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Perspective

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Tunneling Control of Chemical Reactions: The Third Reactivity Paradigm

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ABSTRACT: This Perspective describes the emergence of tunneling control as a new reactivity paradigm in chemistry. The term denotes a tunneling reaction that passes through a high but narrow potential energy barrier, leading to formation of a product that would be disfavored if the reaction proceeded by passage over kinetic barriers rather than through them. This reactivity paradigm should be considered along with thermodynamic and kinetic control as a factor that can determine which of two or more possible products is likely to be the one obtained. Tunneling control is a concept that can provide a deep and detailed understanding of a variety of reactions that undergo facile (and possibly unrecognized) tunneling.

Tunneling is a fundamental quantum mechanical property that enables particles to overcome potential energy barriers despite a lack of energy to surmount them. This effect is directly related to the wave nature of particles, allowing them to penetrate their surrounding potential energy barriers. As a consequence, quantum mechanical tunneling (QMT) is particularly relevant when the de Broglie wavelength of the particle is on the order of the barrier width[1] of the associated barrier. In chemical reactions, this is almost always the case for electrons (the basis for tunneling microscopy and many other techniques) and common for the transfer of hydrogen or hydride atoms and protons. There are several examples for QMT involving atoms heavier than hydrogen, and these naturally appear when the barriers are very narrow. QMT is neither a new nor an uncommon phenomenon in chemistry and biology.[2] Quite the contrary: when H-atom, proton, or hydride transfers (or that of one of their isotopologues) are part of the rate-limiting step of a reaction, QMT must nearly always be invoked to compute accurate rate constants.[3] There is a multitude of experimental examples in enzymatic catalysis[4] (not without criticism[5]), sigmatropic rearrangements,[6] radical abstractions,[7] eliminations,[8] organometallic reactions,[9] and, in particular, the reactions of carbenes[10] as well as, just recently, nitrenes.[11] With regard to H-tunneling, we are now at a point where the "expectation has changed from being surprised to see the dominance of tunneling in hydrogen transfer to where we would be very surprised if we did not see it."[12]

What is new is the manifestation that tunneling is not merely a way to account for chemical reaction rates that are faster than anticipated (based on classic transition-state theory) but that tunneling may be *the* decisive factor for the *selectivity* of a chemical system. Furthermore, there are situations where no reaction is expected because of insufficient total energy. Yet, the starting material is depleted only on the basis of a tunneling reaction for which the most likely product cannot readily be predicted without full consideration of the shape of the underlying potential energy surface (PES).[10,13a−c] These realizations have only surfaced in the past few years, but they appear to be at work in many more cases than anticipated.

The present Perspective is not concerned about the theory of tunneling, as there are excellent recent reviews on the topic.[12,14a−e] Rather, we present and discuss the manifestations and consequences of *selective* tunneling in (organic) chemical reactions and why it is important to recognize this as a general and relevant phenomenon, even for chemical synthesis.

Tunneling often is attributed to Gamow for his early work related to the α-decay of atomic nuclei in 1928, which he called "artificial disintegration".[15] However, in 1927, Hund already discussed—with a great sense of chemical relevance—the enantiomerization of molecules and noted that enantiomers can principally be mutually interconverted through a quantum mechanical mechanism that does not require an over-the-barrier process: "Dem Übergang aus der einen Anordnung in das Spiegelbild entspricht eine Frequenz" (the transition of an [atomic] arrangement into its mirror image relates to a frequency).[16] Hund excluded such enantiomerizations as he estimated the time scales for such interconversions of chiral molecules to be in the range of geological ages, but he had clearly recognized tunneling as an important phenomenon for chemistry. The idea of a frequency associated with a tunneling probability was picked up again by R. P. Bell in his groundbreaking and practically very useful formulation of the tunneling effect.[17] He defined the corresponding frequency as imaginary because it disappears as the energy increases along a one-dimensional reaction coordinate.

More importantly, kinetic data of several chemical reactions that were often not backed by the congruent development of theory would now be rationalized through tunneling processes. Certainly one of the first examples is the very fast fluorination of hydrocarbons at very low temperatures by H. Moissan and J. Dewar that was reported in 1903.[18] Similarly, Bodenstein elaborated on the fast oxidation of nitric oxide (overall $2NO + O_2 \rightarrow 2NO_2$) in 1918.[19] This reaction follows rare third-order kinetics and is characterized by little temperature dependence, with the reaction being somewhat faster at lower temperatures; this was the first example of such an unusual temperature dependence. Only very much later (1976), Goldanskii interpreted these examples as the earliest hints at tunneling reactions.[20] These and other findings culminated in the realization that tunneling can be an important factor in chemical kinetics with the early work of Bourgin[21] in 1929,

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Roginsky and Rosenkewitsch[22] in 1930, and the seminal contributions of Bell[23] in 1933–1937.[3,24] The actual term "tunneling" was used for the first time in chemistry, at least to the best of our knowledge, by Wigner in 1932.[25]

Although H-atom tunneling is strictly a quantum phenomenon, this is often disguised, for instance, through the absence of a negative temperature dependence. Hence, H-atom tunneling has often been considered merely as a perturbation of transition-state theory.[23] McKinnon and Hurd have criticized[26] the view of tunneling being just a "correction" to classic behavior,[13a] as originally formulated by Wigner.[25] There are multiple examples that the full quantum nature of atom tunneling has to be taken into account, in particular also for biological systems,[27] in which it is also highly prevalent.[4b,28]

■ WHY TUNNELING OFTEN IS NOT CONSIDERED

In his seminal work on the automerization of cyclobutadiene in the 1980s, Carpenter cunningly starts with the statement that "It is probably fair to say that many organic chemists view the concept of tunneling, even of hydrogen atoms, with some skepticism,"[13c] a situation that, at least in our subjective view, has not changed very much. Bell wrote already in 1933 that "reaction processes have been considered as taking place according to the laws of classical mechanics, quantum-mechanical theory being only employed in calculating interatomic forces,"[3] and one wonders why this statement often still is very true, in particular when (organic) reaction mechanisms are considered. He goes on to acknowledge that effects similar to—and solely based on quantum mechanics—"radioactive disintegration" (*vide supra*) are "essential for the true explanation of chemical processes, [...] where it is well established that classical considerations are unable to explain the phenomena observed." Bell is quite firm in his conclusions when he writes that "a quantum-mechanical treatment is necessary for any reaction involving the motion of a hydrogen atom or proton". Are we, some 85 years later, doing that yet? As noted above, QMT becomes relevant when the de Broglie wavelength of a particle is of similar dimensions as the width of the potential energy barrier for the reaction under consideration. Do we routinely consider barrier widths when we draw PESs or teach reaction mechanisms? PESs are typically drawn with careful attention to the relative energies of all species involved (proper ordering along the ordinate), but along the abscissa, we generally fit it to the width of the paper. So why is the barrier width generally not considered, or in other words, for which reaction types are barrier widths on the same "length" scale as the energy of the resting mass of the tunneling atom or group?

It is rather odd that quantum mechanics is appreciated on the one hand in the sense that reaction barriers originate from the fact that electrons experience exchange repulsion,[29] while on the other hand the notion of tunneling as a closely associated phenomenon originating from a quantum-mechanical treatment of a particle in a box with finite walls is largely neglected.[20] An obvious reason may be that we, as humans, live in a classical world where quantum phenomena without analogs such as a hard-sphere model in the case of repulsion do not manifest themselves to the unheeding. Hence, it is no surprise that we pay much attention to the energy input into a system because we are familiar with this *sine qua non* condition for any (re)activity. Tunneling through a barrier is at odds with our daily experience, even though we all know that it is an undisputable consequence of the quantum nature of particles, namely that they have a finite probability to appear "on the other side of the wall" as long as the walls are not infinitely high. Still, the quantum nature of matter is very natural for physicists, and this may be telling us something on how we describe, view, and advance our science. It should begin by including quantum phenomena in introductory textbooks, where they are, at least in organic chemistry, blatantly absent. To put this oversight in words similar to those used much earlier by Frank Weinhold in a different context: "When will chemistry textbooks begin to serve as aids, rather than barriers, to this enriched quantum-mechanical perspective?"[30]

Let us return to the seductively beautiful and useful depiction of PESs (Figure 1), which essentially captures most of chemistry, especially the notion of kinetic (reaction to the product with the lowest barrier) vs thermodynamic (reaction to the thermodynamically most stable product) control. Who has drawn such a scheme for the first time, and why are arrows indicating tunneling not commonplace? One might naturally think of Eyring[31] or Evans and Polanyi,[32] but these giants of chemical reaction rate theory have never published such a picture. They did invoke the notion of tunneling by stating, "Tunneling may occasionally play some role in the motion [of nuclei]" (Eyring),[31] and, more forcefully, "For light masses, such as hydrogen and deuterium, the statistical probability must be calculated according to the principles outlined by Wigner, which will result in the appearance of tunnelling effects" (Evans and Polanyi).[32] To the best of our knowledge, it was Woodward and Baer who drew such a picture to convey the selectivity of a common Diels–Alder reaction that kinetically favors the *endo*-product, while the *exo*-product is the more stable one: "the *endo* isomer will pass relatively easily over the same (low) barrier, while the *exo* compound is stabilized by the higher barrier over which it must pass during the dissociation process. The situation is symbolized in Fig. 1, and is not an unfamiliar one in organic chemistry."[33] The tunneling arrows were left out in Figure 1 in their paper because light atoms are not involved in the key mechanistic steps. It may well be that the notion of tunneling was largely forgotten henceforth when drawing PESs describing reaction mechanisms because of the relation to this original paper.

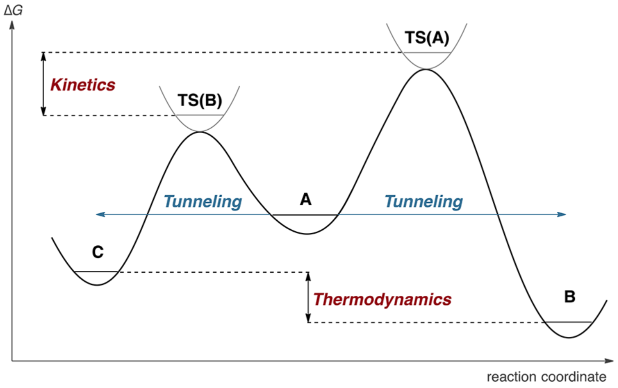

Figure 1. Standard potential energy hypersurface exemplifying kinetic (to product **C**) vs thermodynamic control (to product **B**) and the notion of tunneling through barriers of different heights and widths. For simplification, the transition-state potentials are not drawn perpendicular to the PES.

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■ EMERGENCE OF TUNNELING CONTROL

We have deliberately drawn two "tunneling arrows" in Figure 1 because when we began our tunneling studies, we saw no reason why one would assume that tunneling is possible in one direction (toward either the kinetic or the thermodynamic product) only. Yet, it turned out at the time that there was no documented example of a tunneling reaction in the thermodynamic direction of a given transformation. As noted above, tunneling was by and large considered as a correction to the rate of a reaction into the kinetic direction. As the tunneling probability depends to different degrees on the mass of the moving particle, the barrier height, and the barrier width, we reckoned that there may well be circumstances where a narrow but high barrier could be overcome through tunneling, thereby leading to the thermodynamic product. This is not a trivial issue because starting from **A**, this opens a second "choice" for the molecule that either coincides or overrides kinetic or thermodynamic control, a principle that most of us take for granted. In 2011, we identified a molecule for which this indeed was the case: methylhydroxycarbene.[34]

It should be clear from visual inspection of Figure 2 that, although the PES is properly drawn with respect to barrier heights *and* widths, it is not obvious how the molecule is going to react at low temperature. We had trapped methylhydroxycarbene in noble gas matrices at temperatures of around 10 K. Given the PES shape and large activation enthalpies above, methylhydroxycarbene should *not* react at all because the barriers surrounding it are too high to be overcome at this temperature. Still, we observed a smooth first-order reaction with a half-life τ of about 1 h, a transformation that is largely temperature and matrix material independent.[34] This finding and the fact that the OD-deuterated methylhydroxycarbene does not show this reactivity led to the conclusion that the reaction exclusively occurs through a tunneling mechanism. But what direction would the observed reaction take? Both reaction products result from [1,2]H-shifts, either from the methyl group to the carbene carbon to give vinyl alcohol, the kinetic product, or from the OH group to give acetaldehyde. Both reactions are highly exothermic. We are dragging this out because, from looking at the computed PES, it is *not* at all clear what should happen. The OH bond is the strongest bond in the system—would it break? It does! The only product observed (in the dark) in the unimolecular rearrangement of methylhydroxycarbene is indeed acetaldehyde. This is a clear-cut case where width (**a** is "shorter" than **b**) trumps barrier height,[36] leading to the thermodynamic product. As tunneling thereby controls the outcome entirely, favoring at the given temperature the product that is associated with the higher barrier, we termed this *tunneling control.*[34] The fact that narrow yet high barriers can be involved in tunneling reactions was expressed first by Wigner.[25] This *width trumps height* principle was emphasized by Carpenter in his seminal work on the automerization of cyclobutadiene through carbon tunneling (perhaps better described as tunneling of the entire C−H moiety).[13c,36]

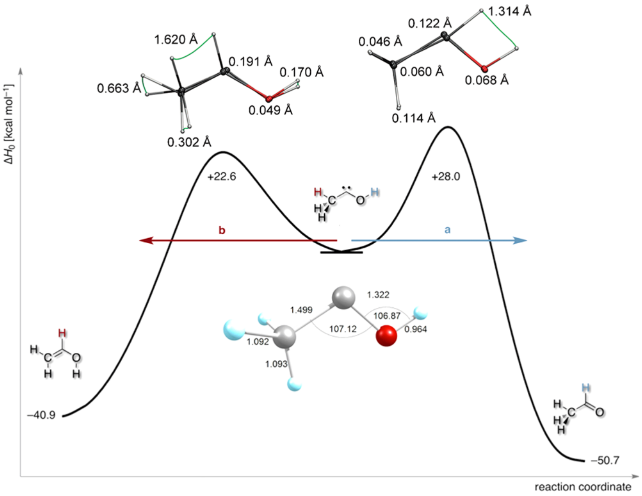

Figure 2. Computed potential energy surface of methylhydroxycarbene (middle: carbon = gray, oxygen = red, hydrogens = light blue) and tunneling paths **a** and **b** to the thermodynamic product acetaldehyde (right) or the kinetic product vinyl alcohol (left). The paths are intrinsic reaction coordinates that depict the proper heights *and* widths of the barriers for a fair visual assessment of the potential reactivity. Focal point energies are extrapolated to fully account for electron correlation and an infinitely large basis set using AE-CCSD(T)/cc-pCVQZ geometries. Parts of the figure are reproduced with permission from ref 34. Copyright 2011 American Association for the Advancement of Science. The top two structures with the green paths are reproduced with permission from ref 35. Copyright 2013 John Wiley & Sons, Inc.

The one-dimensional treatment of PESs in the context of tunneling reactions as employed here often is a reasonable approximation because there is a well-defined path for which the activation energy is the smallest for a given reaction,[3] even though the reaction coordinate is not globally but often locally separable.[12] This approach, however, becomes questionable when the de Broglie wavelength for the tunneling atom is large compared to the barrier width of the PES around the saddlepoint.[37] As it is rather difficult to "make an educated guess" for the barrier width (as opposed to the barrier heights), it is a case-by-case decision whether the one-dimensional treatment is sufficient. Only comparisons of experiment and theory can shed light on a tunneling process and its proper description. As particle positions cannot be determined exactly in quantum mechanics, the notion of a path of a shifting particle (in our case a H-atom) is not rigorous but useful for the interpretation of the experimental results. In the case of methylhydroxycarbene, a multi-dimensional instanton approach was also employed to describe the tunneling path, and the half-life τ is essentially the same.[35] The actual instanton tunneling paths (i.e., the "movement" of the migrating H-atom) are depicted in Figure 2 as green lines, showing that the preferred reaction is associated with the much shorter path length (1.314 Å) of the shifting H atom from the hydroxyl group compared to the path that involves first methyl rotation and then the shift (1.620 Å) to give vinyl alcohol. The excellent agreement of the one-dimensional treatment with this more elaborate approach and the success in reproducing the half-lives of many other tunneling reactions provide confidence in the applicability of this approach. Furthermore, the one-dimensional approach lends itself to actually correlating the actual path length with the distance the tunneling atom or group has to move, thereby allowing some qualitative predictions. As shown in Figure 2, one may have foreseen the predominance of the reaction to acetaldehyde because the "traveling distance" of the migrating H-atom in the [1,2]shift is about 0.3 Å shorter than in the competing reaction. Indeed, when paths lengthen due to atom substitution leading to longer bond distances, the tunneling half-lives react very sensitively. For example, while parent hydroxycarbene (H−C−OH) has a half-live of about 2 h, its sulfur congener mercapto- (H−C−SH) and selenocarbene (H−C−SeH) have computed [at CCSDT(Q)/aug-cc-pCV5Z] half-lives of several months.[38]

■ WIDTH TRUMPS HEIGHT: TUNNELING CONTROL AT WORK

Arguably the first example of tunneling control (albeit not named as such) is probably Zuev and Sheridan's reaction of *tert*-butylchlorocarbene in an N_2 matrix at 11 K (Figure 3).[39]

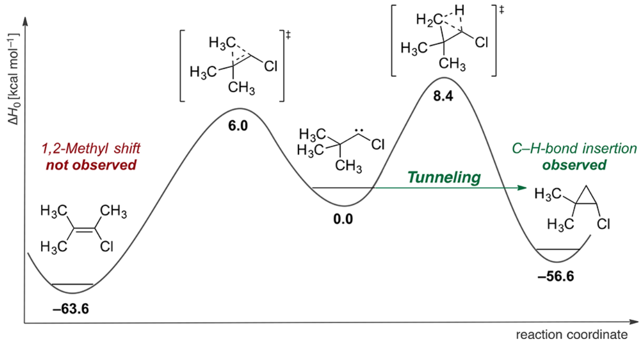

Figure 3. M06-2X/cc-pVDZ + ZPVE potential energy surface of *tert*-butylchlorocarbene (center) and its tunneling-controlled reaction to dimethylchlorocyclopropane (the tunneling product) under the higher but narrower barrier.

How could the formation of dimethylchlorocyclopropane be rationalized on the basis of kinetic and thermodynamic control alone? It is the thermodynamically less stable product whose reaction from the starting material is also accompanied by the higher barrier: it cannot be made by "classic means"! As it does form in the reaction of *tert*-butylchlorocarbene, it must be true (that there is a path to its formation), and this has been rationalized on the basis of a facile tunneling process. Furthermore, one must conclude that the barrier width for the observed C−H-bond insertion is significantly smaller than that for the unobserved [1,2]-methyl shift. Indeed, dimethylchlorocyclopropane can *only* form from tunneling from the carbene precursor, not under thermodynamic nor kinetic control. Dimethylchlorocyclopropane should therefore be termed a *tunneling product*.[40]

Methylhydroxycarbene is not a singular case in the new family of hydroxycarbenes, a long-elusive class of molecules (Figure 4).[41] Indeed, we found tunneling control to prevail for *tert*-butyl-,[42] phenyl-,[43] cyclopropyl-,[44] and trifluoromethylhydroxycarbene[45] by giving the thermodynamic products from [1,2]H-shift tunneling reactions of large but narrow barriers similar to the depiction of Figure 2. It is comforting to see that the tunneling half-lives correlate well with the stereoelectronic properties of the R group and that they very sensitively depend on the absolute barrier height (assuming that the all barriers have very similar overall shapes). Also, as soon as the carbene carbon is stabilized by another π-donor heteroatom (N or O), tunneling is very slow and not observable at laboratory time scales.[46] This provides some predictive power as to when to expect tunneling control to be operative within a series of closely related starting materials.[47] This conclusion is also well supported by the stereoelectronic effects[48] on the tunneling rotamerizations of carboxylic acids.[49]

Tunneling control has been predicted computationally at the B3LYP/6-31G(d,p) level of theory utilizing the canonical variatonal transition state theory (CVT) and small curvature tunneling (SCT) approaches[50] for other carbene reactions as well as tunneling calculations. A particularly intricate example of hydrogen vs carbon tunneling is given by the competing hydrogen vs CH-group shift reactions in noradamantyl methyl carbene (Figure 5). As tunneling control prevails at temperatures below 20 K, leading to vinyl noradamantane owing to the lighter mass of the migrating atom, carbon tunneling takes over at higher temperatures. It should be noted in this context

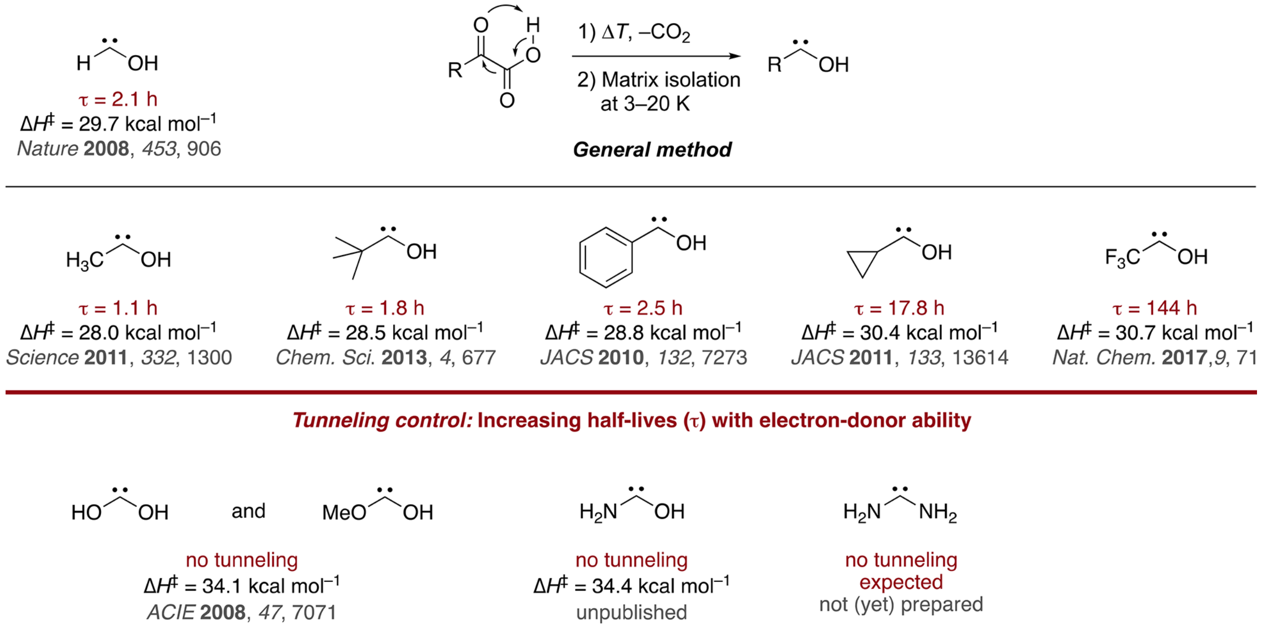

Figure 4. Novel family of hydroxycarbenes with HCOH as the parent (top left) and the general way of preparation through thermal extrusion of CO_2 from α-ketocarboxylic acids. Middle: tunneling half-lives τ and [1,2]H-shift barriers for the associated tunneling process computed at the coupled cluster level of theory with at least triple-ζ basis sets. Bottom: related diheteroatom-substituted carbenes that do not show tunneling.

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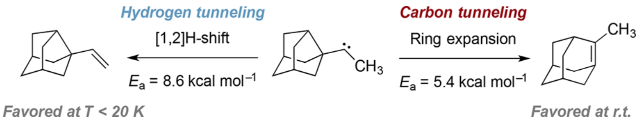

Figure 5. Computational predictions of the tunneling-controlled reactivity of noradamantyl methyl carbene via hydrogen and CH-group tunneling. Activation barriers at B3LYP/6-31G(d,p).

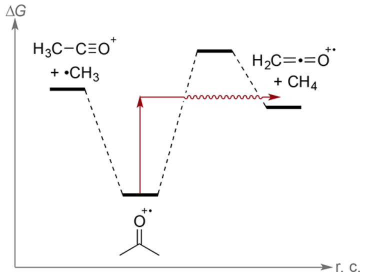

Figure 6. Dissociation of the acetone radical cation and its branching to the acetyl cation and the methyl radical (left) or the ketene radical cation and methane (right). Internal energy of 19−24 kcal mol^{-1}.

that there also is vibrationally (or thermally[51]) assisted[52] (or activated[6f]) tunneling (VAT) when this process occurs from vibrationally excited states. In the case of the reactions depicted in Figure 5,[53] there is slow deep tunneling initially, which accelerates quickly upon raising the temperature. This leads to vibrational excitation of the low-energy C−C scaffold modes in contrast to the higher energy C−H modes. Unlike ground-state tunneling that occurs from the zero-point vibrational energy level, this requires thermal activation, corresponding to the vibrational energy spacing. Note, however, that VAT is typically not so important for tunneling-controlled reactions (for a notable exception see Figure 6, *vide infra*), as all examples we currently know have stiff, high-energy reactive modes that are activated only at very high temperatures, when other competing (thermal) pathways have already become more important through thermal activation. These competing reactions emphasize the sensitivity of the reactivity to barrier heights, widths, and mass of the tunneling particle or group,[53] as well as the spacing of the vibrational energy levels.

There are more examples from both the older and very recent literature alluding to the notion of the barrier shape being essential for understanding chemical reactivity involving tunneling. When studying the large H/D kinetic isotope effects (KIE = 10−24) in the pyridine base-catalyzed iodination of 2-nitropropane in aqueous *tert*-butyl alcohol, Funderburk and Lewis noticed a rather small pre-exponential Arrhenius factor, indicative of a tunneling process.[54] They made an important and counterintuitive connection between steric hindrance and tunneling. As sterically crowded transition structures experience high steric compression, small changes along the reaction coordinate result in large changes in potential energy. In other words: strain leads to "stiff" and hence narrow barriers, thereby more readily allowing for a tunneling process to occur. The authors close with noting that "It seems reasonable that slow sterically hindered hydrogen transfer reactions in other cases will also show extremely large isotope effects, and that tunneling will prove to be more common than was believed."[53] This analysis was supported by Ingold et al. through the analysis of intramolecular hydrogen-atom-transfer reactions from sterically crowded phenyl radicals to their aliphatic side chains.[7] Apart from a masterful outline of the four criteria to recognize a tunneling process (large KIE,[55] nonlinear Arrhenius plot, large differences in the activation energies and the pre-exponential factors for H and for D transfer), Ingold et al. conclude in a similar vein that it is "not unlikely that tunneling is enhanced when the reactants are prevented from achieving their optimum separation and orientation in the transition state."[7]

A more recent example from an entirely different corner of organic chemistry comes from the observed methane loss from the acetone radical cation that very likely follows tunneling control (Figure 6).[56] In the 19−24 kcal mol^{-1} energy regime, the acetone radical cation dissociates either to the acetyl cation and a methyl radical or to the ketene radical cation and methane. Mass spectrometric studies with acetone isotopologues reveal that the yield of CD_3H is about 70 times higher than that of CH_3D, indicating a tunneling mechanism in the decomposition of the acetone radical cation.[57] These conclusions were supported by theory as well[58] but were not left without criticism.[59] The challenge in gas-phase reactions is that the energy is not dissipated as effectively as in matrices, so the tunneling half-lives can be much longer, making mass spectrometric observation challenging.[60] A most recent imaging photoelectron photoion coincidence spectroscopy (iPEPICO) study seems to be putting this controversial discussion to rest: methane loss is initially slow for acetone and not observable in $^2H_6$-acetone.[56a] The thermochemistry is consistent with new and published data only if tunneling control is involved and has a large share in determining reaction selectivity.

In a fascinating recent study, Shaik et al. demonstrated that tunneling contributes to the counterintuitive hydrogen abstraction ability of nonheme iron(IV)oxo systems from alkane C−H-bonds that is at odds with classic transition-state theory.[61] The authors find a reversal of the expected reactivity pattern, thereby supporting the notion of tunneling control and draw the far-reaching conclusion: "Should these predictions be corroborated, the entire field of C−H bond activation in bioinorganic chemistry would lay open to reinvestigation."

A prediction of tunneling control directly pertinent to chemical synthesis comes from a computational study (at the CBS-QB3 level of theory) of the reactions of some 2,2a,5,7b-tetrahydro-1*H*-cyclobuta[*e*]indene derivatives (R = H or Me) by Karmakar and Datta (Figure 7).[6g] Although the barrier for the [1,5]H-shift is higher than that of the 6*π*-cycloreversion to the octatriene derivative, at temperatures below ca. 170 K only the [1,5]H-shift should occur.

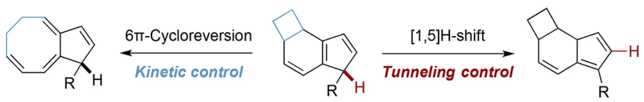

Figure 7. Computational prediction of the tunneling-controlled reactivity of 2,2a,5,7b-tetrahydro-1*H*-cyclobuta[*e*]indene derivatives: at temperatures below 170 K only the [1,5]H-shift product should be detectable.

Excellent tunneling control is also exerted in a process we termed "domino tunneling", as observed for the interconversion of the rotamers of oxalic acid (Figure 8) with half-lives in different matrix sites ranging from 30 to 360 h, even though the barriers of 9.7 and 10.4 kcal mol^{-1} are much too high to be surmounted thermally under cryogenic conditions.[62] As tunneling of the second isomerization is *faster* than the first

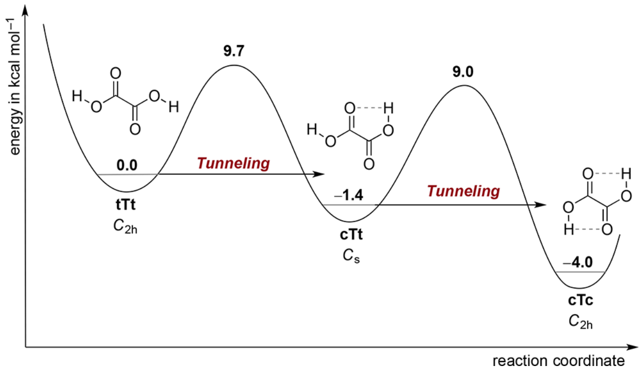

Figure 8. Focal-point computed PES for the "domino tunneling" interconversion of the oxalic acid rotamers **1tTt** to **1cTc**. Bond distances given in Å.

despite a higher barrier, we concluded that the intramolecular hydrogen bond in the **cTt** conformer introduces rigidity, therefore making the second barrier narrower. Hence, this implies that structural design can be used for the control of tunneling processes.

There are certainly many more examples of tunneling control—most of them hidden in peculiar kinetics and selectivities of reactions involving either light atoms or heavy atoms in combination with short reaction paths. It is very likely that the reconsideration of some of these reactions will reveal that tunneling control is indeed a common phenomenon that should be taken fully into consideration.

CONCLUSIONS AND PERSPECTIVES

Recognition of the concept of tunneling control opens a door to probe many other foundations of chemical reactivity that we take for granted. For instance, just recently we demonstrated that the Curtin–Hammett principle is not applicable in the tunneling [1,2]H-shift reactions of trifluoromethylhydroxycarbene (τ = 144 h): While the *trans*-isomer provides for the first instance of a *conformer-specific* tunneling process, the *cis*-isomer remains unchanged over the observation time frame (Figure 9).[45]

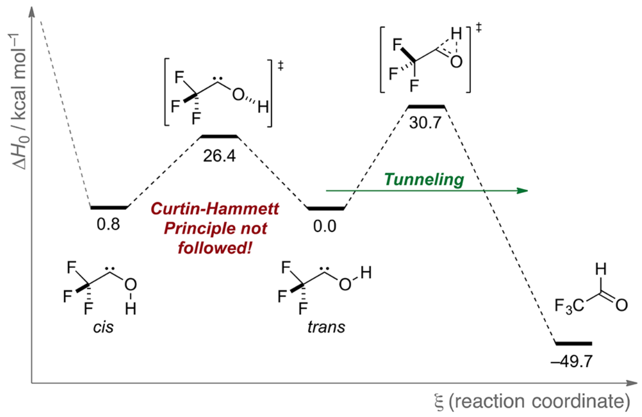

Figure 9. Tunneling [1,2]H-shift reaction of trifluoromethylhydroxycarbene to trifluoroacetaldehyde: the *trans*-isomer disappears while the *cis*-isomer remains unchanged. That is, the Curtin–Hammett principle is not followed (or does not apply, depending on the viewpoint), as the *trans*-isomer is not replenished through equilibration with the *cis*-isomer. Level of theory: CCSD(T)/cc-pVTZ + zero point vibrational energy corrections.

As both catalysis (via lowering reaction barriers) and tunneling (via cutting through barriers) at the end lead through accelerated reactions to the same products, this is a clear indication that catalysis can be linked to reaction dynamics through the concept of tunneling. One may term this "tunneling catalysis", which is likely to be highly important for enzymatic reactions.[27] It has even been suggested that vibrations of enzymes compress reaction barriers in the active site to enable tunneling processes;[4c,5b] again, this has not been left without criticism.[5a] As the chemical environment clearly affects tunneling processes also in the simple reactions considered here, this suggests that these reactions can also be externally controlled, implying that catalysis of such reactions is indeed possible.

Finally, the notion of *stimulated tunneling* (also referred to as VAT, *vide supra*)[6b,f,49d,63] through specific electronic ground-state vibrational excitation of molecules from their ground into a higher vibrational state (where the barrier is thinner) is a highly exciting option for precise control of reactivity. This could be accomplished using, e.g., modern laser setups potentially providing access to products that could not be made in any other way, thereby allowing an unprecedented degree of maneuvering on potential energy surfaces. Of course, the challenge here lies in the control of internal vibrational energy redistribution that can be very fast and much faster than the tunneling dynamics under consideration.[64]

It is highly likely that *tunneling control* is a common phenomenon and that we will learn to appreciate it as the third paradigm next to kinetic and thermodynamic control.

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(1) The barrier width is not as easily explained and defined without actually going into the mathematical models that can be found in the expert reviews noted in the references. It may sound counterintuitive, but in order to define the width of a barrier, the tunneling path must be determined first. In contrast to the conventional model with a fixed barrier width, one can consider tunneling between single energy levels through a potential barrier whose transmission ratio depends on the barrier width. The barrier oscillates about its idealized equilibrium width at a frequency that corresponds to the thermal vibrations of the connected sites. The other extreme that ignores the height and minimizes the width, is a straight-line that connects reactant with product; this is what we typically (incorrectly!) do when we draw reaction diagrams. At a given energy, barriers can have the same height

and curvature at the transition state but their widths may be very different, depending what shape (Eckart, parabolic, etc.) is used.

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