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Racing Carbon Atoms. Atomic Motion Reaction Coordinates and Structural Effects on Newtonian Kinetic Isotope Effects

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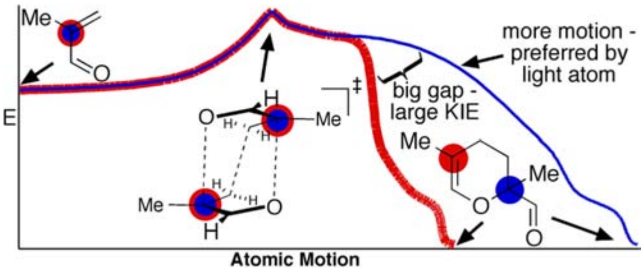
ABSTRACT



Intramolecular ^{13}C kinetic isotope effects were determined for the dimerization of methacrolein. Trajectory studies accurately predict the isotope effects and support an origin in Newton's second law of motion, with no involvement of zero-point energy or transition state recrossing. Atomic motion reaction coordinate diagrams are introduced as a way to qualitatively understand the selectivity.

Kinetic selectivity in organic reactions is normally determined by the free energies of competitive transition states (TSs). Complicating factors such as tunneling have been well recognized, but the ideas used to understand selectivity and the experiments or computations used to probe its origins have generally focused on TS energies. From theory, it has long been recognized that selectivity can also arise from the competition between downhill pathways after a TS.[1] When looked for, these competitions have been regularly seen in theoretical studies.[2] We have uncovered experimental evidence for such selectivity in simple organic reactions in solution, and we have sought to characterize and understand the unusual observations associated with these reactions.[3−6]

An exciting aspect of this alternative paradigm for selectivity is that it suggests new experiments, and these can in turn lead to the observation of new physical phenomena. The two examples of interest here are *Newtonian* kinetic isotope effects (KIEs)[4] and *recrossing* KIEs.[5] Ordinary KIEs originate mainly in the quantum effects of zero-point energy (ZPE) and tunneling. In contrast, Newtonian KIEs appear to result simply from the greater acceleration of lighter masses in response to a force (i.e., $F = ma$, Newton's second law). Recrossing KIEs arise from the dynamics of

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cycloadditions that involve substantial TS recrossing, and the observed effect was in the opposite direction from Newtonian KIEs. Little is known about either of these KIEs from the single published examples. From our observations of recrossing in the Diels–Alder reaction of acrolein with methyl vinyl ketone,[6] the dimerization of methacrolein (**1**) appeared to be a candidate to exhibit both effects.

We describe here an experimental, standard computational, and dynamic trajectory study of the Diels–Alder dimerization of **1**. The results show how structure impacts the multiple phenomena affecting selectivity in this ordinary organic reaction. We introduce the idea of an *atomic motion* reaction *coordinate* diagram to provide insight into the race between carbon atoms underlying the selectivity in this system.

Newtonian KIEs can arise on symmetrical bifurcating energy surfaces (Figure 1a). In the area past the TS, molecular forces are pushing atoms toward two possible products. With isotopic substitution, the products are inequivalent and Newton's second law favors the product arising from the steepest-descent path in mass-weighted coordinates (the intrinsic reaction coordinate, or IRC). This technical idea mathematically defines the direction of the isotope effect, but it provides little intuition, indeed none at all with regard to the magnitude of the selectivity. Instead, we find it enlightening to consider reaction coordinate diagrams that follow the motion of individual atoms. In such diagrams, separate paths may be drawn for each atom in a molecule, and the diagrams become interesting when they compare the motions of two atoms competing for two distinct positions in the product. In forming an asymmetric product starting from a symmetrical TS, the initially equivalent atoms of such "racing pairs" take separate paths. With reflection, it may be recognized that the preferred path, the IRC, will be that in which the lighter isotope moves more as the atomic motion paths separate. This idea will be examined later in the context of the current example. Initially, since the system here is subject to recrossing, we did not know whether the race would be decided by light atoms accelerating faster or heavy atoms recrossing less.

The dimerization of **1** is well set up for such a race. Caramella had found that the lowest-energy TS (**2**) for the dimerization is stabilized by "bis-pericyclic" character and has C_2 symmetry.[7] The product **3** is asymmetric, so the geometry must formally break symmetry after the TS to afford two structures that are indistinguishable in the absence of isotopic labeling. When a ^{13}C is present in **1**, the product may contain the ^{13}C in either the diene (*a*, *b*, *c*, *d*) or dienophile (*a*′, *b*′, *c*′, or *d*′) portion of **3**. The ratio of products labeled in the paired positions is an intramolecular KIE. Four intramolecular KIEs are observable in this reaction, resulting from the pairs of products formed with a label in position *a*, *b*, *c*, or *d* of **2**. These ratios and KIEs were measured directly at natural abundance by NMR analysis[8] of samples of cycloadduct generated from the dimerization of **1** at 70 °C. The results from a total of 12 measurements using two independent samples of **3** are shown in Figure 2.

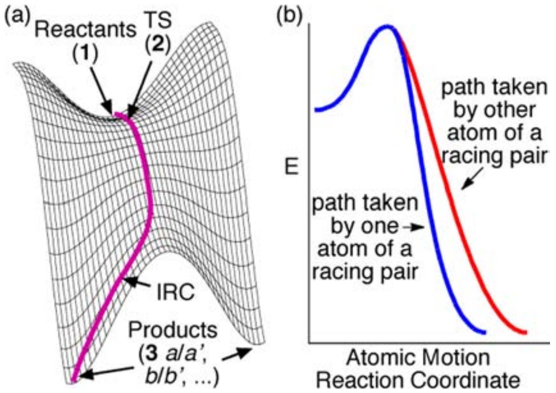
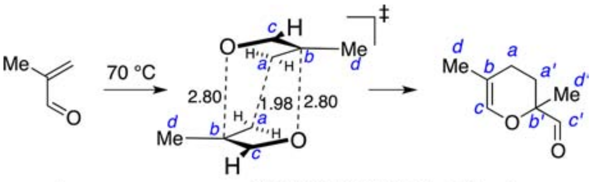


Figure 1. (a) Symmetrical bifurcating energy surface. The IRC is asymmetric due to isotopic substitution. (b) An atomic motion reaction coordinate diagram. The two paths do not represent separate reactions, but instead represent the differing motion of two atoms of a racing pair as the product is formed.



1 **2** (C_2) (B3PW91/6-31+G**) **3**

KIE = $(k^{12}/k^{13})x'/(k^{12}/k^{13})x$ = relative amount of ^{13}C in x/x′			
a/a′ 1.011(2)	b/b′ 1.019(2)	c/c′ 0.994(1)	d/d′ 0.999(1)

Figure 2. TS and KIEs for the dimerization of **1**.

In ordinary isotope effects resulting from ZPE changes, ^{12}C usually undergoes σ-bonding making/breaking faster than ^{13}C. The observed preference for ^{12}C in position *b*′ over *b* is in this direction, but the preference would only make sense from a conventional perspective if the TS were not symmetrical. With the symmetrical TS favored in a wide variety of calculational methods (see the Supporting Information (SI)), the positions in **2** leading to *b* and *b*′ products are equivalent, so TS ZPE cannot explain the *b*/*b*′ KIE. The KIEs at *a*/*a*′ and *c*/*c*′ are not obviously amenable to any conventional explanation.

All of the KIEs, however, fit with Newtonian expectations. IRCs were followed forward from **2** in B3PW91/6-31+G** calculations (chosen because they fit best here with high-level ab initio methods; see the SI), with a ^{13}C placed in position *a*, *b*, *c*, or *d* (Figure 3). For positions *a* and *b* of **2**, the IRC is desymmetrized toward placing the ^{13}C in the diene portion of **3** (positions *a* and *b* as opposed to *a*′ and *b*′), while a ^{13}C in position *c* of **2** ends up in the

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(7) Toma, L.; Romano, S.; Quadrelli, P.; Caramella, P. *Tetrahedron Lett.* **2001**, *42*, 5077–5080.

(8) Singleton, D. A.; Szymanski, M. J. *J. Am. Chem. Soc.* **1999**, *121*, 9455–9456.

dienophile portion of **3** in position *c*′. The desymmetrization of the IRC correctly predicts the major product in each case, and the amount of IRC desymmetrization corresponds strikingly well with the magnitude of the experimental isotope effects. For position *d*, the IRC follows a nearly symmetrical path for a long distance from TS **2**, before finally falling to position *d* in **3**, and no significant selectivity is observed.

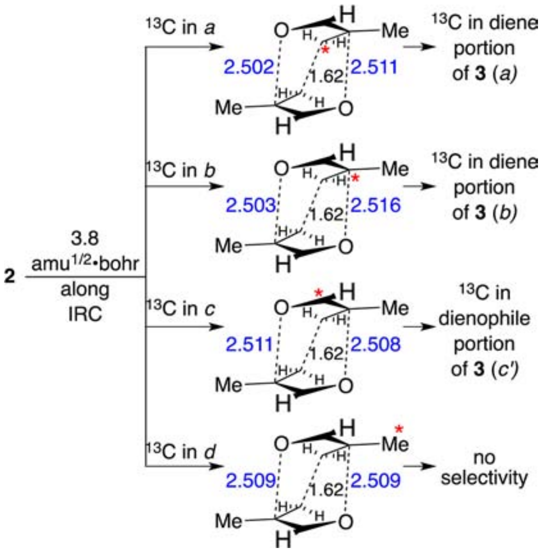

Figure 3. Structures on the IRCs after **2** with ^{13}C substitution, showing the desymmetrization toward the major product.

Dynamic trajectory calculations were employed to gain quantitative insight into the KIEs. Due to the difficulty of obtaining statistically significant predictions of ^{13}C KIEs from trajectories, our trick of using, *in silico*, superheavy isotopes of carbon was employed.[4] Quasiclassical direct-dynamics[9] trajectories on a B3PW91/6-31G* energy surface were initiated from isotopomers of **2** containing a single ^{16}C, ^{20}C, ^{28}C, ^{44}C, ^{76}C, or ^{140}C ($12 + 2^N$ amu, $N = 2, 3, 4, 5, 6$, or 7). Each normal mode in **2** was given its zero-point energy (ZPE) plus a Boltzmann sampling of additional energy appropriate for 70 °C, with a random phase. Because the lowest-energy real normal mode in **2**, "mode 2," desymmetrizes the structure in a way that has a large effect on trajectory outcomes, an equal number of trajectories were given positive versus negative velocities in this mode. The transition vector was given a Boltzmann sampling of energy 'forward' from the col. The trajectories were integrated until either the product was formed (median time 90 fs) or the starting materials were reformed. The results are given in Table 1.

In each case the trajectories correctly predict the major product, and the magnitude of the selectivity in the trajectories follows the same trend as the experimental KIEs. With a label in position *d*, a small selectivity was observed for ^{140}C but no selectivity was observed for ^{76}C, as fits with an experimental KIE that is within error of unity. With superheavy carbons in position *c*, the trajectory selectivities were in the experimental direction but they were low, and no attempt was made to observe the selectivity with a mass less than ^{44}C. Statistically significant selectivities were found with masses as low as ^{16}C for position *b* and ^{20}C for position *a*, and in these cases the KIE could be extrapolated to ^{13}C. The extrapolated KIEs are in excellent agreement with the experimentally observed KIEs. The fit of these results with experimental observations suggests that the trajectories are reflecting the underlying physics that gives rise to the experimental KIEs.

Table 1. Quasiclassical Trajectories Started from **2**

position/ isotope	total runs	mode 2 negative x:x':recrossed	mode 2 positive x:x':recrossed	KIE
a 140	8168	16.3:75.7:8.1	87.2:6.7:6.0	1.26 ± 0.05
a 76	2530	14.5:78.7:6.8	86.2:6.9:6.9	1.18 ± 0.07
a 44	2604	13.7:77.3:8.9	84.5:8.0:7.5	1.15 ± 0.06
a 28	4066	14.5:77.1:8.4	82.9:9.6:7.5	1.12 ± 0.05
a 20	5688	13.9:77.1:9.0	79.3:10.8:9.9	1.06 ± 0.04
			extrapolated to ^{13}C	1.013
b 140	9312	21.5:67.2:11.3	85.1:3.7:11.2	1.50 ± 0.05
b 76	3082	18.8:70.4:10.8	84.3:4.2:11.5	1.38 ± 0.09
b 44	3050	17.0:71.9:11.1	83.5:6.4:10.2	1.28 ± 0.07
b 28	7824	15.0:75.2:9.7	81.4:8.9:9.7	1.15 ± 0.04
b 20	14828	14.2:75.6:10.2	79.1:10.8:10.1	1.08 ± 0.03
b 16	20932	14.3:75.5:10.2	78.3:11.9:9.8	1.06 ± 0.02
			extrapolated to ^{13}C	1.017
c 140	3214	9.1:77.8:13.0	76.9:13.7:9.4	0.94 ± 0.05
c 76	3074	10.9:77.7:11.5	76.7:12.8:10.5	0.97 ± 0.06
c 44	7848	11.2:77.4:11.4	75.9:13.8:10.3	0.96 ± 0.04
d 140	3666	17.0:73.6:9.4	69.2:19.1:11.6	0.93 ± 0.06
d 76	6512	17.5:72.1:10.5	71.7:16.7:11.6	1.00 ± 0.04

Three aspects of the trajectory results are striking. First, the outcome of most of the trajectories is preordained by the positive versus negative sign of the velocity in mode 2 in **2**. This is a form of dynamic matching and is an effect that we have observed and discussed in other reactions.[5,6] Second, the small KIEs interestingly arise from a proportionately large effect on the small number of "crossover" trajectories. For example, with a ^{140}C in position *b*, the trajectory KIE of 1.5 results from a factor of 6 difference in the number of mode 2-positive trajectories that afford *b*′ product (3.7%) versus the number of mode 2-negative trajectories that afford *b* product (21.5%). Third, the amount of recrossing in the methacrolein system is surprisingly low. This is qualitatively different from what was observed in the reaction of acrolein with methyl vinyl ketone, where greater than half of the trajectories recrossed.[6] Why should the modest change of the positioning of methyl groups make such a difference? The apparent answer to this question lies in the slope of the energy surface after the cycloaddition TS. With the methacrolein dimerization, trajectories proceed from the area of TS **2** toward the area of the structures shown in Figure 2 by

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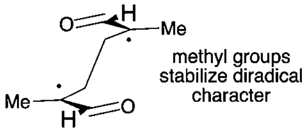
[9] Hase, W. L.; Song, K. H.; Gordon, M. S. *Comp. Sci. Eng.* **2003**, *5*, 36–44. Sun, L.; Hase, W. L. *Rev. Comput. Chem.* **2003**, *19*, 79.

progressing in C–C bond formation. In the extreme of full C–C bond forming with no C–O bond formation, the structure would become a diradical as in **4**, and the radicals would be recognizably stabilized by the methyl groups. In actuality, the structure never takes on full diradical character (the IRC is spin-unrestricted stable), but the structure in this area of the energy surface is still highly stabilized by methyl-group donation to low-lying σ^* orbitals associated with the incipient C–O bonds, as in **5**. As a result, the energy surface in the area past TS **2** is more downwardly sloped with the methyl groups present than absent, and in the absence of any statistical dynamical bottleneck the more highly sloped surface resists recrossing. With minimal recrossing, the Newtonian preference dominates the selectivity.



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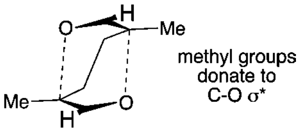

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To learn whether the KIEs are related to ZPE, as is true of normal isotope effects, a second set of trajectories was calculated with the ZPE turned off, giving each normal mode a classical distribution of energy. The results (see the SI) are statistically indistinguishable from those in Table 1, so quantum-mechanical ZPE did not change the dynamics. Since a fully classical simulation accounts for the KIEs, they do not arise from any quantum-mechanical effect and hence the KIEs are Newtonian in origin.

The IRC and trajectory results are each impressively predictive, but they are not explanatory.[10] Atomic motion reaction coordinate diagrams (Figure 4) provide insight into both the direction of the isotope effects and their magnitude. These diagrams are readily generated; at each point in an IRC the distance that each atom moved versus the previous point (with a fixed center of mass and rotational orientation) is calculated, and the sum of these distances up to that point is plotted versus the energy. There are two striking observations in the diagrams. The first is that the major product is *not* defined by what position moves the lightest atom the farthest in going from the TS to the product geometry. This can be seen for the *a*/*a*′ diagram; the path to position *a* in the product ultimately requires greater atom motion, yet the heavier isotope preferentially goes to this position. The direction of the isotope effect is instead determined by the relative atomic motion in the small area of the reaction coordinate diagram where the paths first separate. After this point, the product has already been decided and the atomic motion becomes irrelevant to the selectivity. In each case the preferred product moves the lighter atom farther in the "selection area." The second observation is that the largest KIE, that for the *b*/*b*′ pair, is associated with a large gap between the paths taken by the racing pairs. The C_b–O bond formation that consummates product formation requires extensive motion on the part of the carbon atom forming this bond, and as a result the lighter isotope is strongly preferred for this position.

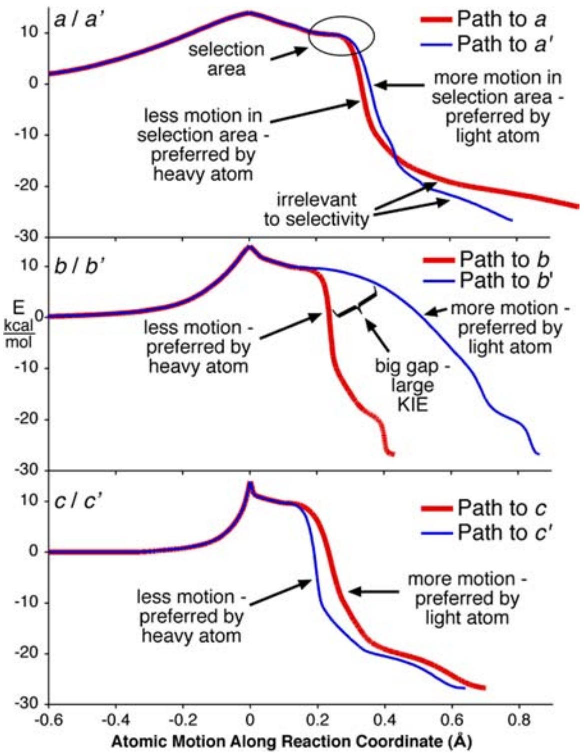

Figure 4. Atomic motion reaction coordinate diagrams for the *a*/*a*′, *b*/*b*′, and *c*/*c*′ racing pairs. The *y*-axis has its zero of energy at separate reactants, and the *x*-axis has the TS at zero.

In most reactions, isotopic selectivity or any other form of product selectivity would be simply understandable from the free energies of TSs. Here, the story is more complex and more interesting. The race between carbon atoms to positions in the product is not decided by TS energies, and it is not decided by the dynamic effect of recrossing in this case. Rather, the selectivity is decided by forward motion in the small area of the energy surface that selects the product. Even so, dynamic matching predecides most races, but a substantial number are won by the greater motion of lighter atoms. The ideas here are all quite qualitative, but they appear useful for insight into experimental observations in the growing list of reactions known to involve dynamic effects.

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Supporting Information Available. Experimental and computational procedures, and energies and full geometries of all calculated structures. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.

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(10) For a caveat on IRCs, see: López, J. G.; Vayner, G.; Lourderaj, U.; Addepalli, S. V.; Kato, S.; de Jong, W. A.; Windus, T. L.; Hase, W. L. *J. Am. Chem. Soc.* **2007**, *129*, 9976–9985.