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Concert along the Edge. Dynamics and the Nature of the Border between General and Specific Acid-Base Catalysis

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ABSTRACT: Reactions that involve a combination of proton transfer and heavy-atom bonding changes are normally categorized by whether the proton transfer is occurring during the rate-limiting step, as in the distinction between general and specific acid-base catalysis. The experimental and computational study here of a β -ketoacid decarboxylation shows how the distinction between the two mechanisms breaks down near its border due to the differing time scales for proton versus heavy-atom motion. Isotope effects in the decarboxylation of benzoylacetate support a transition state in which the proton transfer is complete. In quasiclassical trajectories passing through this transition state, the new O-H bond after proton transfer undergoes several vibrations before heavy-atom motion completes the reaction. The bonding changes are thus temporally separated at a “dynamic intermediate” structure that acts equivalently to an ordinary intermediate in the trajectories, including the reversal of trajectories at the intermediate when the second “step” fails, but the structure is not an energy minimum. The results define a border between mechanisms where the usual energetic definition of intermediates is not meaningful.

INTRODUCTION

Acid-base chemistry is the most common basis for catalysis. Experimental observations divide Bronsted acid-base catalysis into two forms, general catalysis and specific catalysis. General catalysis has the set interpretation that a proton is transferred in the rate-limiting step, while specific catalysis implicates reversible proton transfer prior to the rate-limiting step.¹ In broad terms, any acid-base catalyzed reaction may be viewed on a More-O’Ferrall Jencks diagram as consisting of a combination of proton motion and heavy-atom motions that accomplish the reaction or a key step in its mechanism (Figure 1). Specific acid-base catalysis is then limited to reactions in which the rate-limiting transition state (TS) is along the bottom edge of Figure 1, and all such reactions necessarily involve an intermediate. General acid-base catalysis would apply to all concerted reactions as well as those in which the proton transfer is by itself the rate-limiting step. General and specific catalysis would then normally be viewed as having transition states in separate areas of a More-O’Ferrall Jencks diagram. Using the Bronsted relation, extensive experimental efforts have been made to define the locations of transition states in general acid-base catalysis.

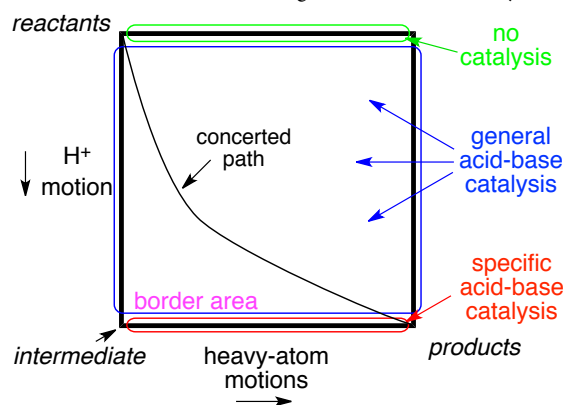


Figure 1. Generalized More-O’Ferrall Jencks diagram for acid-base catalysis.

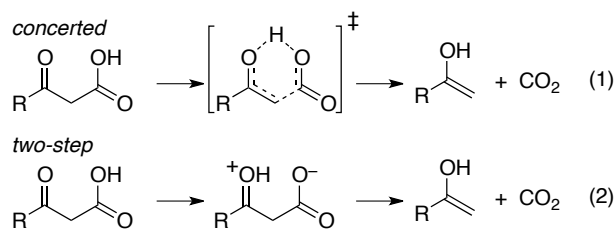
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Any mechanistic spectrum has its border areas, but the border area in the lower-left corner of Figure 1 is unusual in two ways. The first is that the usual view of the competition between general and specific catalysis eschews transition states in this area. The free-energy advantage of general catalysis is that it avoids high-energy intermediates. This is the principle behind the Jencks “libido rule.”² The free-energy advantage of specific catalysis is that it avoids the organization of the concerted process. A concerted reaction that closely approaches the intermediate corner would have neither advantage, so it is then not clear why such a reaction should ever be favored.³ The second and more fundamentally intriguing aspect of the border area in acid-base catalysis is its physics. That is, because of the difference in mass between protons and heavy atoms, their motions are on different time scales. This is reminiscent of proton-coupled electron transfer.⁴ From a classical perspective, a proton may be expected to explore its potential as the heavy-atom motion proceeds slowly. From a quantum perspective, the proton is a more delocalized particle, and its position should not be viewed as a point. This may make little difference in the understanding of mechanisms on paths through the center of Figure 1; a path defined by a simple line can still reflect the *average* position of the proton. However, the delocalization of the proton confuses the description of paths that pass near the bottom of Figure 1. In particular, what does it mean when a concerted path passes near the lower-left intermediate corner?

Here, we explore this border area between general and specific acid-base catalysis allowing for the dynamics of the proton transfer versus heavy-atom motions. The results suggest that this border area is different in character from what would be expected from the More-O’Ferrall Jencks diagram, and they provide insight into a common nature of the catalysis in this area. Our results complicate the understanding of “concert” in reactions involving a combination of heavy-atom and hydrogen motion. The distinction between specific and general catalysis in borderline mechanisms, always a matter requiring care, is ultimately less meaningful than normally supposed.

The reaction studied here is the decarboxylation of a β -ketoacid. This reaction is not acid or base catalyzed under the conditions studied, but it combines proton and heavy-atom motion in a way that is parallel to acid-base catalysis, with the advantages that the reaction is mechanistically simple and experimentally and computationally readily tractable. This made the reaction attractive for our goal of understanding the interplay of proton and heavy-atom motions. It is also attractive from a different perspective, due to its historical mechanistic ambiguity.

β -Ketoacid decarboxylation and related reactions are critical steps in both biological processes and synthetic organic sequences, while the reverse process is a key step in C_3 carbon fixation in photosynthesis. The mechanism has been studied extensively by classical means.^{5,6,7,8} A topic of debate stretching over 70 years concerned whether the decarboxylation was a concerted process in which the intramolecular proton transfer and carbon-carbon bond cleavage occurred in a single step (eq 1) or involved an initial proton transfer to afford an intermediate followed by a separate decarboxylation (eq 2).



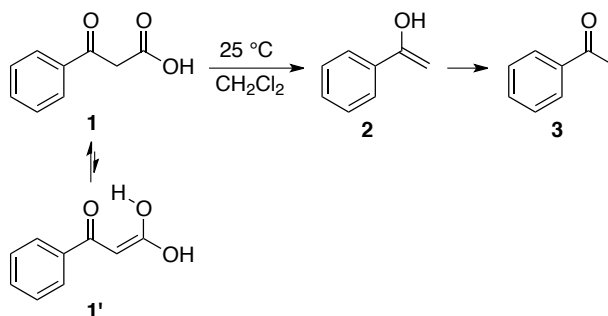
Resolving this question was complicated by many factors, including changes in observations depending on the reaction conditions or substrate, inconsistency of observations,^{6c,7} and unrecognized complications in early work. However, it was ultimately limited by the inadequacy of the classical experiments. That is, the interpretation of experimental substituent effects, isotope effects, solvent effects, etc., left much room for speculation in a borderline case. For example, the last relevant experimental study in 1975 interpreted a hydrogen / deuterium isotope effect of 1.3 ($k_{\text{H}}/k_{\text{D}}$) in decarboxylation as requiring a half-transferred but unmoving proton in a concerted TS, a conclusion that would seem highly unusual today.

Though these decarboxylations, or their reverse carboxylations, are often a key step in larger mechanisms, specific theoretical and computational studies of the decarboxylation mechanism have been rare. A qualitative theoretical study by Guthrie applying no-barrier theory favored a stepwise pathway for the decarboxylation.⁸ A gas-phase study of simple decarboxylations by Bach in 1996 found concerted TSs.⁹ For the current study, it was particularly interesting that Bach's TSs involved "essentially complete proton transfer." This places the TS near the bottom edge of Figure 1. However, the ability of even today's best computational studies including a solvent model to definitively decide between stepwise and concerted reactions in a borderline case is questionable. As will be seen, the mechanistic question is itself not as simple as the classical "stepwise or concerted" question envisions.

Our approach here is to experimentally characterize an example reaction by its kinetic isotope effects (KIEs), then carefully examine the reaction computationally in order to understand the combination of computational method and theoretical model that accounts for the experiments. We then apply dynamic trajectory studies to understand the physics that underlie the experimental observations.

RESULTS

Experimental KIEs. The clean and quantitative decarboxylation of benzoylactic acid (**1**) was chosen for study. The ^{13}C KIEs for this decarboxylation were determined at natural abundance by NMR methodology.¹⁰ Samples of **1** at a concentration of 0.05 M in CH_2Cl_2 were taken to 15.6% and 18.4% conversion at 25 °C and the reaction was quenched by rinsing with aqueous sodium bicarbonate. The product acetophenone (**3**) was then isolated in satisfactorily pure form by an extraction process and analyzed by ^{13}C NMR in comparison with product from reactions of the same batch of **1** taken to 100% conversion. The relative differences in the isotope composition of the low-conversion versus 100%-conversion samples were then calculated using the *meta* position as an internal standard, with the assumption that its isotopic fractionation in the reaction is negligible. From the changes in the relative isotope composition in the various positions and the conversions of the samples, the ^{13}C KIEs were calculated in standard ways.



The H/D KIE for this reaction was studied by absolute kinetics. Swain and coworkers had previously measured the H/D KIE for **1** and substituted analogs by following the evolution of CO_2 , but an unrecognized complication was the presence of substantial amounts of the enol **1'**. Pollack and Vitullo viewed this as compromising the Swain results, and they avoided the problem by studying the α,α -dimethyl analog of **1**. Our kinetic method directly followed the conversion of **1** and **1'** to **3** by NMR, simulating the concentration of all species. The amount of **1'** was consistently $\approx 25\%$. Because deuterated **1** is obtained by exchange, the α - CH_2 group was also deuterated. Side-by-side samples of **1** and **1-d**₃ at 0.02 M in CDCl_3 were followed by NMR and the observations were fit to a first-order decay (See the Supporting Information (SI)). Our H/D KIE of 1.35 ± 0.15 fits reasonably with Swain's 1.41 in benzene at 50 °C and Pollack and Vitullo's 1.20 in water at 47.7 °C.

The ^{13}C and H/D KIEs obtained are summarized in Figure 2. The methylene carbon between the two carbonyls shows a substantial KIE, as would be expected for a rate-limiting cleavage of a bond to this carbon. The ketonic carbonyl exhibits a small but significant normal effect, while the KIE is negligible in the remaining carbon positions. The H/D KIE is normal but it is sufficiently small that it cannot be used to distinguish between concerted and stepwise mechanisms. Qualitatively, little information is gained from these KIEs. A more quantitative and detailed interpretation will be possible with the aid of calculations.

Computational method selection. Before exploring the solution reaction of **1**, we sought to identify a computational method that would be both practical for a broad study and energetically accurate on the gas-phase energy surface. For the prediction of KIEs, it is particularly important that the energy surface be accurate in the

area of the TS. A wide range of DFT methods were explored in comparison with G3B3, G4, and CCSD(T) energies for the model decarboxylation of formylacetic acid. Our choice of M06-2X/6-311+G** calculations was based on a very close match with CCSD(T)/jun-cc-pvtz energies (within 0.05 kcal/mol) for structures along the reaction coordinate in the area of the TS for this model reaction. (See the SI.) For the decarboxylation of **1** in solution, this method was employed in combination with a PCM implicit solvent model for CH₂Cl₂.

¹³C (k_{12}/k_{13}) and ²H (k_H/k_D) KIEs

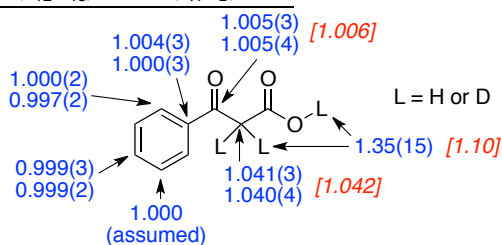
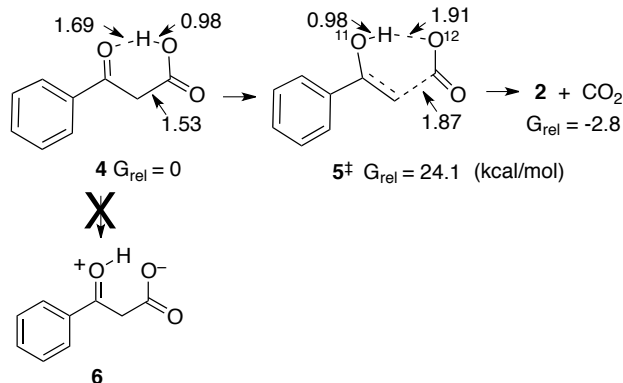


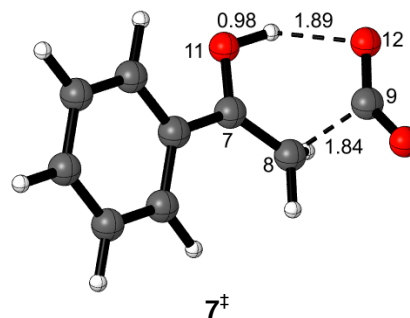
Figure 2. Experimental (blue) and CVT-SCT predicted (red, italicized in brackets) KIEs for the decarboxylation of **1** at 25 °C.

Qualitative Mechanism and the Variational Transition State. On the M06-2X/6-311+G**/PCM potential energy surface, the decarboxylation proceeds from the intramolecularly hydrogen bonded structure **4** through the saddle point **5[‡]** to the initial products **2** + CO₂. An important point for later consideration is that there is no potential energy minimum corresponding to the potential zwitterionic intermediate **6**. In this way, the calculated energy surface would be considered as corresponding to a concerted mechanism.



The canonical variational transition state (CVTS) **7[‡]** for the decarboxylation of **1** was located using GAUSSRATE / POLYRATE.^{11,12} The CVTS is somewhat earlier than the saddle point **5[‡]** (0.03 Å shorter in the breaking C⁸-C⁹ bond) due mainly to the effect of increasing entropy as the decarboxylation proceeds, but it is notable that there is no significant difference between the O¹¹-H bond length in the CVTS versus **5[‡]**. This is because the proton in **7[‡]** has been completely transferred from O¹² to O¹¹ prior to the TS. The O¹¹-H distance of 0.98 Å can be compared with the corresponding O¹²-H distance of 0.98 Å in the reactant **4**. It will be of interest below to consider in detail what this “complete” proton transfer really means, but first it is important to consider whether **7[‡]** is an accurate depiction of the experimental reaction.

The predicted rate constant for decarboxylation based on **7[‡]** including small-curvature tunneling (SCT)¹³ is $1.2 \times 10^{-5} \text{ s}^{-1}$, while the experimental rate constant is $1.7 \times 10^{-5} \text{ s}^{-1}$. The agreement between experiment and observation at this level involves a substantial degree of fortuity, but it is clearly consistent with the accuracy of **7[‡]**.



Although the calculated mechanism is concerted, the completeness of its proton transfer makes the mechanism subject to a prominent argument against a stepwise mechanism. That is, it has long been argued that the decarboxylation cannot proceed by the mechanism of eq 2 because a mechanism involving a zwitterionic intermediate should occur much faster as the solvent polarity increases. Experimentally, no such effect is observed.^{5c,14} Such a conventional argument is worded imprecisely, as the rate of reaction depends only on the TS energy versus that of the reactant, and the intermediate is technically irrelevant. However, it might be expected that a TS following a zwitterionic intermediate would also be very polar, making the reaction occur faster in polar solvents. Since **7[‡]** is structurally identical to the TS expected from the stepwise mechanism, then it too might be argued against based on the solvent observations. Calculations, however, dispose of this old argument. The calculated dipole moment of **7[‡]** is 8.35 D, while the calculated dipole moment of **4** is a nearly identical 8.40 D. With such similar polarity in the reactant versus the TS, no substantial effect of solvent polarity would be expected, in accord with observations. The low change in the dipole moment between **4** and **7[‡]** should also minimize the solvent reorganization required along the reaction coordinate, an important factor for the trajectories below.

A more detailed evaluation of **7[‡]** comes from consideration of the experimental KIEs versus predicted values. The computational prediction of the KIEs for this reaction is complicated by tunneling, by variational transition state effects, and by the involvement of tautomeric equilibria in the starting **1** and **1'**. The tunneling and TS effects on the KIEs were calculated using POLYRATE and the SCT approximation,¹³ ensuring that the path step-size was sufficiently small for numerical convergence (see the SI). Allowance for the starting material equilibria was based on a 3 : 1 ratio of **1** and **1'**, as observed by NMR. Previous observations have suggested that **1** is largely monomeric in organic solvents,^{5d} and structure **4** is the lowest-energy monomeric structure. To allow for the combination of **4** and enol **1'**, the reduced isotopic partition functions for the two components were calculated^{15,16} and their weighted average was used to adjust the POLYRATE H/D KIE. This allowance for the starting material components is expected to be incomplete based on literature observations,^{17,18} and it should be noted that this adds uncertainty to the H/D KIE prediction. The effect of the equilibria on the ¹³C KIEs was negligible.

The predicted KIEs are shown in Figure 2. The predicted H/D KIE is normal but it is slightly out of the uncertainty range of the experimental value. This discrepancy might be rationalized in a couple of ways, either based on the complications in the H/D KIE prediction described above, or based on the common observation that H/D KIEs are difficult to predict with high precision.¹⁹ However, we will consider below a more specific and interesting explanation based on the dynamics of the atomic motions. The predicted ¹³C KIEs are in each case within the uncertainty of the experi-

mental values. The striking agreement between the predicted and experimental ^{13}C KIEs supports the general accuracy of 7^\ddagger as the CVTS for the decarboxylation.

How far off could 7^\ddagger be in its geometry? We have previously described an approach to gauging the precision of measurements of TS distances using KIEs, based on the consideration of a diverse set of TSs and their associated KIEs.^{20,21} As a simplified version of this approach, we considered the KIEs expected for two alternative TSs, one for the decarboxylation of **1** in the gas phase (8^\ddagger) and one for the decarboxylation of the *p*-nitrobenzoyl-acetic acid [9^\ddagger , M06-2X/6-311+G**/PCM(CH₂Cl₂), Figure 3]. In these two cases, the zwitterionic extreme structures, **6** or its *p*-nitro analog, would be destabilized. The resulting TSs become more synchronous than 5^\ddagger / 7^\ddagger , as judged by small but significant increases in the O¹¹-H distance in the TS. For TS 8^\ddagger , the predicted KIEs are far from those observed experimentally for **1**, suggesting that the geometry of 8^\ddagger with its elongated O¹¹-H distance and short O¹²-H distance is an inaccurate depiction of the real TS. On the other hand, the KIEs predicted for 9^\ddagger are as consistent with experiment as those for 7^\ddagger . In other words, the KIEs are unable to distinguish between the geometries of 7^\ddagger versus 9^\ddagger , but they likely exclude a structure as geometrically different as 8^\ddagger .

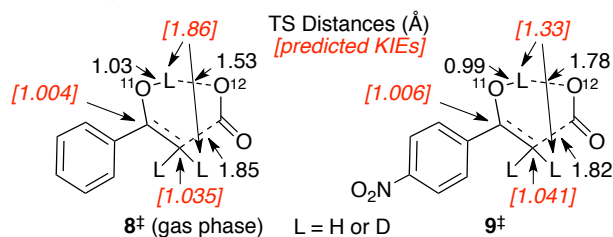


Figure 3. Geometries and predicted KIEs at 25 °C for alternative TSs, as a guide to the uncertainty in 7^\ddagger .

Trajectories. The fundamentally confusing trait of 7^\ddagger is that the proton transfer appears complete, but there is no energy minimum corresponding to **6**. This places the TS on the bottom edge of Figure 1, despite the absence of an intermediate. To gain insight into this process, structure 7^\ddagger was used as the starting point for quasi-classical direct-dynamics trajectories²² on the M06-2X/6-311+G**/PCM surface. Each normal mode in 7^\ddagger was given its zero-point energy (ZPE) plus a randomized excitation energy based on a Boltzmann distribution, along with a randomized displacement of the modes. The transition vector was treated classically and given a Boltzmann-random amount of energy. The trajectories were then propagated forward and backward in time taking 0.5 fs steps until either the decarboxylation had completed ($\text{C}^8\text{-C}^9 > 2.3 \text{ \AA}$) or **4** was reformed ($\text{O}^{12}\text{-H} < 1.0 \text{ \AA}$, $\text{C}^8\text{-C}^9 < 1.6 \text{ \AA}$). Of 83 trajectories, 59 (71%) were productive, proceeding from starting material to product. The remainder recrossed, with 10 proceeding from **4** across the TS and back to **4** and 14 proceeding from **2** + CO₂ across the TS and back to **2** + CO₂. The median time for the productive trajectories was only 65 fs.

Figure 4a shows a composite of 20 productive trajectories, plotted in three dimensions with the $\text{C}^8\text{-C}^9$ distance on the vertical axis and the $\text{O}^{12}\text{-H}$ and $\text{O}^{11}\text{-H}$ distances on the horizontal axes. Trajectories proceed along a diagonal from front-right to back-left as the proton is transferred from O¹² to O¹¹, then proceed vertically as the carbon-carbon bond breaks.

The striking feature of these trajectories is that the proton undergoes a series of O¹¹-H bond vibrations as structure **6** before pass-

ing through the transition state. This can be seen most easily from the plots of representative trajectories in Figure 4b. After the proton is transferred from O¹² to O¹¹, the O¹¹-H bond vibrates in an ordinary way for the remainder of the reaction coordinate. On average, the O¹¹-H bond undergoes 3.4 full vibrations before the CVTS. Every trajectory allows the O¹¹-H bond to vibrate at least once, because the heavy-atom motion associated with C⁸-C⁹ bond breakage simply cannot occur within the ≈ 10 fs period of the O¹¹-H vibration. Often, trajectories are prolonged in the area of **6**, with the O¹¹-H bond vibrating up to 10 times.

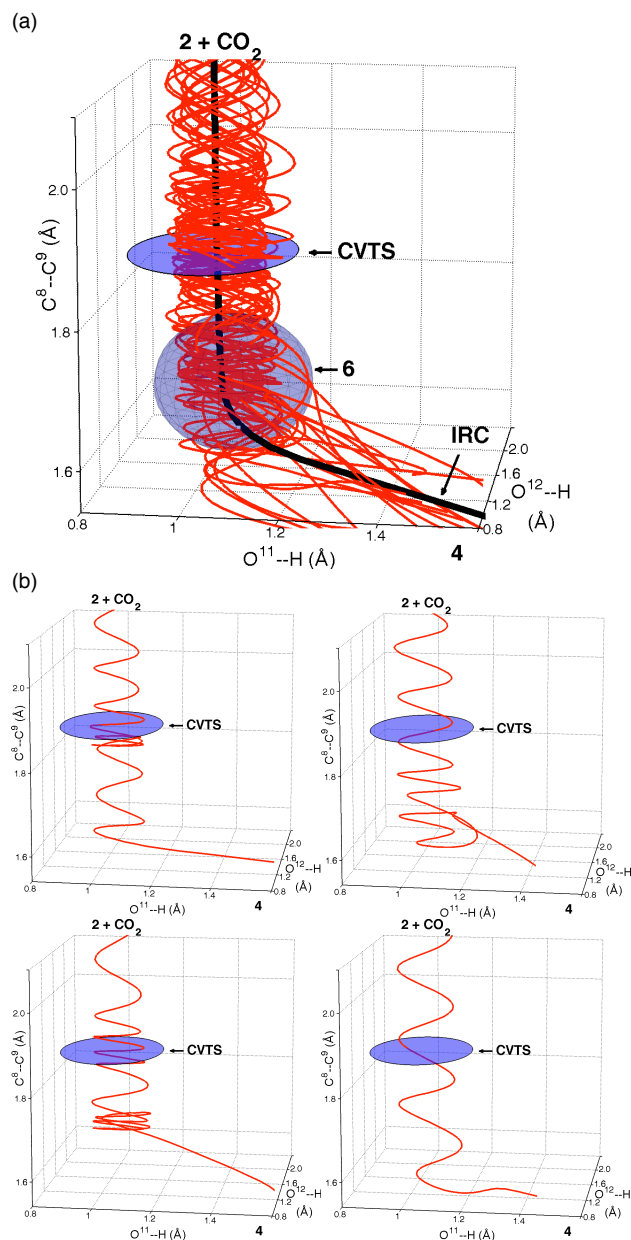


Figure 4. (a) A composite drawing of the path of 20 productive trajectories for the decarboxylation of **1** in the O¹¹-H, O¹²-H, and C⁸-C⁹ dimensions. The trajectories start from the general area of **4**, undergo proton transfer to take them into the area of **6**, and complete decarboxylation along a vertical path. (b) Typical individual trajectories show the vibrations of the O¹¹-H bond before decarboxylation.

An intermediate in a mechanism is defined by IUPAC by two characteristics, a lifetime appreciably longer than a molecular vibration and a local potential energy minimum with a depth greater

than RT .²³ Since vibrations vary in their period by over two orders of magnitude (10 to 1000 fs), the first part of the definition is nebulous. In the context of the relevant O^{11} -H motion, the exceedingly short lifetime of structures in the area of **6**, averaging ≈ 35 fs, is long enough for several vibrations. However, **6** is not a potential-energy minimum. Structure **6** then meets one criterion for an intermediate but not the other. We would suggest that such structures be referred to as “dynamic intermediates.”²⁴

Anharmonicity Effects. Transition Structures versus the Varied Path of Trajectories. The trajectories depicted in Figure 4 have the potential to be misleading in a subtle way. That is, the starting points for the trajectories are based on random displacements of normal modes from the central structure **7**[†], assuming the harmonic approximation. Because of this, such a study cannot well gauge the diversity of paths taken by actual trajectories. This problem is difficult to overcome in general. In principle one could start trajectories in an essentially unbiased way at a starting material, but this approach fails due to the long times required awaiting reaction and the limited time span of quasiclassical trajectories.

As an attempt to mitigate the issue, we initiated a series of trajectories from the area of an IRC point 0.5 bohr (in total atomic motion) past the CVTS. Most (87%) of the trajectories initiated from this area with Boltzmann-random energies and motions afford **2** + CO_2 , as would be expected. However, a portion of trajectories cross the transition state and proceed to **4**. While the starting points for these trajectories assumed harmonicity, their paths in the area of the CVTS are not restricted and reflect the anharmonicity of the energy surface. The striking observation (Figure 5) is that a portion of the trajectories take a path that is far from the IRC as it passes through the CVTS. We will describe such trajectories as “corner cutting” though of course all trajectories pass through the CVTS hypersurface. The O^{11} -H distance is extended by over 0.1 Å (the approximate classical limit for the O-H stretching mode in **7**[†]) in 27% of the trajectories, and the average O^{11} -H distance at a C-C distance corresponding to the CVTS is 1.018 Å. The longest O^{11} -H distances at the CVTS are accompanied by relatively short O^{12} -H distances, giving these trajectories a much greater degree of synchronicity than would be expected from the IRC. While most trajectories still involve complete proton transfer, with the O^{11} -H bond vibrating multiple times before decarboxylation as described above, a substantial portion of the trajectories combine both C-C and O-H motion as they pass the transition state. A similar trend is seen in trajectories started 1.5 bohr on the reactant side of the CVTS (see the SI).

This observation is, of course, a manifestation of anharmonicity in the CVTS hypersurface, and it is of interest to consider how it affects the prediction of the H/D KIE in this reaction. The reactant **4** also involves an anharmonic O-H stretching mode. It might be assumed that the errors due to anharmonicity would partially cancel when the harmonic approximation is applied to both the reactant and the TS in the KIE predictions. However, the short O^{12} -H distances in the corner-cutting trajectories suggest the importance of the O^{12} motion, which is not a contributor to the O-H stretching mode. This is a cross-term anharmonicity effect, and its impact is difficult to assess quantitatively. It seems plausible that this effect could account for the error in the predicted H/D KIE. At the least it highlights the difficulty of computationally predicting the H/D KIEs in this system.

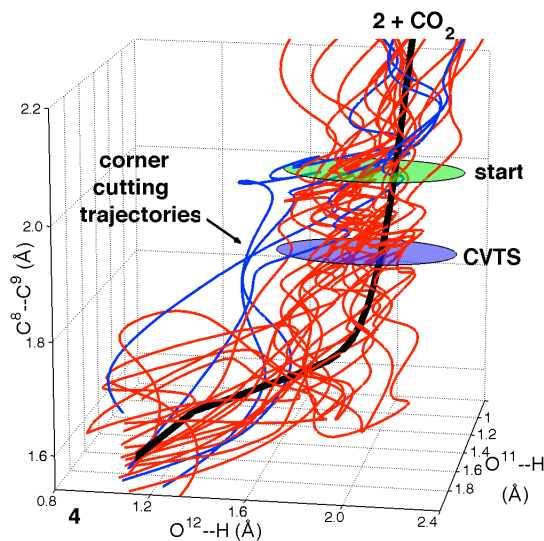


Figure 5. The paths of productive trajectories started from a position past the CVTS. The trajectories shown in blue have relatively long O^{11} -H and relatively short O^{12} -H distances in the area of the CVTS.

Deep recrossing. Transition state recrossing was seen in $\approx 30\%$ of the trajectories. One feature of the recrossing trajectories was fascinating and highlighted the peculiar nature of the mechanism. Figure 6 shows the paths of trajectories that recross the CVTS, either proceeding from reactant **4** to reactant **4** or from products **2** + CO_2 to **2** + CO_2 . The former behave in an ordinary way, passing the CVTS to only a modest extent before recrossing. Such recrossing is ubiquitously observed in trajectories, and it is often not meaningful; unreal recrossing can arise from the limitations of using the harmonic assumption in the initiation of trajectories.

The trajectories that recross in the opposite sense, however, have the unusual feature that they go far past the CVTS. These trajectories proceed to where the C^8 - C^9 bond is fully formed, with a median minimum C^8 - C^9 distance of 1.58 Å. At this point the trajectories are fully in the area of **6**, but they cannot consummate the reaction in the carboxylation direction. Why? In each case the O^{12} distance is relatively long, generally greater than 2.0 Å. As a result, the O^{12} atom is not positioned well to accept the proton. After several O^{11} -H vibrations, the trajectories return to **2** + CO_2 . In this way, the rate of the carboxylation step depends on the motion of atoms in an area of the energy surface that is far removed from the transition state. The recrossing is linked to the temporal separation of the proton-transfer and heavy-atom motions seen in the decarboxylation direction; the carboxylation reaction is abortive because the second requisite bonding change, the proton transfer, fails to occur. The reaction then acts like an ordinary stepwise mechanism in which the intermediate, here a dynamic intermediate, returns to the starting material.

This “deep recrossing,”^{25,26} seen in 17% of the trajectories, is a new and structurally distinct example of the nonstatistical recrossing that we have previously observed in reactions.²⁷ It should be noted that this recrossing is not predictable from a normal statistical analysis of the free energy surface in the area of the CVTS, and the CVTS would not be optimally placed to minimize recrossing. It is also of note that the conversion of **2** + CO_2 to **4** is a model for the ribulose-1,5-bisphosphate carboxylase catalyzed carbon fixation in photosynthesis. It may be of future interest to consider whether similar recrossing affects such enzymatic reactions.

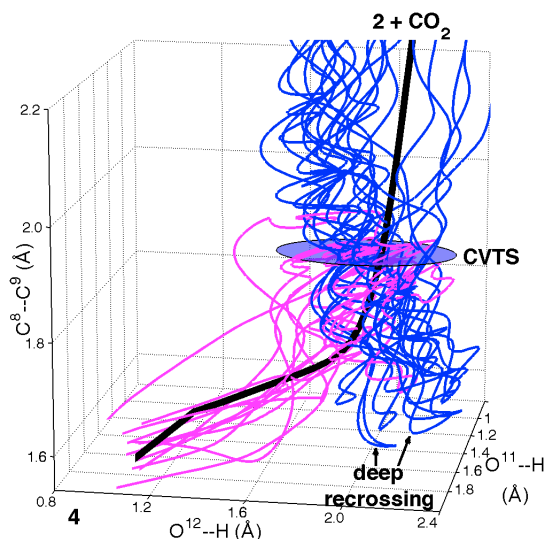


Figure 6. The paths of recrossing trajectories started from the CVTS. The magenta trajectories pass from **4** across the CVTS and return to **4**, while the blue trajectories start from **2 + CO₂**, cross the CVTS, then return to **2 + CO₂**.

DISCUSSION

We first consider whether the trajectory results are sufficiently accurate for reliable analysis. This devolves into two questions: is 7^\ddagger accurate, and are the quasiclassical trajectories a reasonable representation of the quantum-mechanical real reaction. For the first question, the accuracy of 7^\ddagger is fully supported by the comparison of predicted and experimental ^{13}C KIEs but not so well supported by the comparison for the H/D KIE. The anharmonicity effects in the trajectory observations suggest one possible explanation for the discrepancy. Another possibility is that the actual transition state more closely resembles 9^\ddagger than 7^\ddagger , recognizing that the KIEs predicted for 9^\ddagger match essentially perfectly with experiment. Since the structures of 9^\ddagger and 7^\ddagger are so similar anyway, we view 7^\ddagger as sufficiently accurate. The second question regarding the quasiclassical trajectories arises because the trajectory motions are unavoidably classical. The ability of quasiclassical trajectories to mimic quantum-mechanical features of systems, including some subtle features, has long been recognized,²⁸ with the main limitation being the leakage of ZPE from the vibrational modes.²⁹ The short duration of the trajectories here should minimize the effect of ZPE redistribution.

The trajectories then provide a view of the β -ketoacid decarboxylation reaction that differs intriguingly from the normal understanding of a concerted process. In these trajectories, the proton transfer occurs fully and the resulting structure, neither a potential energy nor free energy minimum, has the opportunity to undergo several O-H bond vibrations before and while the heavy-atom motions proceed. It is well understood in chemistry that concerted multibond reactions often involve highly asynchronous bonding changes.³⁰ However, the normal understanding of asynchronous concerted reactions is that the bonding changes overlap. If otherwise, why should the reaction be concerted at all? This view fails to take into account the differing physics of the heavy-atom versus proton motions. Because of the uneven contribution of the motions, their separation is arguably intrinsic and unavoidable whenever the reaction is highly asynchronous.

It is useful to view the motion along a reaction coordinate as involving a *swath*, rather than a point, in the proton-motion dimension.³¹ The decarboxylation of β -ketoacids may then be understood

using the More-O'Ferrall Jencks diagram of Figure 7. As the reaction coordinate progresses, the proton wavefunction is transferred from O^{12} to O^{11} , and the swath of the delocalized proton reaches and exceeds the equilibrium position corresponding to complete transfer, defined by the bottom edge of the More-O'Ferrall Jencks diagram. This is just the quantum mechanical description; in quasiclassical terms, one would say that the proton is fully transferred then undergoes a series of vibrations before the TS. In either description, there is no particular direction for motion of the proton as the molecular geometry passes the TS. The proton is certainly being transferred in the single kinetic step of the reaction, but in no meaningful sense is that transfer associated with the transition state. The transition state is not well described by either of the conventional labels "concerted" or "stepwise."

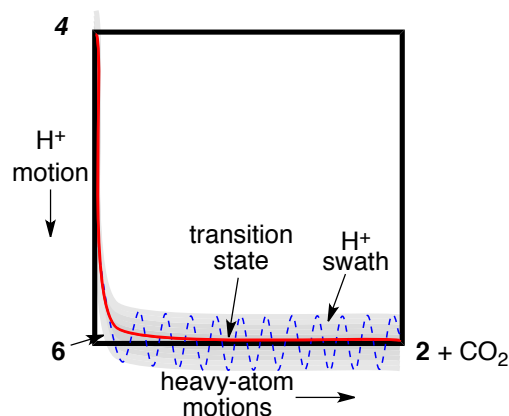


Figure 7. More-O'Ferrall Jencks depiction of β -ketoacid decarboxylation, allowing for the delocalization of the proton.

This has experimental consequences. Since a proton is not being transferred in the TS, the reaction does not exhibit a primary H/D KIE. Instead, its KIE is best understood as a secondary and essentially equilibrium KIE, reflecting the difference in ZPE between the starting material and that of the *fully-bound* potential energy well of the proton at the TS. As a result, the H/D KIE for the decarboxylation is small, though it need not trend toward precise unity.

A longstanding observation in general acid-base catalysis is that H/D KIEs are at a maximum when the proton transfer is approximately symmetrical, and they then decline when the transition state is more product-like or reactant-like.^{32,33} The qualitative understanding of this observation, due to Westheimer,³² is that the KIE is a function of the ZPE associated with symmetric and antisymmetric stretches at the TS (Figure 8). The antisymmetric stretch has an imaginary frequency (\neq) so it does not contribute to the ZPE, while the symmetric stretch is real but will involve minimal H/D motion when the TS is symmetrical, so its ZPE will not change from H to D. For an unsymmetrical product-like TS, the approximately symmetric mode gains ZPE with the involvement of proton motion. The KIE goes down but the reaction coordinate still involves substantial hydrogen motion.

Here, however, the antisymmetric motion has completed the proton transfer and it can no longer be the reaction coordinate. Instead, the reaction coordinate involves separation of the fragments, and it most closely resembles the original *symmetric* motion. This is what happens as the reaction path on the More-O'Ferrall Jencks diagram nears the bottom edge.³⁴ The geometry and atomic motion of the TS are indistinguishable from that for a stepwise reaction with specific acid catalysis. Because the TSs are indistinguishable, the KIEs for the two mechanisms would be identical. It

matters not whether there is a energy minimum prior to the TS because this in itself does not impact experimental observations or, apparently, the qualitative behavior of trajectories.

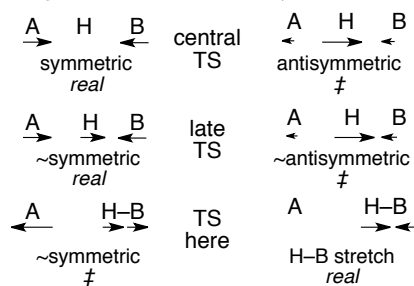


Figure 8. Changes in the normal modes as the transition state gets later for general acid-base reaction.

The involvement of an intermediate in acid-base catalysis would still be recognizable if it is sufficiently long-lived to be diffusible. When a reaction involves a long-lived intermediate after a proton transfer, the concentration of that intermediate must reflect the overall acidity of the medium. The reaction rate then does not depend on the concentration of acid or base catalysts at a constant buffered medium acidity. This is the classic test for general versus specific acid-base catalysis. However, it should be recognized that in a great many cases, such as intramolecular catalysis and enzymatic catalysis, this test cannot be applied. The observation of a low or inverse H/D KIE by itself cannot establish that there is an intermediate. The same would be true of the results of substituent effect studies.

CONCLUSIONS

From the perspective that there is no *stable* intermediate along the reaction coordinate, the decarboxylation of the β -ketoacid **1** is certainly a concerted reaction. However, the proton-transfer and heavy-atom bonding changes are separated in time, so separated that a species along the reaction coordinate can undergo many bond vibrations before the heavy-atom motion can complete the reaction. This is unlike the ordinary asynchrony seen in most concerted multibond reactions, where one bonding change leads but overlaps with another. The bonding-change overlap with ordinary asynchrony is detectable experimentally, for example in asynchronous Diels-Alder reactions.³⁵

Here, it is not clear to us that any experimental observation can even in principle distinguish the concerted decarboxylation from a stepwise process. The reaction dynamics in fact emulate a stepwise mechanism, despite their short duration. This is perhaps seen most poignantly in the deep recrossing seen for trajectories passing the transition state in the carboxylation direction. The carboxylation “step” occurs but the structure obtained, a dynamic intermediate in the area of **6**, reverts to starting material when the second proton transfer “step” fails. The proton transfer is barrierless, but it takes time, and in the mean time the trajectory recrosses. A barrierless stage of a concerted reaction is having the same effect here as would a barrierless step in a stepwise mechanism.

On the border between general and specific acid-base catalysis, the delocalization of protons (or, quasiclassically, their fast motion) enforces an overlap in their mechanisms. Experimental observations such as the H/D KIE then become unable to distinguish whether there is an intermediate. However, this is not just a matter of the isotope effect decreasing because a late TS has a nearly complete proton transfer, as in the ideas of Westheimer. Rather, the proton transfer is entirely complete and the dynamic intermediate

undergoes a series of relevant bond vibrations, as would any intermediate, and it can proceed from this structure in either forward or backward directions, as true of any intermediate. The experimental distinction fails, not because two mechanisms would give similar observations, but because there is no experiment-impacting difference in the mechanisms.

ASSOCIATED CONTENT

Supporting Information

Complete descriptions of experimental procedures, calculations, and structures. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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Notes

The authors declare no competing financial interest.

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