

Controlling Selectivity by Controlling Energy Partitioning in a Thermal Reaction in Solution

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S Supporting Information

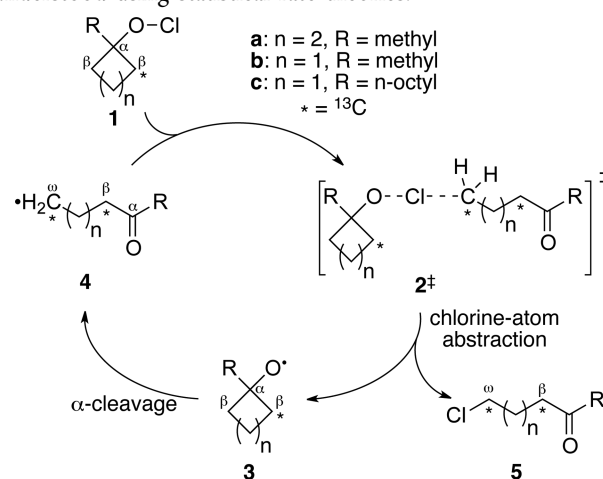
ABSTRACT: The comparison of experimental and predicted kinetic isotope effects in the α -cleavage of alkoxy radicals is used here to judge the applicability of statistical rate theories. It is found that the governing rate theory and the statistical versus nonstatistical nature of the cleavage depend on the cleavage barrier and how much energy is imparted to the radical. The latter can then be controlled by changing the size of substituents in the system. With a large alkyl group substituent, the vibrational energy of the alkoxy radical is increased, but this energy is not statistically distributed, leading to a lower isotope effect than predicted by statistical theories. The observed isotope effect can be approximately rationalized using a semistatistical localized RRKM model.

In any reaction passing over an energy barrier, the products are initially imbued with excess energy. The partitioning of that energy between translational, rotational, and vibrational forms has long been a core interest of the field of gas-phase reaction dynamics, in part due to the ambition of selectively promoting or controlling reactions.¹ Some general expectations for the energy partitioning are specified by the Polanyi rules, which relate the position of the transition state (TS) to vibrational versus translational energy in the reactant and products in the simplest atom-transfer reactions.² Energy partitioning in larger molecules and in condensed phases is much less well understood.³ The literature provides no guidance as to how one might structurally control energy partitioning in an ordinary solution reaction or how this might be used to affect product selectivity.

We describe here a simple structural effect on the amount of vibrational energy that is partitioned to a reactive intermediate in an atom-transfer step and how that engenders nonstatistical dynamics⁴ and changes the selectivity of a reaction. The results show how ideas from collision dynamics can be used to influence complex organic reactions in solution.

The reaction of interest is the conversion of cycloalkyl hypochlorites (**1a–c**) to ω -chloroalkylketones (**5a–c**). This reaction involves a chain mechanism in which a chlorine atom is abstracted from **1** to afford the alkoxy radical **3**.⁵ Radical **3** then undergoes a facile α -cleavage to afford the ring-opened radical **4**. Chlorine atom transfer to **4** from **1** affords the product **5** and a new molecule of **3** to continue the chain. These reactions are clean and highly exothermic (37 kcal/mol for $n = 2$, 55 kcal/mol for $n = 1$ (CCSD(T)/cc-pvtz//M11L/6-311+G**)). The α -cleavage of alkoxy radicals is important in

diverse areas of chemistry and has been assumed to be fully understood using statistical rate theories.⁶



When a ^{13}C is in the β -position of **1**, the α -cleavage of **3** partitions the ^{13}C between the β and ω positions of the ring-opened radical **4**. The selectivity in this cleavage can be measured from the ratio of ^{13}C in the two positions and expressed as an intramolecular kinetic isotope effect (KIE). This selectivity is readily determined by analysis of samples of **5** at natural abundance by NMR methodology.⁷ In all cases, the ^{13}C content in the β position of **5** was in excess over that in the ω position, reflecting the qualitative expectation of a faster cleavage of a β - ^{13}C in **3**. However, there were surprising variations in the magnitude of the excess.

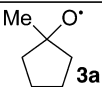
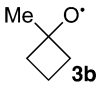
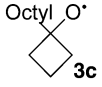
The results are summarized in Table 1. At 6.1%, the large KIE observed for α -cleavage in the five-membered ring **3a** is comparable to that observed previously for the ring-opening of the cyclopropylcarbinyl radical, a high heavy-atom tunneling system. The KIE is then strikingly decreased for the methylcyclobutoxy radical **3b**, at 4.4%. Most surprisingly, the KIE is further decreased to 2.9% for the octylcyclobutoxy radical **3c**, less than half that observed for **3a**.

To interpret these results, we turned to computational and dynamic trajectory studies. Diverse DFT methods were explored in comparison with CCSD(T)/jun-cc-pvtz single-point energies for the **1a,b–5a,b** energy surface. In this comparison, UM11L/6-311+G** calculations provided a highly accurate description of the α -cleavage (barriers within 0.1 kcal/mol, see the Supporting Information (SI)), but the

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Table 1. Experimental and Predicted KIEs (42 °C)

alkoxy radical	exptl KIE ^a	CVT / SCT KIE	α -cleavage barrier ^b (kcal/mol)	available vibrational energy	RRKM KIE
 3a	1.061(2)	1.063	10.8	5.8	-
 3b	1.044(1)	1.060	3.0	4.8	1.043
 3c	1.029(1)	1.062	2.6	7.2	1.038 (1.033 ^c)

^aBased on the ratio of ¹³C in the β versus ω positions of 5. The 95% confidence limit on the last digit is shown in parentheses. ^bUM11L/6-311+G** potential energy barrier, in kcal/mol. ^cPrediction using a localized RRKM model in which the excess energy is limited to a molecular subset.

chlorine-atom abstraction was more accurately modeled in UM11/6-31+G** calculations.

We first explored how the observations compared with predictions from transition state theory. Rate constants for the α -cleavage of β -¹³C-substituted **3a–c** were calculated using canonical variational transition state theory (CVT) including small-curvature tunneling (SCT) using the GAUSSRATE/POLYRATE set of programs.^{8,9} The KIE predictions are subject to a series of complicating issues. For **3a**, there are two competitive low-energy TSs. For **3b**, the two C α –C β bonds are not equivalent (differing by 0.04 Å), with bond-length isomers separated by a 0.4 kcal/mol barrier. This required allowance for the isotopically perturbed equilibrium between the isomers. For **3c**, the octyl-group conformation desymmetrizes the ring opening, and it was assumed that conformational interconversion in the octyl group was slower than the very rapid ring opening. The tunneling contribution to the KIEs was in all cases substantial, at 1.0–1.2%. After allowing for each complication (see the SI for details), the predicted KIEs are shown in Table 1.

For **3a**, the CVT/SCT-predicted KIE matches closely with the experimental value, within the error of the measurement. However, the experimental KIEs for **3b** and **3c** are far below the predicted values. The first-order interpretation of this difference is that it is associated with the differing barriers for α -cleavage in the systems. The cleavage barrier for **3a** is relatively large, at 10.8 kcal/mol, and this leads to a lifetime that is sufficiently long for full energy equilibration to occur. As a result, the ring opening is governed by transition state theory and the CVT/SCT KIE prediction is accurate. With **3b** and **3c**, the α -cleavage barriers are much smaller. If the ring opening is faster than thermal equilibration, transition state theory is not applicable. This would cause the CVT/SCT predictions to be inaccurate.

A more detailed interpretation of the results requires consideration of the amount of energy available to the intermediates **3a–c**. The excess energy of ~39 kcal/mol that is generated in the abstraction of a chlorine atom from **1** and **4** is partitioned into the two products, **3** and **5**, and within each product that energy is partitioned into rotational, translational, and vibrational components (Figure 1). Of these, only the

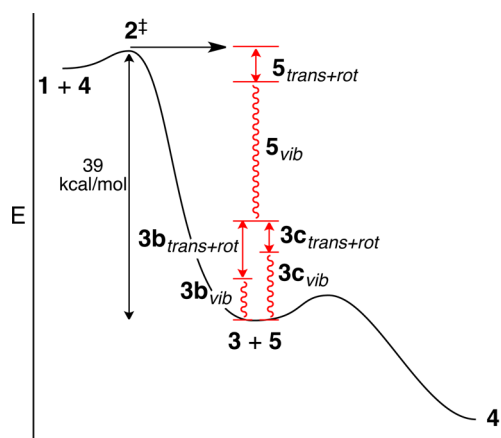
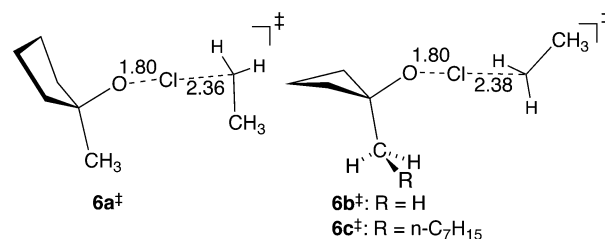


Figure 1. Energy partitioning in the chlorine-atom abstraction. Only the vibrational energy in **3** can promote the second step.

vibrational energy in **3** is available to promote α -cleavage. To assess this pivotal portion of the energy, we applied a modified version of the classical single-trajectory approximation of Hase.¹⁰ Series of trajectories were started from TSs **6a–c** for chlorine-atom abstraction from **1a–c** by an ethyl radical, providing no zero-point energy for the real normal modes and a Boltzmann-random energy in the transition vector. The trajectories were then integrated forward in time, and the components of the energy were evaluated as the products **3** and chloroethane separated. Average energy partitionings were then calculated for each series.



The exothermic atom abstractions **6a–c** have early TSs, so the Polanyi rules would predict that the largest proportion of the excess energy ends up as vibrational energy in **5**. This prediction is correct; the chloroethane receives two-thirds of the energy, 26 kcal/mol, with 21 kcal/mol ending up as vibrational energy. The incipient alkoxy radical **3** receives 13 kcal/mol of excess energy. For **3a**, 5.8 kcal/mol is put into vibrational energy, but this is not enough to overcome the α -cleavage barrier so the intermediate radical must await ordinary thermal activation. For **3b** and **3c**, however, their initial excess vibrational energy exceeds the cleavage barrier. This by itself would not guarantee that the α -cleavage would occur before thermal equilibration, but it signals the possibility.

For the 13 kcal/mol of excess energy in **3a–c**, the partitioning depends strikingly on the structure. In particular, the presence of the octyl chain in **3c** leads to a much higher proportion of the energy partitioned into vibrational energy (Table 1).

To explain this novel observation, we consider a limiting pure impulsive¹¹ model for **3** in which the impulse from the repulsion between the oxygen and chlorine atoms after TS **2‡** acts only on these atoms, imparting a size-independent energy of E_0 to the oxygen atom, with all other atoms in the alkoxy fragment at rest. The initial momentum of the oxygen atom p_O would be defined by eq 1, where m_O is the oxygen-atom mass.

Ignoring rotations for now, the E_{O} would sometime later be partitioned into translational energy E_{trans} and vibrational energy E_{vib} . Assuming that the molecular momentum p_{mol} is conserved over short times in solution, so that $p_{\text{mol}} = p_{\text{O}}$, the E_{trans} would be defined by eq 2, where m_{alkyl} is the mass of the alkyl group in **3**. In going from **3b** to **3c**, m_{alkyl} increases from 69 amu to 167, and E_{trans} would fall by more than a factor of 2. This model shows clearly why the translational energy should decrease as the alkyl group size increases from **3b** to **3c**, leaving more energy in E_{vib} (eq 3). A parallel but more complex analysis can be made for rotational energy (see the SI). Overall, the effect in Table 1 is dramatic and has experimental consequences.

$$|p_{\text{O}}| = (2m_{\text{O}}E_{\text{O}})^{1/2} \quad (1)$$

$$E_{\text{trans}} = p_{\text{O}}^2 / 2(m_{\text{O}} + m_{\text{alkyl}}) \quad (2)$$

$$E_{\text{vib}} = E_{\text{O}} - E_{\text{trans}} \quad (3)$$

The effect of the differing excess energies in **3b** and **3c** was analyzed in two ways, statistically and with dynamic trajectories. If the excess energy in **3b** and **3c** is distributed statistically and if it is temporarily assumed that no energy is lost from **3** to the solvent on the time scale of the α -cleavage, then RRKM theory would apply. RRKM KIEs were predicted for **3b** and **3c** based on an energy distribution in each that is the sum of the canonical distribution and the excess vibrational energies derived above, including approximate SCT tunneling corrections of 1.002–1.004 (see the SI). As shown in Table 1, the RRKM KIE matches well with that observed for the α -cleavage of **3b**. The RRKM-predicted KIE for **3c** is however far too high versus experiment. Why?

Some insight into this question comes from trajectory studies. Quasiclassical direct-dynamics trajectories¹² were initiated from the area of TSs **6b[‡]** and **6c[‡]**. Each normal mode in **6b[‡]** and **6c[‡]** was given its zero-point energy (ZPE) plus a randomized excitation energy based on a Boltzmann distribution at 42 °C, with a random phase and sign for its initial velocity. The trajectories were then propagated forward and backward in time until either α -cleavage occurred to afford **4** or until **1** and ethyl radical were reformed. For both sets of trajectories, the ring-opening α -cleavage ensues within a few hundred femtoseconds after **3b/3c** has separated from the chloroethane. However, the **3c** α -cleavage occurs much more quickly; the average trajectory time starting from **6b[‡]** was 377 fs, while for **6c[‡]** the time is reduced to 259 fs. After formation of **3b** and **3c**, approximately 80 fs after **6b[‡]** and **6c[‡]**, their decay was approximately exponential (see the SI) with half-lives of 200 and 125 fs, respectively. For comparison, the RRKM half-lives would be 340 and 300 fs, respectively. Both radicals are decaying faster than expected from their energies, but with **3c** the α -cleavage is more accelerated.

Our hypothesis is that the energy in **3c** is not statistically distributed and that little energy has been distributed to the octyl chain at the time of α -cleavage. The effect of the nonstatistical distribution of the energy is that the cyclobutyl ring moiety is much “hotter” than would be expected from the available vibrational energy. In the single-trajectory study starting from **6c[‡]**, about 1 kcal/mol of the 7.2 kcal/mol of vibrational energy is passed down the octyl chain rapidly, within 100 fs, by ballistic energy transfer.¹³ Over the course of the next 300 fs, about 1 kcal/mol of additional energy makes its way into the chain. At equilibrium ~ 4.8 kcal/mol of the vibrational

energy, over half of the excess vibrational energy, would be in the alkyl chain, but **3c** never lasts long enough for either the chain or the solvent to take up much energy. Instead, the nonstatistically localized excess energy promotes the rapid α -cleavage of **3c** before equilibration can proceed.

We have previously applied a “localized RRKM” model,¹⁴ adapted from Rabinovitch,¹⁵ that assumes that the excess energy is localized within a “molecular subset” of the molecule. This process allows an approximate statistical prediction of the rate or selectivity when only a portion of a larger molecule is vibrationally excited. In the current case, our molecule subset replaces the *n*-heptyl chain of **3c** with a hydrogen atom (making it **3b**). The model is then applied simply in an RRKM calculation by replacing the frequencies of **3c** and its cleavage TS by those of **3b** and its cleavage TS. When this is done, the predicted RRKM KIE is decreased to 1.033. While this is still higher than the experimental value, the model prediction is close enough to support the general idea that the low KIE with **3c** is the result of a combination of greater excess energy in **3c** relative to **3b** and a nonstatistical distribution of that energy.

Overall, the governance of statistical rate theories in the α -cleavage of alkoxy radicals depends on the barrier for the cleavage, the amount of vibrational energy available from their formation, and the size of the system. With **3a**, the barrier is larger than vibrational energy engendered by its formation, and TST governs the α -cleavage. With **3b**, the available vibrational energy is greater than the barrier, but the system is small and RRKM theory provides a reasonable prediction of the selectivity. By increasing the size of the alkyl chain, the vibrational energy in **3c** is increased and the α -cleavage occurs faster than equilibration of the vibrational energy. The α -cleavage selectivity becomes nonstatistical, but it can be approximately rationalized using a localized statistical model.

The results here illustrate one new rule with respect to energy partitioning in reactions and how control of that partitioning can lead to nonstatistical effects in experimental observations. We expect that other rules await discovery. On a more general level, our results show how the behavior of a reactive intermediate can depend on how it is formed, and we are pursuing reactions that will make use of this history-dependence to affect selectivity.

■ ASSOCIATED CONTENT

📄 Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.6b09052.

Complete descriptions of experimental procedures, calculations, and structures (PDF)

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Notes

The authors declare no competing financial interest.

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