Atom Tunneling

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Atom Tunneling in Chemistry

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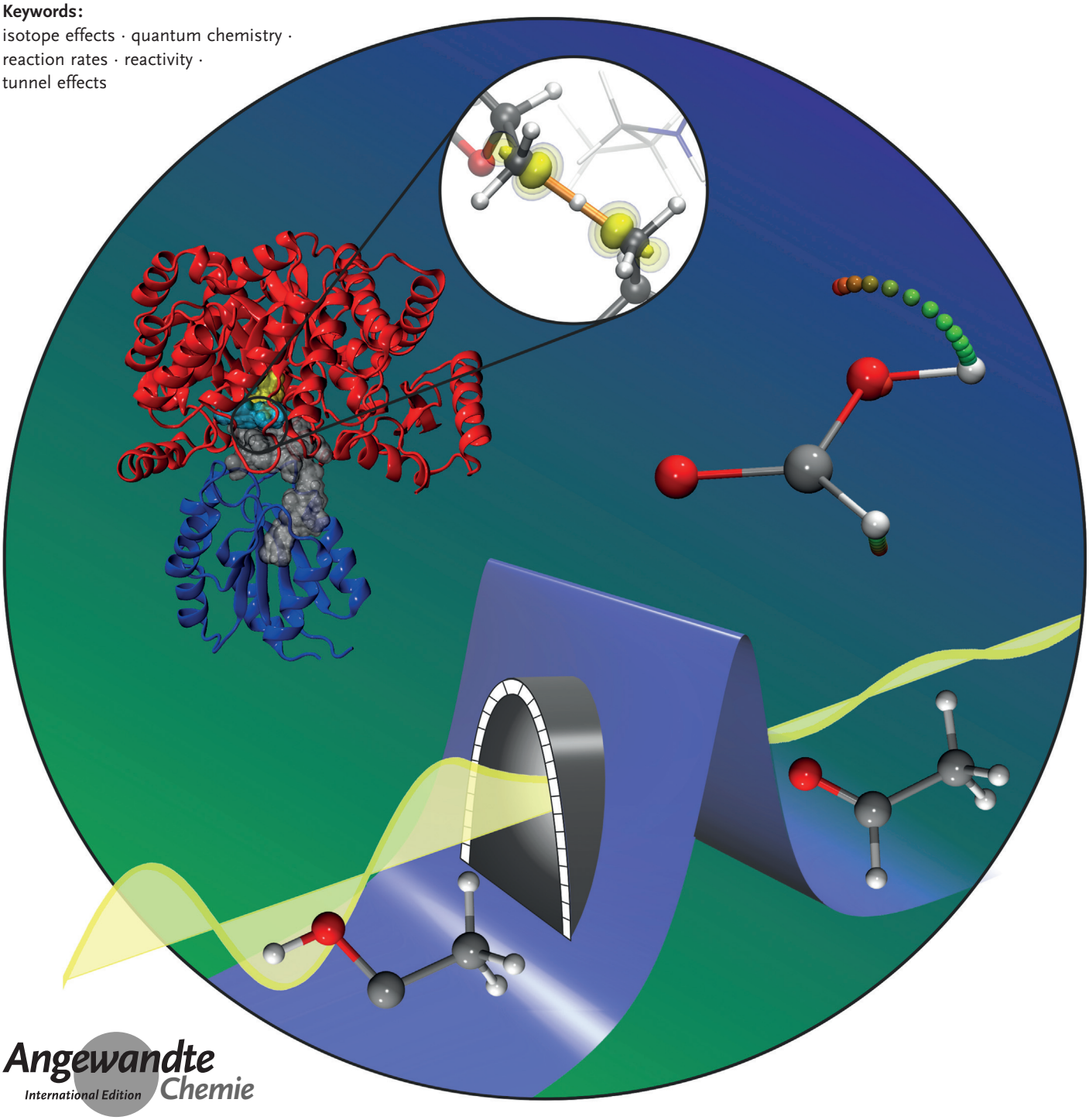

Quantum mechanical tunneling of atoms is increasingly found to play an important role in many chemical transformations. Experimentally, atom tunneling can be indirectly detected by temperature-independent rate constants at low temperature or by enhanced kinetic isotope effects. In contrast, the influence of tunneling on the reaction rates can be monitored directly through computational investigations. The tunnel effect, for example, changes reaction paths and branching ratios, enables chemical reactions in an astrochemical environment that would be impossible by thermal transition, and influences biochemical processes.

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1. Introduction

The tunnel effect is the quantum mechanical phenomenon whereby particles can penetrate and pass areas of configuration space with a potential energy higher than their total energy. Although phenomenological descriptions appeared earlier, the effect was discovered and understood in 1927 by Hund.[1] Subsequently, Gamow[2] as well as Gurney and Condon[3] used the tunnel effect independently of each other to explain the α decay of atomic nuclei. It was understood early on that the process of tunneling can contribute to chemical reaction rates in addition to or as an alternative to the thermal barrier crossing.

A number of quantum mechanical effects can be found in the movement of atoms in chemical systems. Examples are the quantization of vibrational and rotational energies, the zero point vibrational energy, and the tunnel effect. The first two lead to line spectra and Fermi resonances, whereas the last two can influence the rate constants of chemical reactions. Since atoms, like all matter, have particle properties as well as wave properties, they have a finite probability of appearance in regions of configurational space which would be classically forbidden due to a potential energy which is higher than the total energy of the atom (Figure 1). If such a region is narrower than the extent of the particle wave, there is a finite probability for the particle to appear on both sides, that is, the reactant and product sides. This is the cause of the quantum mechanical tunnel effect. Thus, atoms can tunnel through potential energy barriers.

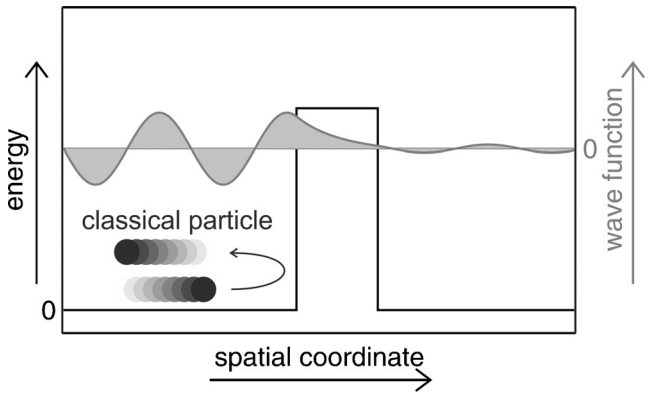

Figure 1. Wave function during the tunneling through a rectangular barrier.

The basic properties of the tunneling probability can be easily analyzed by assuming a rectangular barrier of height $E^{\neq}$ above the energy of the particle, as depicted in Figure 1. The wave function within the barrier region is proportional to $exp\left(-x\sqrt{mE^{\neq}}\right)$. The width of the barrier (x) enters linearly in the exponent, while only the square roots of both the mass (m) and the barrier height ($E^{\neq}$) enter. Similar equations hold for differently shaped barriers. This simple example illustrates the strong dependence of the tunneling rate on the barrier shape and somewhat weaker dependence on the mass and the barrier height, in contrast to the thermal rate described by the Arrhenius equation, which mainly depends on the barrier height.

There is also the almost philosophical question of how the particle can be present in an area for which its energy is not sufficient. In principle, in the classically forbidden region, the total energy is lower than the potential energy of the particle, namely, the kinetic energy would be negative. That is not only counterintuitive but also physically meaningless. The paradox can be resolved by looking at the relevant time and length scales. Finding a particle within the classically forbidden region with a known kinetic energy would violate Heisenberg's uncertainty principle. In fact, the uncertainty in these two quantities is always large enough that either the position or the kinetic energy (through the momentum) escape the classically forbidden region.

At room temperature, atom tunneling is mostly relevant for hydrogen atoms due to the mass-dependence of the tunnel effect. Usually, many atoms of a molecule move during a chemical reaction. A typical reaction path (either classical or including tunneling) involves motions of several atoms other than hydrogen (Figure 2). Therfore, it is generally impossible to assign a specific mass to a particular reaction. Even an effective mass frequently changes during the course of a transformation. Accordingly, many (or all) atoms of a molecule involved in a specific reaction are tunneling, which

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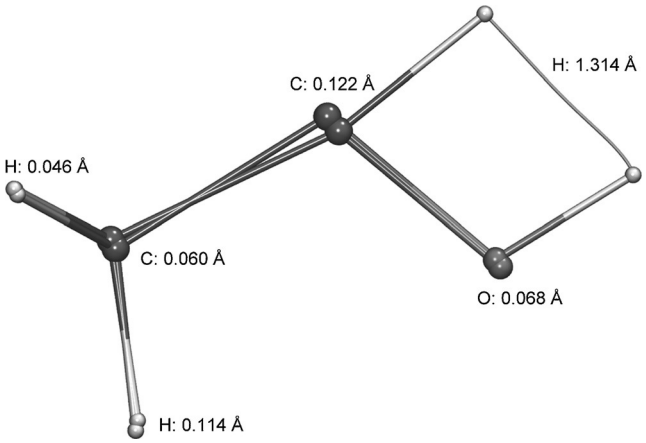

Figure 2. Displacement of atoms during the tunneling process from methylhydroxycarbene to acetaldehyde. The length of the tunnel path is indicated for each atom. Although the motion is dominated by one hydrogen atom, it is clear that the whole molecule contributes to the tunneling motion. Reproduced from Ref. [4].

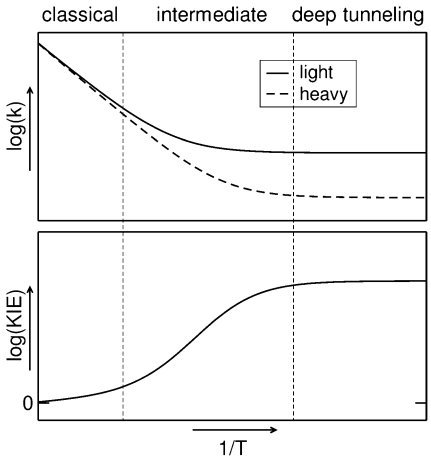

Figure 3. Top: Different temperature regimes of atom tunneling for two isotopologues shown in an Arrhenius plot. Bottom: The resulting logarithmic KIE as a function of inverse temperature.

makes it generally difficult to distinguish between hydrogen tunneling and the tunneling of heavy atoms (Figure 2). There is no doubt, however, that the mass-dependence of the tunneling rate leads to large kinetic isotope effects (KIEs). A KIE is the ratio of the reaction rate of two isotopologues or isotopomers of a reaction, with the rate of the heavier isotopologue divided by the rate of the lighter one. This normally leads to KIEs larger than one even without tunneling. Values less than 1 are called inverse isotope effects. Large KIEs are the main experimental indication that atom tunneling is happening. In the case of chemical reactions where one single atom—mostly a hydrogen atom—is transferred, for example, in sigmatropic [1,5] shifts or hydrogen abstraction reactions, one can distinguish between a primary KIE and a secondary KIE: the primary KIE is defined as the KIE arising from the substitution of the transferred atom by the heavier isotope. Secondary KIEs are thus defined as KIEs arising from substitution of atoms other than the transferred one by a heavier isotope.

Figure 3 shows the typical temperature dependence of rate constants and KIEs. At high temperature, $k(T)$ follows the Arrhenius law, which results in a linear Arrhenius plot. The intermediate temperature regime marks the onset of tunneling and a curved Arrhenius plot. At low temperatures, in which the tunneling regime dominates, the reaction rate is temperature-independent as tunneling occurs exclusively from the ground state. Figure 3 actually shows the rate constant for the unimolecular reactions H_3C-C-OH$\rightarrow H_3C$-CHO (light) and H_3C-C-OD$\rightarrow H_3C$-CDO (heavy). Further details can be found in the literature.[4] Tunneling is more efficient for the light isotopologue, which causes a large KIE, especially at low temperature.

Tunneling is most relevant at low temperatures. At high enough temperatures, any reaction will be dominated by thermal transitions. The crossover depends on the specific reaction. For hydrogen transfer reactions, it is often around room temperature. In intermediate temperature regimes, the overall reaction rate is often found to be higher than the (extrapolated) thermal rate and the low-temperature limit of the tunneling rate combined. This phenomenon is referred to as temperature-assisted tunneling or vibrationally activated tunneling (VAT).[5]

The tunnel effect and its relevance for chemistry has been covered in many reviews and even textbooks over the last century. The original reference work is probably the textbook by Bell,[6] with other books and reviews following it.[7–12] Further review articles deal with special aspects, such as atom tunneling in enzymes[13–15] or methods to calculate tunneling rates.[16–19] Of course, quantum effects such as

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tunneling also occur in many areas other than chemistry. Electrons tunnel much more readily than atoms because of their lower mass. This enables scanning tunneling microscopy, tunnel junctions, and tunnel diodes. All these are outside the scope of this Review, which summarizes the development of the field of atom tunneling in the last decade, with a focus on its consequences for chemistry.

2. Methods To Determine Atom Tunneling

Atom tunneling happens to some extent in any chemical reaction. At high temperatures, however, its contribution to the rate is negligible. An experimental quantification of the tunneling effect is impossible, whereas the effect can easily be switched on and off in simulations. The most important technique to experimentally assess the importance of tunneling is to measure KIEs, which are caused by tunneling and the zero point vibrational energy (ZPE; Figure 4). Whereas the potential energy of the atomic movement is independent of

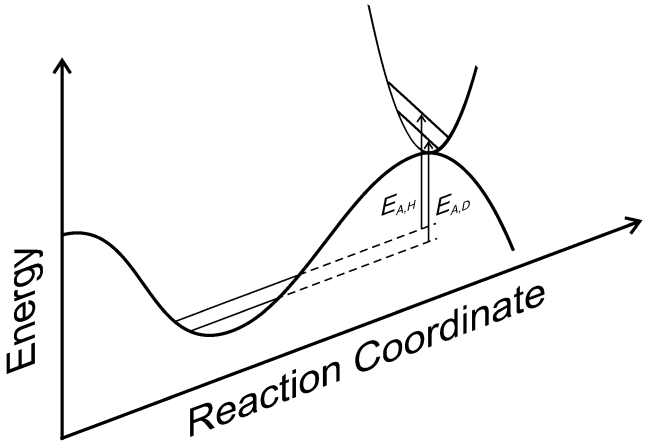


Figure 4. Schematic representation of the effect of the mass on the zero point energy on a potential energy surface.

the mass of the atoms, the vibrational frequencies, and consequently the ZPE, are mass-dependent. Higher masses lead to lower ZPEs in both the reactant state and the transition state. In unimolecular reactions, this change is generally larger in the reactant state than in the transition state, partly because there is one more vibrational mode in the former and the modes perpendicular to the reaction path are often stiffer in the reactant state. The difference in ZPE normally increases the vibrationally adiabatic barrier (namely, potential energy plus ZPE) for the reaction of the heavier isotopologue, and thus reduces the reaction rate. Primary KIEs between protium and deuterium of up to 6–7 at 300 K can be explained by the difference in the ZPE between the H and D isotopologues (Figure 4). If a higher KIE is found, this generally indicates tunneling. Since specific values depend on the system under study, more broadly applicable criteria were proposed. Fitting kinetic data with an Arrhenius expression $k(T) = A\exp(-E_A/k_BT)$ with a pre-exponential factor A and an activation energy E_A, which results in a straight line in an Arrhenius plot, as in Figure 3 in the classical regime. Here, k_B is the Boltzmann constant and T is the absolute temperature. Note, that the activation energy is not the height of the potential energy barrier. It merely reflects the slope of the Arrhenius curve. At low temperatures, E_A vanishes since the rate becomes temperature-independent. The following approximate criteria have been proposed for H/D KIEs:[20] a difference in the activation energy $E_A(D) - E_A(H) > 5.0\ \mathrm{kJ\,mol^{-1}}$ and a ratio of the pre-exponential factors of $A(H)/A(D) < 0.7$. Other criteria, such as Swain–Schaad exponents,[21] despite being frequently used,[10,22–26] were shown to not always be suitable as indicators for tunneling.[20,27,28] Techniques to measure KIEs, especially in biochemical systems, are reviewed elsewhere.[24] All these can, of course, only serve as indications, since no reaction will proceed exclusively by atom tunneling or exclusively without it.

In theoretical studies, atom tunneling can be switched on and off, and its effect on reaction rates can be directly monitored. Different techniques exist to calculate reaction rates, including atom tunneling. The simplest ones are based on harmonic transition state theory[29] (HTST) and the multiplication of the HTST rate constant by a tunneling correction factor κ. This can be obtained by assuming a specific functional form for the potential energy along the reaction coordinate, for which κ can be obtained analytically. The Eckart barrier[30] models some bimolecular reactions quite realistically, simple forms are a parabola[31] or a simple rectangular barrier. The latter is, despite its apparent shortcomings, still sometimes used in astrochemical modeling.[32–35] These simple approximations assume, however, that the tunneling process occurs along the same reaction coordinate as the thermal reaction. They are sometimes referred to as one-dimensional tunneling corrections.[17]

In reality, atom tunneling leads to corner cutting on the potential energy surface.[36] This is taken into account in multidimensional tunneling methods[37,38] such as the small-curvature tunneling correction (SCT),[39] a popular and successful method to approximate tunneling rates, or in the large-curvature tunneling correction (LCT)[40,41] and more recent similarly based methods.[42–44] The tunneling path is fully optimized in the Feynman-path-based instanton theory,[45–61] sometimes also referred to as harmonic quantum transition state theory (HQTST).[62] Ring-polymer molecular dynamics,[63,64] or a special case thereof, centroid molecular dynamics[56,65–67] and the related quantized classical path method,[68–71] the centroid density method,[72–74] and the reversible action-space work QTST (RAW-QTST)[75,76] are all based on Feynman's path integral formulation.[77] Quantum dynamics in the form of wave packet dynamics,[78] the multiconfiguration time-dependent Hartree (MCTDH) approach,[79–82] and several other methods, only a few of which can be mentioned here,[83,84] were also used to simulate atom tunneling. Computationally demanding methods such as wave packet dynamics and MCTDH are typically applied to potential energy surfaces, which need to be fitted in advance.[85]

It is worth mentioning an inconsistency in the semantics in the literature. KIEs which can be explained by differences in

the vibrational zero point energy (ZPE) without tunneling are sometimes regarded as being explicable by *semiclassical* approaches. This terminology, probably introduced by Bell[6,86] and widely used in the biochemical literature, is rather unfortunate, since the physics community generally terms methods related to the WKB approximation (WKB = Wentzel–Kramers–Brillouin)[87–91] as semiclassical. The latter include SCT, LCT, and the most common variant of instanton theory, and are perfectly able to describe tunneling phenomena.

3. Impact of Tunneling on Different Fields of Chemistry

Atom tunneling has been found in many different areas of chemistry. Here, we use the most prominent examples to illustrate common concepts and facilitate the interpretation of results. Since, for example, astrochemistry mostly happens at cryogenic temperatures while only ambient temperature is relevant for biochemistry, the implications of tunneling on these fields are fundamentally different. We aim to depict these differences as well as common concepts.

3.1. Biochemistry

The majority of enzymatic reactions involve a hydrogen transfer step: hydride, hydrogen radical, or proton transfer. At room temperature, most hydrogen transfer reactions are influenced to some degree by tunneling. Therefore, it is clear that tunneling is a vital component in many biological processes. Experimental evidence has been found mainly through large H/D KIEs.[8,9,22,23,92] Values above the range that can be explained by differences in the zero point energy alone have been found in dozens of enzymatic reactions, the most prominent being lipoxygenases,[93,25] taurine/α-ketoglutarate dioxygenase (TauD),[94] and aromatic amine dehydrogenase (AADH).[95] A recent more extensive list is given by Klinman.[23] The temperature window accessible by biochemistry is narrow, but H/D KIEs >500 were still observed.[96] The tunnel effect can be quantified directly in theoretical investigations. Probably the most promising method[97] to simulate enzymatic processes is the QM/MM approach.[98,99] It has been used to confirm several experimentally found KIEs[15,100–102] and shed light on the mechanistic implications of tunneling. Cluster models and the investigation of surrogate systems as well as the reaction-specific fit of force fields, such as the EVB approach, have also been broadly applied.[103–105] Overall, it is clear that atom tunneling does occur in biological systems, although does not cause the main catalytic effect.[106]

KIEs can, in many cases, be estimated quite accurately by theory,[104,105,107–111] while there is often poor agreement between the absolute reaction rates found by theory and experiment. In many cases, this can be explained by different quantities being compared. Computational simulations of enzymatic processes focus on the chemical step of an enzymatic process. This should not be compared to, for example, the experimental turnover rate k_{cat}, which often represents the product release. The whole process contains many more elementary steps that can become rate limiting, for example, diffusion, substrate binding, conformational changes, or product release.[112] They all have their different kinetics and most of them are isotope-insensitive. Thus, the apparent KIE based on either k_{cat} or the catalytic efficiency k_{cat}/K_m differs from the intrinsic KIE of the isotope-sensitive step. The intrinsic KIE can be estimated by using commitments to forward and reverse reactions.[8,10,24,113,114] Careful comparison between theory and experiment results in excellent agreements. For example in the reaction with dihydrofolate reductase (DHFR), experimental intrinsic H/D KIEs[115,116] and values calculated at a high level of theory[117,118] both result in a KIE of 3.5 ± 0.1, independent of the temperature and almost independent of the pH value.[119] Apparent KIEs, measured with different techniques result in KIEs less than 3.0,[120] which strongly indicates that steps other than the chemical transformation mask the KIE.[112]

A particular challenge in describing a biochemical proton transfer is that the proton transfer is often coupled to an electron transfer (PCET).[13,121] Both the proton and the electron move according to quantum mechanics. In many cases, however, the electron movement is much faster than the proton movement.

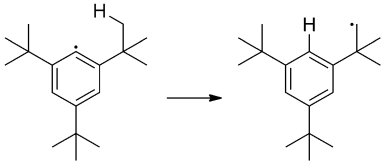
The temperature-dependence of H/D KIEs of enzymes has been measured in many cases. It turned out that the intrinsic KIE of almost any natural enzyme is rather temperature-independent,[23,122,112] at least over the limited temperature range available to biochemical reactions. In many mutants, a temperature-dependence, also of intrinsic KIEs, was found. A temperature-independent KIE could be explained by deep tunneling, that is, tunneling out of a single quantum state rather than from a thermal ensemble (Figure 3). For enzymes, this explanation does not apply, however, since the rate constant itself still strongly depends on the temperature. The observations have been rationalized by a pretunneling state[123] with an energy above that of the reactant state but below the barrier. Tunneling occurs from that pretunneling state rather than from the bottom of the reactant well. A high-lying pretunneling state causes tunneling from that state for both H and D at ambient temperature, which explains the moderate, temperature-independent KIEs and a temperature-dependent rate constant.

There is a longstanding and partially heated debate on whether or how protein vibrations, which couple to the hydrogen transfer reaction coordinate, enhance enzymatic hydrogen transfer reactions. The proposal is[14] that a slow global reorganization of the enzyme structure forms a configuration ready for tunneling, possibly by proper alignment of quantum states which allows efficient resonant tunneling. Orthogonal to that slow reorganization, the system moves fast along the hydrogen transfer coordinate in the tunneling-ready configuration. Promoting vibrations were proposed,[124,125] which lead to donor–acceptor compression on the timescale of barrier crossing and increase the tunneling probability. To be effective, such promoting vibrations must be very fast, comparable to C–H stretching frequencies.[126] This may be

possible if such vibrations are highly localized.[127,126] However, they were used to explain the effects of remote mutations.[125,128] At present, there are only indirect indications, but no direct experimental evidence, that such a vibronic model can explain the temperature-dependence of KIEs.[14] No detectable dynamic coupling of protein motions to the hydrogen transfer step was found experimentally with DHFR.[120] Barrier compression was claimed to favor quantum effects in the catalysis;[129] however, other researchers found that it enhances the reaction rate mostly by lowering the barrier which, in fact, reduces the amount of tunneling compared to the thermal rate.[130,131] Comparison of the turnover rate in a wild-type enzyme with its heavily deuterated counterpart ("heavy enzyme") showed that no specific protein motions are responsible for enhancing the tunneling.[132] Part of the current dispute is probably semantics: whereas a vibrational model can be set up by using equilibrium dynamics exclusively,[112] non-equilibrium (non-statistical) dynamics were sometimes employed, which raised criticism.[104,130,131] The pressure-dependence of KIEs was used to argue in favor of the vibronic model,[133,134] but was shown not to provide evidence that promoting vibrations enhance the catalytic effect.[130,131,135]

3.2. Barrier Width

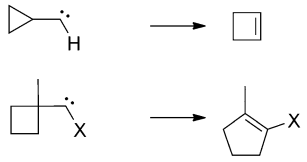
In chemical reactions, tunneling is most efficient if light atoms move just a short distance during the rate-determining step of a reaction, as the barrier width determines the probability of tunneling: The narrower a barrier is, the more likely tunneling is.[4,136–138] It was shown decades ago in the reaction of a 2,4,6-tri-*tert*-butylphenyl radical to 3,5-di-*tert*-butylneophyl (see Scheme 1) that the H atom has to travel just a small distance of 1.34 Å in the transformation from the reactant to the product.[139] This leads to a kinetic isotope effect of 13000 at −150 °C and still of 80 at −30 °C.



Scheme 1. Reaction of 2,4,6-tri-*tert*-butylphenyl to form 3,5-di-*tert*-butylneophyl.

Carbenes are generally known to be highly unstable molecules. For a few simple ones, namely hydroxycarbene (H-C̈-OH), methylhydroxycarbene (Me-C̈-OH), and phenylhydroxycarbene (Ph-C̈-OH) among others, it was shown that they are even unstable at cryogenic temperatures.[140–144] A [1,2] H shift to formaldehyde, acetaldehyde, or benzaldehyde, respectively, is enabled by tunneling because of the small distance the corresponding hydrogen atom has to overcome. By contrast, dihydroxycarbene (HO-C̈-OH) does not react to the respective product, formic acid, probably because of the strong π donation of the oxygen atoms reducing the electron deficiency of the carbene.[145] Methylhydroxycarbene exhibits two different reaction pathways:[146] one results in vinyl alcohol, the other in acetaldehyde. The energy barrier of the former reaction is lower, while that of the latter is narrower. At high temperatures, the classical thermal reaction causes vinyl alcohol to be formed preferentially, while at low temperatures, tunneling happens through the narrower barrier and acetaldehyde is formed. This result nicely shows the impact of the shape of potential energy barriers, in particular the length of reaction paths on tunneling. The concept that the barrier width determines the tunneling probability led to Schreiner's formulation of tunneling control of chemical reactions:[26,147] whereas the concepts of thermodynamic control (the lowest-energy products will be formed after a long time) and kinetic control (the reaction with the lowest barrier happens first) are widespread, tunneling determines the selectivity at low temperatures. Further examples of tunneling control are found in the ring expansion of noradamantylcarbenes:[148,149] different substituents change the reactivity at cryogenic temperatures and suppress tunneling or lead to different products.[149,150]

The question if the [1,2] H shift to the alkene or to the corresponding aldehyde takes place preferentially in different hydroxymethylcarbene analogues was answered computationally. This study concluded that the tunneling path length is the decisive quantity.[4] The possibility of the [1,2] H shift is suppressed by using cyclopropylcarbene or 1-methylcyclobutylhalocarbenes. Instead, ring-insertion reactions take place, facilitated by carbon tunneling (Scheme 2).[143,151,152]



Scheme 2. Ring expansion as a result of carbon tunneling, as observed in carbenes.[143,151,152] X = Cl, F

3.3. Organic Chemistry

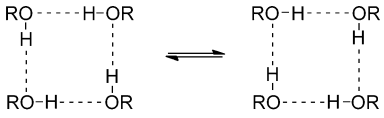
Hydrogen atoms are frequently found to tunnel, even at room temperature, in classical reactions of organic chemistry. In the case of reactions of closed-shell molecules with radicals, hydrogen is abstracted if the emerging radical is more stable than the previous one. Various reactions of small organic molecules with hydrogen atoms,[153–156] hydroperoxyl radicals,[64] chlorine atoms,[157–160] or the activation of H_2[161] have been studied experimentally as well as computationally. These reactions are influenced by tunneling, even at room temperature, thereby raising the reaction rate constants. For Claisen rearrangements it was necessary to computationally include a model of tunneling through a parabolic barrier to explain the experimental ^{13}C KIEs,[162–164] and in a Swern oxidation, multidimensional tunneling had to be included in computations to reproduce the experimental results.[165]

Several studies on the tautomerization of small or medium-sized molecules show the impact of tunneling on

proton shifts. Tunneling decay of particular conformers of glycine,[166,167] alanine,[168] cytosine,[169] and other small molecules with relevance to biology[170,171] was observed as well as the tunneling-accelerated tautomerization of tetrazole acetic acid.[172] Hydrogen peroxide is chiral if the rotation around the O–O bond is restricted at low temperature. The racemization was investigated by six-dimensional quantum dynamics[173] and shown to proceed efficiently by tunneling. Rotation of the OH group in phenol was shown by FTIR spectroscopy to happen through tunneling, while deuteration of the *ortho* or *meta* positions suppresses the tunneling motion at low temperature.[174] The *cis–trans* isomerization reactions of carboxylic acids were studied extensively.[175–182] These reactions are mostly carried out at cryogenic temperatures in noble gas or N_2 matrix environments. It was shown that such an environment can influence the tunneling rates of the isomerization reactions significantly. This might be taken as a caveat when comparing with, for example, quantum chemical gas-phase calculations.[178,179,183–186]

In larger, bio-organic molecules, tunneling supports radical reactions such as in the autoxidation of tetraline.[187] The regeneration of vitamin E (tocopherol) by ubiquinol was shown to be accelerated more than 4000 times by tunneling.[188] Furthermore, high experimental KIEs denote that the tocopherol-mediated peroxidation of fatty acids and 7-dehydrocholesterol might be promoted/supported by the tunneling of hydrogen atoms.[189,190]

Tunneling in different hydrogen-bond networks has been investigated. One of the most interesting findings is the simultaneous tunneling of protons in solid *p-tert*-butylcalix-[4]arene at low temperatures.[191] By using NMR relaxometry it was possible to investigate the phonon-assisted tunneling in the quadruple synchronous proton transfer of calix[4]arenes (Scheme 3).[192,193] The coupling of hydrogen-bond dynamics to large-amplitude motion in the vicinity was studied by NMR spectroscopy.[194]



Scheme 3. Quadruple proton transfer in calix[4]arenes.[191–193]

Tunneling splittings caused by double proton transfer were observed in various porphycenes.[195–197] In these cases, the initial and final state are equivalent: resonant tunneling takes place, which is particularly fast. The flux of electronic and nuclear densities in a resonant tunneling pericyclic reaction shows that only a rather small fraction of particles actually has to move to accommodate such reactions.[198] Rotation of hydrogen-bonded water molecules was also shown to be facilitated by tunneling.[199,200] The fluctuation between hydride and dihydrogen ligands of Fe^{II} was demonstrated by quasielastic neutron scattering and computational investigations to be dominated by tunneling.[201]

Tunneling was observed in many cases of sigmatropic rearrangements. Suprafacial [1,5] sigmatropic rearrangements were studied exhaustively, using derivatives of 1,3(*Z*)-pentadiene.[202,203] Although, it was unclear initially if tunneling plays a crucial role,[204,205] various studies have in the meantime confirmed the involvement of tunneling.[61,203,206–210] An antarafacial [1,7] sigmatropic hydrogen shift can happen in 1,3(*Z*),5(*Z*)-heptatrienes (Figure 5). By using 7-methylocta-

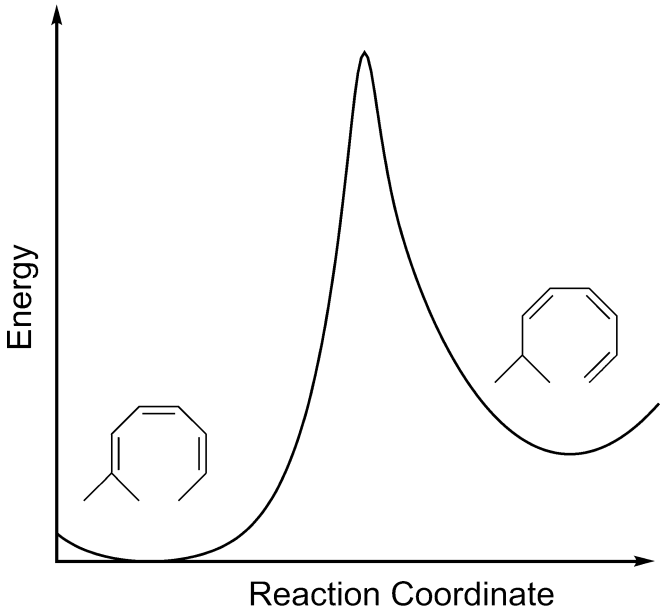


Figure 5. Schematic reaction profile of the [1,7] sigmatropic hydrogen shift of 7-methylocta-1,3(Z),5(*Z*)-triene to 2-methylocta-2,4(Z),6(*Z*)-triene. The narrow barrier facilitates tunneling.

1,3(*Z*),5(*Z*)-triene as model system, it was shown that the isomerization from provitamin D to vitamin D is accelerated by tunneling.[61,211–213] For the antarafacial [1,7] sigmatropic hydrogen shift, the hydrogen atom just moves a small distance in the high-energy region of the reaction, although the potential energy minima are quite far away because of reorganization of the carbon framework.

Despite the large number of studies, further investigation is necessary to elucidate the impact of multidimensional tunneling on the different variants of sigmatropic rearrangements or other pericyclic reactions.

3.4. Catalysis

Some reactions in organometallic chemistry and homogeneous catalysis show high KIEs, thus indicating tunneling to be important for the rate-determining step.[214,215] One of the most impressive cases is a hydrogen exchange reaction in a titanium complex: here, the exchange of a β H atom at 200 K is suppressed when deuterium is used.[216] This is equivalent to a KIE of >16000. The homolytic cleavage of a C–H bond enforced by an osmium-centered radical at room temperature has a KIE larger than 16.[217] The protonolysis of palladium and platinum complexes and the reductive elimination of methane from a gold complex have also been shown to have a significant tunneling contribution.[218–221] Tunneling

is even more pronounced in different reactions of biomimetic model complexes involving iron in high oxidation states: these exhibit large H/D KIEs, such as in the case of a C–H hydroxylation reaction with an oxoiron(IV) porphyrin radical cation, which showed a H/D KIE of 360 at −30 °C.[222–224] At +23 °C, a KIE of 28 has still been reported for the same reaction. High KIEs in oxoiron(IV) complexes require a two-state reactivity model for explanation.[225–228] Although the ground state of the reactant is a triplet, the low-lying quintet state plays a significant role, since there the reaction barrier is significantly lower. A C–H vibration lowers the quintet state below the triplet state and a spin crossover during the reaction was proposed.[224] In this way, a dependence of the C–H bond length on the reactivity can be explained.[227] Analogously to these reactions of the oxoiron compounds, an oxoruthenium-(IV) complex featuring comparable structural motifs was shown to display a KIE of 49 for the hydrogen abstraction reaction of dihydroanthracene.[229,230]

Even though this Review mainly focuses on molecular systems, we will now briefly discuss atom tunneling on surfaces. Hydrogen atoms have been frequently observed to tunnel in surface processes.[231–233] It was shown that the motion of hydrogen on Cu(001),[234–237] Pd/Cu(111),[238,239] Ru(0001),[240] W(110),[241] and Ni(100)[242–244] surfaces is enhanced by tunneling at low temperatures. Even the motion of CO on a Cu(111) surface was shown by scanning tunneling microscopy (STM) to occur below 6 K, with a temperature-independent hopping rate.[245]

In the field of heterogeneous catalysis, the CO oxidation and the dissociative H_2O desorption as well as the OH dissociation on various metal(111) surfaces were shown to be affected by tunneling.[142,246,247] The dissociation of CH_4 on Pt(111) and Ni(111) was found to involve thermally assisted tunneling.[248,249] Furthermore, the dissociation and recombination rates of H_2 on Ni(100) and the formation of NH on a Ru(0001) surface and the following successive H addition reactions—important in the process of NH_3 formation—are found to be accelerated by tunneling, especially at lower temperatures.[250–254] Even oxygen tunneling was observed in dissociative adsorption on Ag(111)[255] and on Pt(111) surfaces.[256] Heterogeneous catalysis, however, is often carried out at high temperatures, where tunneling is less important.

3.5. Tunneling of Heavy Atoms

All atoms in a molecule are generally involved to some extent in the tunneling motion (see Figure 2). Thus, the tunneling of heavy atoms also happens in the reactions mentioned previously, but usually plays a minor role. Nevertheless, for a few well-known textbook reactions, clear-cut heavy-atom tunneling was shown to be involved. While the increase in the absolute reaction rate constants as a result of heavy-atom tunneling is often rather small, it leads to KIEs of heavy atoms such as $^{12}C/^{13}C$ being detectable by, for example, mass spectrometry.

In the Bergmann cyclization, the tunneling of carbon atoms accelerates the reaction rate by 38–40 % at 30 °C, as determined by DFT and CASSCF calculations.[257] In the Roush allylboration of *p*-anisaldehyde, multidimensional tunneling involving heavy atoms is necessary to explain the experimental $^{12}C/^{13}C$ KIEs at −78 °C,[258] a temperature commonly used in organic synthesis. At this temperature, the reaction is accelerated by a factor of 1.36 by the tunneling of heavy atoms, which can not be observed directly by experiments.[258] Thus, the $^{12}C/^{13}C$ KIEs are a suitable probe to investigate the agreement of experimental and theoretical methods. The tunneling of oxygen is found in the ring-opening reaction of cyclic O_3 to its usual (open) form.[259] This rearrangement is even observed below 150 K. In this temperature regime, the reaction rate constants are calculated to be almost constant, with a $^{16}O/^{18}O$ KIE of up to 10 for the reaction of $^{18}O_3$.

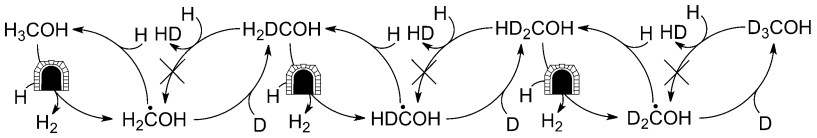
Even though the tunneling of second-row elements contributes perceptibly to these reactions, it generally plays a limited role for most chemical reactions such as catalysis or synthesis. Most chemical reactions are performed at relatively high temperatures and the conformational change during the rate-limiting step likely involves a significant motion of carbon, oxygen, or other heavy atoms. However, at lower temperatures, where the kinetic energy of the nuclei is too low to overcome the potential energy barrier, the tunneling of heavy atoms becomes more important. It is worth studying chemical reactivity in the low-temperature regime to gain insight into the elementary processes of kinetics, stability of molecules, and the nature of atom tunneling. For example, heavy-atom tunneling can spoil chemical stability even at temperatures close to 0 K, as molecules expected to be stable classically will decay by tunneling. Examples of this are the rearrangement of tetrahedryltetrahedrane or the decomposition of a hypercoordinated carbocation.[260,261]

A noteworthy case is the carbon tunneling in the automerization of cyclobutadiene and its derivates, which probably provided one of the first examples of heavy-atom tunneling in chemistry.[262–266] Tunneling in other anti- or non-aromatic systems, such as the automerization reactions of pentalenes and heptalenes or the isomerization of cyclopropenyl anions and the impact of substituents, was found more recently.[267,268]

Besides the reactions of the carbenes introduced above, other automerizations, ring-opening or -closing reactions, and rearrangement reactions—in particular of strained molecules—are also influenced by the tunneling of heavy atoms at low temperatures.[136,268–275] Reactions of strained organic molecules often involve unusually strong heavy-atom tunneling: a high activation energy from the breaking of a C–C bond combined with little movement of the involved atoms lead to narrow barriers, which enhance the probability for tunneling. For example, heavy-atom tunneling is prominent in the Cope rearrangement of semibullvalene[276] and the ring-opening reaction of cyclopropylcarbinyl radicals.[277–281] In the former case, $^{12}C/^{13}C$ KIEs of more than 5 at 40 K are predicted.[276] In the latter case, the reaction rate is nearly constant below 20 K.[279]

3.6. Astrochemistry

Astrochemistry describes the formation, distribution, and destruction of chemical substances in space. Noteworthy features, when considering reactions and reaction rates in the interstellar medium, are the low particle density and the strong radiation fields as well as the low temperature.



Scheme 4. Reaction network for the deuteration of methanol. The abstraction of protium is facilitated by a tunneling mechanism, but the abstraction of deuterium not.

Although more than 170 molecular species have been detected so far (not including isomers and isotopologues), all of them except fullerenes are smaller than 14 atoms. Temperatures in diffuse clouds are around 100 K and can be as low as just a few Kelvin in dark clouds.[282] Thus, chemical reactions only occur if they are barrierless, for example, induced by photons or cosmic rays, or through tunneling.

The de Broglie wavelength of particles increases with decreasing momentum and, thus, with decreasing temperature. Consequently, at the temperatures predominant in the interstellar medium, atom tunneling has to be considered for nearly all reactions featuring a potential energy barrier, especially when hydrogen is involved.

Many bimolecular reactions exhibit a prereactive minimum—a van der Waals complex—in the entrance channel before the barrier. Such complexes increase the attempt frequency for the reaction. Their lifetime increases as the temperature decreases. In combination with atom tunneling, the increasing attempt frequency can even lead to an increase in the rate constant as the temperature decreases. Experimental evidence for this counterintuitive effect exists in a few cases, for example in the gas-phase reactions

$$H_2 + NH_3^+ \rightarrow NH_4^+ + H^{[283]}$$

and

$$CH_3OH + OH \rightarrow CH_3O + H_2O.^{[284]}$$

In a full quantum mechanical picture, tunneling occurs from bound metastable states.[285]

Chemistry in space happens frequently on surfaces of dust grains.[286,287] These often consist of silicates or carbonaceous compounds and are usually coated by frozen CO, water, methane, and other small molecules.[286]

For example, the surface reaction of hydrogen addition to CO, a key step in the formation of methanol in space, is governed by tunneling and leads to large H/D KIEs.[288–290] Tunneling is also important for the hydrogenation of formaldehyde to methoxy radicals.[291]

Many small molecules are found to be heavily deuterated in space.[292–294] For some of them, such as methanol[295] and formaldehyde,[291] this can be explained by tunneling: the lighter protium can be abstracted by a hydrogen atom to form H_2 while deuterium remains bound to the COH_x fragment. Subsequent barrierless recombination with another protium or deuterium atom leads to deuterium enrichment (Scheme 4).

Although tunneling also takes place in reactions involving only non-hydrogen atoms, such as $O + CO \rightarrow CO_2$, it was shown in this case that the temperature at which tunneling becomes relevant is too low to be of astrochemical importance.[296]

One model to simulate H_2 formation on carbonaceous dust grains is the hydrogenation of benzene, which was studied by quantum chemical methods.[297] In this case, tunneling contributes to the reaction rate of the first hydrogen chemisorption, while the addition of the second hydrogen atom is barrierless.[297–299] Amorphous solid water is among the most common surfaces in the interstellar medium, as most dust grains are covered by water. It was found experimentally that water can be formed from H_2 and OH on water surfaces even at 10 K,[33] even though the gas-phase reaction exhibits a barrier of 17.5 kJ mol^{-1}. For further reactions on water surfaces enhanced by atom tunneling, we refer to Ref. [300].

4. Conclusions

Quantum mechanical tunneling of atoms, despite being known for almost 90 years, still provides challenging and surprising results regarding chemical reactions. Although it is dominant at low temperatures and for reactions involving atoms with low masses, hydrogen transfer reactions are often accelerated at room temperatures and above by the tunnel effect. Tunneling causes large KIEs, thus making it detectable by experiment. Simulations, on the other hand, are able to directly monitor the tunneling process and can quantify its influence on the rate constant of the reaction. Different computational techniques, from simple one-dimensional corrections to classical TST over semiclassical approaches to full quantum dynamics, are available. Symmetric reactions, where the reactant and product are chemically indistinguishable, show resonant tunneling, which causes a splitting of the vibrational energy levels. In contrast, thermal reaction rates are typically influenced by nonresonant tunneling. Atom tunneling has been found in organic chemistry, inorganic chemistry, surface science, astrochemistry, and biochemistry. Astrochemistry is typically governed by very low temperatures. Thus, reactions involving a barrier can only happen if they are dominated by tunneling. In the area of biochemistry, however, tunneling is limited to hydrogen transfers. Although the observed KIEs are typically smaller than in the other fields discussed, they are a valuable probe for the reaction mechanism and, therefore, studied extensively. Overall, judging from the dynamic development in the field of atom tunneling in chemistry in recent years, new and exciting findings can be expected for the future as well.

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