

Energy Read-out as a Probe of Kinetically Hidden Transition States

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Most experimental methods for the study of reaction mechanisms are directed at the composition and structure of transition states. This includes the determination of rate laws and activation parameters, the observation of substituent effects, solvent effects, and isotope effects, or most simply the consideration of a reaction's stereo- or regioselectivity. In each, the mechanistic probe gauges the nature of a transition state by the rate of passage through *that* transition state, which must be either a rate-limiting step or one that determines an observable product selectivity. For multistep mechanisms, it is typical for most of the steps to be kinetically hidden, having no experimentally observable effect on the rate or selectivity.

We have reported, however, that under certain circumstances the selectivity in a mechanistic step may be determined by the energy provided to an intermediate by the mechanistic pathway leading to that intermediate.^{1,2} In this way, a *previous* transition state labels an intermediate with an amount of energy that can be read out in the subsequent selectivity. Our hypothesis was that the read-out energy could be used to define kinetically hidden steps in mechanisms. We describe here an example of this process, and how this unique mechanistic probe implicates a different mechanism from one previously proposed.

In recent years a series of new synthetic methods have arisen that activate alcohols by their nominal conversion to an intermediate alkoxy radical or a reactively similar structure.^{3–11} The possible mechanisms for these conversions are multifold, as they may involve either direct processes, such as hydrogen atom transfer (HAT) or proton-coupled electron transfer (PCET), or indirect processes in which the alcohol is first transformed to an RO-X species. Adding to the complexity is that many of the methods are promoted by light, as this impedes the use of many ordinary kinetic probes. Reactions involving excited states, electron transfer, or PCET are also problematical to assess computationally.

The example studied here is the conversion of cycloalkanols such as 1 to ω -bromoketones (e.g., 2) mediated by phthaloyl

peroxide (PPO) and $Bu_4N^+Br^-$, with promotion by visible light (eq 1), as reported by Shi and co-workers.¹¹ The key step in



the proposed mechanism for this reaction was suggested to be HAT from the alcohol to the PPO-derived radical anion 3 (eq 2). The mechanism of the reaction was studied computationally, but aspects appeared questionable to us. These included a high calculated barrier ($\sim 24-26$ kcal/mol) for the HAT of eq 2, along with a proposed selective radical-radical recombination to afford the product 2. However, the kinetically hidden nature of these steps precluded ordinary approaches to the experimental evaluation of the proposed mechanism.

To circumvent this problem, we employed the probe alcohol **5**. When the alkoxy radical **6** derived from **5** undergoes a ring opening reaction to afford 7, molecules that contain a ¹³C at the β position of **6** have that ¹³C partitioned between the β and

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 δ positions of 7. The ratio of ¹³C in the β versus δ positions defines an intramolecular kinetic isotope effect (KIE), and we have previously found that this KIE varies depending on how **6** was formed.¹ Reactions that provide a high amount of energy to **6** on formation exhibit a low KIE in the subsequent ring opening, while reactions that afford **6** with little excess energy exhibit a much higher KIE in the ring opening. In this way, the distribution of ¹³C between the β and δ positions in the product derived from 7 could be associated both qualitatively and quantitatively with the mechanism of the step forming **6**. Our hypothesis was that the energy read-out from the KIE could be used to assign the mechanism.



The conversion of **5** to 5-bromo-2-pentanone (**8**) was carried out under the Shi PPO/Bu₄N⁺Br⁻/blue LED conditions at 25 °C. The formation of **8** is not quantitative, as a number of trace byproducts were observed in the baseline of an NMR of the crude product, but **8** appeared to be ~90% of the material formed. The relative ¹³C content at the β versus δ positions of purified samples of **8** was determined at natural abundance by NMR methodology.¹² From the ratio of ¹³C in these two positions in 12 analyses on two independent samples, a KIE of 1.048 with a 95% confidence range of 0.001 was found (see the Supporting Information).

5
$$\xrightarrow{\text{PPO}}_{\begin{array}{c}\text{Bu}_4\text{N}+\text{Br}\\\text{ClCH}_2\text{CH}_2\text{CH}_2\text{Cl}\\25 \ \circ \text{C}\end{array}}} \xrightarrow{\text{Me}}_{\begin{array}{c}\beta\\0\\0\\8\end{array}} \xrightarrow{\delta}_{\begin{array}{c}\text{Br}\\\delta\\13\text{C} \text{ at }\beta\\13\text{C} \text{ at }\delta\end{array}} = 1.048(1)$$

If **6** were thermally equilibrated before undergoing ring opening, the expected KIE would be 1.063.¹ The lower observed KIE is then indicative of excess energy in **6** on formation. Using RRKM theory and a tunneling correction as previously described, ¹ it was calculated that an excess energy of 3.5 ± 0.2 kcal/mol would give rise to the observed KIE.

We now consider whether this energy fits with the proposed HAT by phthalate radical anion 3 as in eq 2. The vibrational energy that arises initially in 6, or in any molecular fragment expelled during a reaction, may be qualitatively thought of as arising from two components. The first component is the change in the fragment's geometry as it morphs into the product geometry. A large geometry change could in principle lead to a large excess of vibrational energy in a fragment, but here the changes from 5 to 6 are minor (the largest change is a shortening of the C–O bond by 0.08 Å).

The second component of the initial vibrational energy in a leaving molecular fragment arises from the *impulse* provided by the repulsive energy surface after the transition state.¹³ As a hydrogen atom is transferred away from 5, the oxygen atom of 5 is pushed away by the hydrogen, and this impulse provides energy to 6. However, the hydrogen atom is much lighter than the oxygen atom, so it is mainly the hydrogen atom that moves. This is reflected in the motion in the transition vector, and any HAT involves a transition vector that is dominated by the motion of the hydrogen atom. The HAT then puts vibrational energy into the new bond to hydrogen, but little impulse is provided to the fragment giving up a hydrogen atom. As an

analogy, when a bus collides with a person, it is the person that is most accelerated and damaged.

Calculations support this qualitative expectation. In the case of transition structure 9^{\ddagger} for the HAT from 5 to 3 (Figure 1),



Figure 1. HAT between **5** and **3** would pass through a transition state 9^{\ddagger} involving predominantly hydrogen atom motion, with little vibrational energy imbued to the product alkoxy radical.

the motion of the hydrogen atom is 15 times greater than that of any other atom in the transition vector. To analyze the energy in 6 on formation, structure 9^{\ddagger} was used as the starting point for our modified version of the classical single-trajectory approximation of Hase.^{14,15} A series of trajectories were started from 9^{\ddagger} with no zero-point energy for the real modes and a Boltzmann-random energy in the transition vector. The trajectories were integrated forward in time, and the average translational, rotational, and vibrational components of the energy in 6 and 4 were determined as the molecules separated. Only 0.5 kcal/mol of extra vibrational energy is predicted to be formed in 6. At this energy, half of the molecules of 6 are formed with insufficient energy to overcome the ring-opening barrier. This means that $\sim 1/2$ of the reaction at a minimum should be governed by a thermal KIE of 1.063. Allowing for this, the predicted minimum KIE is 1.060. This is not consistent with the experimental observation.

From the general logic above, the large initial excess energy in **6** suggested to us that a *heavy* atom is being transferred in the mechanistic step forming **6**. This led us to consider a hypobromite radical chain process as the source of the ω bromoketones. The corresponding ring-opening reaction of cycloalkyl hypochlorites are well-known and mechanistically well studied, since the hypochlorites are often sufficiently stable for full characterization.¹⁶ By comparison, alkyl hypobromites are less stable, generally only at low temperatures in the dark. Most have been characterized solely by titrimetric and UV–visible spectrophotometric methods.^{17,18} Ring-opening reactions of putative hypobromites have afforded products analogous to **2** or **8**.¹⁹

In a hypobromite chain mechanism, a bromine atom would be abstracted from the hypobromite **10** by 7 to afford the product **8** and alkoxy radical **6**. The α -cleavage/ring opening of **6** then gives 7 which feeds back into the chain. The initial radicals to start the chain could be readily formed from the blue LED irradiation. The computational study of the key bromine-atom abstraction step was carried out in M06-2X/6-31+G** calculations using the ethyl radical as a model for 7. The abstraction step is highly exergonic (by 28.0 kcal/mol), and no potential energy barrier could be located. However, an approximate variational transition state **11**[‡] was located by a scan process that found a maximum in the free energy at a relatively early point along the abstraction path, with a ΔG^{\ddagger} of 4.3 kcal/mol above the separate reactants.



Our single-trajectory process was used again to analyze the energy in 6 when formed from 10. A series of trajectories were started from 11^{\ddagger} (R = Et), and the average translational, rotational, and vibrational components of the energy in 6 and EtBr were determined as the molecules separated. Of the 27.6 kcal/mol energy available, 16.8 kcal/mol went to the EtBr and 10.8 kcal/mol went to 6. The vibrational, rotational, and translational energies supplied to 6 were then 3.3, 4.0, and 3.5 kcal/mol, respectively.

The expected KIE for the ring opening of molecules of **6** containing 3.3 kcal/mol of excess vibrational energy was calculated using RRKM theory. This calculation intrinsically makes the assumption that intramolecular vibrational energy redistribution (IVR) is rapid but that transfer of energy to the solvent (intermolecular energy transfer, IET) is negligible. Neither assumption is likely to be perfectly correct, but this process has previously predicted KIEs for the ring opening of **6** with reasonable accuracy.¹ The RRKM-predicted KIE is then 1.050, within the experimental error of the measured value.

To explore experimentally the feasibility of the hypobromite **10** as an intermediate in the formation of **8**, **5** was subjected to a series of reaction conditions expected to form **10**, including treatment with $Br_2/NaOH$,²⁰ with Br_2/HgO ,²¹ and with Br_2/Ag_2SO_4 .¹⁷ In each case, **8** was formed as the major product. Unfortunately, attempts to observe directly the formation of **10** by NMR were unsuccessful in each of these cases, as well as in the PPO/Bu₄N⁺Br⁻/blue light conditions. In this regard it should be noted that the O–Br bond of **10** is relatively weak due to stabilization of the radical **6** by donation from the strained ring, and that the chain process is made more facile by the rapid ring opening (unlike the easily observable *t*-BuOBr).

$$5 \xrightarrow[]{0}{} Br_2, NaOH, H_2O \\ CH_2Cl_2, AcOH \\ \hline 0r \\ HgO, Br_2, H_2O \\ or \\ Ag_2SO_4, Br_2, H_2O \end{bmatrix} 8$$

Consideration of a possible mechanism for formation of the hypobromite **10** provides an interesting story. Shi and coworkers suggested that the PPO/Bu₄N⁺Br⁻/blue light conditions initially form the acyl hypobromite **12**, which was claimed to have been observed by NMR in two papers.^{11,22} Unfortunately, there was a significant error in the NMR identification. The ¹H NMR pattern of four separate aromatic peaks that was attributed to **12** included second-order coupling peaks that are unambiguously inconsistent with the ABCD coupling pattern that would be exhibited by **12**. Rather, this pattern can only arise from two separate ABB'A' spin systems. Recognizing this, we were able to replicate the Shi observations and then identify the observed NMR peaks as resulting from phthalic anhydride (**14**) and phthalate dianion (**15**), based on spiking with authentic material.



Although 12 was not observed, these experiments do not exclude the possible intermediacy of 12 or its importance in the formation of 10. To explore this issue, we irradiated PPO/ $Bu_4N^+Br^-$ in the absence of alcohol and then added the alcohol. This process resulted in no product formation, though the addition of 2-methyl-2-butene at this point leads to the formation of the alkene dibromide. These results suggest that irradiating PPO/ $Bu_4N^+Br^-$ gives rise to Br_2 , a logical byproduct from the formation of 15, but that some prior transient intermediate is responsible for the formation of the hypobromite. It is plausible that this intermediate is in fact 12. In this regard, we note that the reaction of 12 with 5 to form 13 plus 10 is downhill by 4.8 kcal/mol in M06-2X/6-31+G**/PCM (dichloroethane) calculations.

At 3.3 kcal/mol, the vibrational energy generated in **6** from the reaction of the hypobromite **10** is strikingly less than the 4.8 kcal/mol observed previously for the reaction of the corresponding hypochlorite. The heavier weight of a bromine atom compared to a chlorine atom might have suggested that a greater impulse on the incipient **6**, and so a greater vibrational energy, would arise from the hypobromite. However, the reaction of the hypobromite is less exothermic than that of the hypochlorite by ~10 kcal/mol. As a result, much less total energy is available from the formation of **6** + RBr (27.6 kcal/ mol) than from the corresponding reaction of the hypochlorite (39 kcal/mol). As a result, less energy is given to **6** and the observed isotope effects are larger.

Transition state theory relates the rate of a reaction to the free energy of a transition state, and that free energy is in turn related to the structure of the transition state. This logical interrelationship defines the nature of ordinary mechanistic probes, where rates or selectivities are used to assess transition state geometry. Compared to this comfortable framework, the discussions here are foreign. The focus is on the vibrational energy in an intermediate. At the experimental end, the vibrational energy affects a selectivity, the KIEs. At the interpretational end, the vibrational energy is related to new types of structural effects, including the mass of the atom transferred and the total energy available in going from the prior transition state to the intermediate. Although the basic ideas here are in their infancy, the results here suggest that this approach to mechanistic studies can be of considerable value. Our plan is to apply this approach to the evolving multitude of reactions of alcohols and to expand the available probe molecules for the study of a broad range of reactions.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.1c00324.

Complete descriptions of experimental and computational procedures and structures (PDF)

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Notes

The authors declare no competing financial interest.

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