by methods allows a better understanding of the different factors responsible for the measured kinetic isotope effects. The separate measurement of the SKIEs of the IN and OUT hydrogens, combined with the interpretation by *ab initio* theory, will provide a better picture of transition states than the averaged SKIE's of the IN and OUT protons commonly used in current mechanistic interpretations.

Supporting Information Available: Tables of energies, zero-point energies, imaginary frequencies, reduced partition functions and Cartesian coordinates of all structures reported (16 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, can be ordered from the ACS, and can be downloaded from the Internet, see any current masthead page for ordering information and Internet access instructions.

JA950754R

(43) Another consequence of this orbital interaction in aromatic transition states is the exaltation of magnetic susceptibility: (a) Jiao, H.; Schleyer, P. v. R. *J. Chem. Soc., Faraday Trans.* **1994**, *90*, 1559–1567.