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. On the contrary, using computational investigations the influence of tunneling on the reaction rates can directly be monitored. 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.

1 Introduction

The tunnel effect is the quantum mechanical phenomenon that particles can penetrate and pass areas in configuration space with a potential energy higher than their total energy. While phenomenological descriptions appeared earlier, the effect was discovered and understood in 1927 by Hund. Subsequently, Gamow and Gurney & Condon 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 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 former two lead to line spectra and Fermi resonances, the latter 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 in configurational space which would be classically forbidden due to a potential energy which is higher than the total energy of the atom, see 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 at both sides, i.e. 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.](image)

The basic properties of the tunneling probability can be easily analyzed by assuming a rectangular barrier of height $E^\dagger$ above the energy of the particle, as depicted in Figure 1. The wave function within the barrier region is proportional to $\exp\left(-x\sqrt{mE^\dagger}\right)$. 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 $(E^\dagger)$ 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 the almost philosophical question 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, i.e., 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 (via the momentum) escape the classically forbidden region.

At room temperature, atom tunneling is mostly relevant for hydrogen atoms due to the mass-dependence
Figure 2: Displacement of atoms during the tunneling process from methylhydroxycarbene to acetaldehyde. The length of the tunnel path is indicated for each atom. While the motion is dominated by one hydrogen atom, it is obvious that the whole molecule contributes to the tunneling motion. Reproduced from reference 4.

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, see Figure 2. Therefore, 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 makes it generally difficult to distinguish between hydrogen tunneling and heavy-atom tunneling, see 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, the rate of the heavier isotopologue is divided by the rate of the lighter one. This normally leads to KIEs larger than one even without tunneling. Values < 1 are called inverse isotope effects. Strong KIEs are the main experimental indication for atom tunneling to happen. In the case of chemical reactions where one single atom – mostly a hydrogen atom – is transferred, e.g. in sigmatropic [1,5] H-shifts or hydrogen abstraction reactions, one can distinguish between a primary KIE and secondary KIEs: 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 other atoms than the transferred one by the 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 temperature, in the deep tunneling regime, 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 \( \text{H}_3\text{C} \text{C}-\text{OH} \rightarrow \text{H}_3\text{C} \text{CHO} \) (light) and \( \text{H}_3\text{C} \text{C}-\text{OD} \rightarrow \text{H}_3\text{C} \text{CDO} \) (heavy), details can be found elsewhere.4 Tunneling is more efficient for the light isotopologue which causes a large KIE, especially at low temperature.
Tunneling is most relevant at low temperature. At high enough temperature, 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).

The tunnel effect and its relevance for chemistry had been covered in many reviews and even textbooks in the course of the majority of the last century. The main reference work is probably the textbook by Bell, other books and reviews followed it. Further review articles deal with special aspects like atom-tunneling in enzymes or methods to calculate tunneling rates. Obviously, quantum effects like tunneling also occur in many other areas than chemistry. Electrons tunnel much more readily than atoms due to 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 focus on its consequences for chemistry.

2 Methods to determine Atom Tunneling

Atom tunneling happens to some extent in any chemical reaction. At high temperature, however, its contribution to the rate is negligible. An experimental quantification of the tunneling effect is impossible, whereas in simulations the effect can easily be switched on and off. 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). The effect is illustrated in Figure 4. While the potential energy of the atomic movement is independent of 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, partially 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 (i.e. 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 ZPE between H and D isotopologues, see 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 $k(T) = A \exp(-E_A/k_B T)$ results in 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 Boltzmann’s 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. In deep tunneling, $E_A$ vanishes since the rate becomes temperature-independent. The following approximate criteria have been proposed for H/D-KIEs: a difference in activation energy $E_A(D) - E_A(H) > 5.0 \text{ kJ mol}^{-1}$ and a ratio of pre-exponential factors of $A(H)/A(D) < 0.7$. Other criteria, like Swain–Schaad exponents, were shown to not always be suitable as indicators for tunneling. Techniques to measure KIEs, especially in biochemical systems, are reviewed elsewhere. All these can, of course, only serve as indications since no reaction will proceed exclusively via atom tunneling or exclusively without it.

In theoretical studies, atom tunneling can be switched on and off and its effect on reaction rates can directly be monitored. Different techniques exist to calculate reaction rates including atom tunneling. The
simplest ones are based on harmonic transition state theory (HTST) and the multiplication of the HTST-rate constant by a tunneling correction factor $\kappa$. It can be obtained by assuming a specific functional form for the potential energy along the reaction coordinate, for which $\kappa$ can be obtained analytically. The Eckart barrier models some bimolecular reactions quite realistically, simpler forms are a parabola or a simple rectangular barrier. The latter is, despite its obvious shortcomings, still sometimes used in astrochemical modeling. 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.

In reality, atom tunneling leads to corner cutting on the potential energy surface. This is taken into account in multidimensional tunneling methods like the small-curvature tunneling correction (SCT), a popular and successful method to approximate tunneling rates, or in the large-curvature tunneling correction (LCT) and more recent methods of a similar basis. The tunneling path is fully optimized in the Feynman-path-based instanton theory, sometimes also referred to as harmonic quantum transition state theory (HQTST). Ring-polymer molecular dynamics, or a special case thereof, centroid molecular dynamics, and the related quantized classical path method, the centroid density method, and the reversible action-space work QTST (RAW-QTST) are all based on Feynman’s path integral formulation. Quantum dynamics in the form of wave packet dynamics, the multi-configuration time-dependent Hartree (MCTDH) approach and several other methods, where only a few can be mentioned here, were used to simulate atom tunneling as well. Computationally demanding methods like wave packet dynamics and MCTDH are typically applied on potential energy surfaces, which need to be fitted in advance.

It is worth to mention 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 and widely used in the biochemical literature, is rather unfortunate since the physics community generally terms methods related to the WKB (Wentzel–Kramers–Brillouin) as semiclassically. 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, e.g., astrochemistry mostly happens at cryogenic temperature while only ambient temperature is relevant for biochemistry, the implications of tunneling on these fields is fundamentally different. We aim at depicting 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 by tunneling, at least to some degree. Therefore, it is obvious 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 enzymes, the most prominent being lipoxigenases,\[25,93\] 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 still H/D-KIEs $> 500$ were observed.\[96\] The tunnel effect can directly be quantified in theoretical investigations. Probably the most promising method to simulate enzymatic processes is the QM/MM approach.\[97,98\] 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 like the EVB approach, were also applied on a broad scale.\[103–105\] Overall, it is clear that atom tunneling does occur in biological systems, albeit not causing the main catalytic effect.\[106\]

KIEs can in many cases be estimated quite accurately by theory,\[104,105,107–111\] while absolute reaction rates are often in poor agreement between 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, e.g., the experimental turnover rate $k_{\text{cat}}$, which often represents the product release. The whole process contains many more elementary steps that can become rate limiting, e.g. diffusion, substrate binding, conformational changes, or product release.\[112\] They all have their different kinetics and most of them are isotopically insensitive. Thus, the apparent KIE on either $k_{\text{cat}}$ or the catalytic efficiency $k_{\text{cat}}/K_m$ differs from the intrinsic KIE of the isotope-sensitive step. The intrinsic KIE can be estimated by using commitments to forward and reverse reactions.\[110,113,114\] Careful comparison between theory and experiment results in excellent agreements. For example in dihydrofolate reductase (DHFR), experimental intrinsic H/D KIEs\[115,116\] and values calculated on high level\[117,118\] both result in a KIE of $3.5 \pm 0.1$, independently of the temperature and almost independently of the pH.\[119\] Apparent KIEs, measured with different techniques result in KIEs $< 3.0$,\[120\] strongly indicating that other steps than the chemical transformation mask the KIE.\[112\]

A particular challenge in the description of biochemical proton transfer is that the proton transfer is often coupled to an electron transfer (PCET).\[121,122\] Both, proton and electron move according to quantum
mechanics. In many cases the electron movement is much faster than the proton movement, though.

The temperature-dependence of H/D-KIEs in enzymes has been measured in many cases. It turned out that the intrinsic KIE of almost any natural enzyme is rather temperature-independent, 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, i.e. tunneling out of a single quantum state rather than from a thermal ensemble, see 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 pre-tunneling state with an energy above that of the reactant state but below the barrier. Tunneling occurs from that pre-tunneling state rather than from the bottom of the reactant well. A high-lying pre-tunneling state causes tunneling from that state for both H and D at ambient temperature, which explains moderate, temperature-independent KIEs and a temperature-dependent rate constant.

There is a longstanding and partially heated debate whether or how protein vibrations, which couple to the hydrogen transfer reaction coordinate, enhance enzymatic H-transfer reactions. The proposal is that a slow global reorganization of the enzyme structure forms a tunneling-ready configuration, 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, 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. This may be possible if such vibrations are highly localized. However, they were used to explain the effects of remote mutations. At present, there are only indirect indications, but no direct experimental evidence, that such a vibronic model can explain the temperature-dependence of KIEs. No detectable dynamic coupling of protein motions to the hydrogen transfer step was found experimentally in DHFR. Barrier compression was claimed to favor quantum effects in the catalysis, 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. 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 tunneling. Part of the current dispute is probably semantics: while a vibrational model can be set up by using exclusively equilibrium dynamics, non-equilibrium (non-statistical) dynamics was sometimes employed which raised criticism. Pressure-dependence of KIEs was used to argue in favor of the vibronic model, but was shown not to provide evidence that promoting vibrations enhance the catalytic effect.
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 is tunneling. It was shown decades ago that in the reaction of 2,4,6-tri-tert-butylphenyl radical to 3,5-di-tert-butylneophyl, see Scheme 1, the H atom has to travel just a small distance of 1.34 Å in the transformation from the reactant to the product. This leads to a kinetic isotope effect of 13,000 at −150°C and still 80 at −30°C.

![Scheme 1: Reaction of 2,4,6-tri-tert-butylphenyl to 3,5-di-tert-butylneophyl.](image)

Carbenes are generally known to be highly unstable molecules. For a few simple ones, namely hydroxycarbene (H−Ċ−OH), methylhydroxycarbene (Me−Ċ−OH), and phenylhydroxycarbene (Ph−Ċ−OH) among others, it was shown that they are unstable even at cryogenic temperature. 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 surmount. By contrast, dihydroxycarbene (HO−Ċ−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. Methylhydroxycarbene exhibits two different reaction pathways: one results in vinyl alcohol, the other in acetaldehyde. The energy barrier of the former reaction is lower, while the one 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 thinner barrier and acetaldehyde is formed. This 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 lead to Schreiner’s formulation of tunneling control of chemical reactions. whereas the concepts of thermodynamic control (the lowest-energy products will be formed in the long-time limit) 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, e.g., in the ring expansion of noradamantylcarbenes: different substituents change the reactivity at cryogenic temperatures and suppress tunneling or lead to different products.

The question if rather the [1,2] H-shift to the alkene or to the corresponding aldehyde takes place in
different hydroxymethylcarbene-analogs was answered computationally, concluding that the tunneling path
length is the decisive quantity. Using cyclopropylcarbene or 1-methylcyclobutylhalocarbenes the possibility
of [1,2] H-shifts is suppressed. Instead, ring insertion reactions take place, facilitated by carbon tunneling,
see Scheme 2.

![Scheme 2: Ring expansion due to carbon tunneling observed in carbenes.](image)

### 3.3 Organic Chemistry

In organic chemistry hydrogen atoms are frequently found to tunnel, even at room temperature. 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, hydroperoxyl radicals, chlorine atoms, or the activation of H2, have been studied experimentally as well as computationally. Even at room temperature these reactions are influenced by tunneling, 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 KIEs and in a Swern oxidation, multidimensional tunneling had to be included in computations to reproduce the experimental results.

Several studies of the tautomerization of small or medium-sized molecules show the impact of tunneling
on proton shifts. Tunneling decay of particular conformers of glycine and alanine, cytosine, and other small molecules with relevance to biology was observed as well as the tunneling-accelerated tautomerization of tetrazole acetic acid. Hydrogen peroxide is chiral if the rotation around the O–O bond is restricted at low temperature. The stereo-mutation of one enantiomer to the other one was investigated by six-dimensional quantum dynamics and shown to proceed efficiently by tunneling. Rotation of the OH-group in phenol was shown to happen via tunneling by FTIR spectroscopy, while ortho- or meta deuteration suppresses the tunneling motion at low temperature. The cis-trans isomerization reactions of carboxylic acids was studied extensively. These reactions are mostly carried out at cryogenic temperature in noble gas or N2 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 to, e.g., quantum chemical gas phase calculations.
In bigger, bio-organic molecules, tunneling supports radical reactions like in the autoxidation of tetra-
line.\textsuperscript{[185]} The regeneration of vitamin E (tocopherol) by ubiquinol was shown to be accelerated more than
4000 times by tunneling.\textsuperscript{[183]} Furthermore, high experimental KIEs denote that tocopherol-mediated peroxi-
dation of fatty acids and 7-dehydrocholesterol might be promoted/supported by hydrogen tunneling.\textsuperscript{[189][190]}

Tunneling in different hydrogen bond networks has been investigated. One of the most interesting
findings is the simultaneous proton tunneling in solid p-\textit{tert}-butyl calix[4]arene at low temperature.\textsuperscript{[191]}
Using NMR relaxometry it was possible to investigate the phonon-assisted tunneling in the quadruple synchronous
proton transfer of calix[4]arenes, see Scheme 3.\textsuperscript{[192][193] The coupling of hydrogen bond dynamics to large-
amplitude motion in the vicinity was studied by NMR.\textsuperscript{[194]} Tunneling splittings caused by double proton

tunneling in various porphycenes were observed.\textsuperscript{[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.\textsuperscript{[198]} Rotation of hydrogen-bonded water molecules was also
shown to be facilitated by tunneling.\textsuperscript{[197][199]} The fluctuation between hydride and dihydrogen ligands of Fe
\textsuperscript{II} was demonstrated to be dominated by tunneling using quasi-elastic neutron scattering and computational
investigations.\textsuperscript{[201]}

In sigmatropic rearrangements, tunneling was observed in many cases. Suprafacial [1,5] sigmatropic re-
arrangements were studied exhaustively, using derivatives of 1,3(Z)-pentadiene.\textsuperscript{[204][205]} Although, initially it
was unclear if tunneling plays a crucial role,\textsuperscript{[204][205]} various studies meanwhile confirm involvement of tun-
neling.\textsuperscript{[61][203][206][210]} An antarafacial [1,7] sigmatropic hydrogen shift can happen in 1,3(Z),5(Z)-heptatrienes,
see Figure 5. Using 7-methylocta-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.\textsuperscript{[61][213][215]} 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 multi-
dimensional tunneling on the different variants of sigmatropic rearrangements or other pericyclic reactions.
3.4 Catalysis

In organometallic chemistry and homogenous catalysis, some reactions show high KIEs, indicating tunneling to be important for the rate determining step.\cite{214,215} One of the most impressive cases might be a hydrogen exchange reaction in a titanium complex: here, at 200 K the exchange of a $\beta$ H-atom is suppressed when deuterium is used.\cite{216} This is equivalent to a KIE of $> 16,000$. The homolytic cleavage of a C–H bond enforced by an osmium centered radical at 25{\degree}C has a KIE larger than 16.\cite{217} Also, the protonolyses of palladium and platinum complexes and the reductive elimination of methane from a gold complex have shown to have a significant tunneling contribution.\cite{218–221} Tunneling is even more pronounced in different reactions of bio-mimetic model complexes involving iron in high oxidation states: these exhibit large H/D KIEs, like in the case of a C–H hydroxylation reaction with an oxoiron(IV) porphyrin radical cation, showing a H/D KIE of 360 at $-30^\circ$C.\cite{222–224,225–228}

At +23{\degree}C, a KIE of still 28 has been reported for the same reaction. High KIEs in oxoiron(IV) complexes require a two-state reactivity model for explanation.\cite{225,226} 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.\cite{224} In this way, a C–H bond length dependence in reactivity can be explained.\cite{227} Analogously to these reactions of the oxoiron compounds, an oxoruthenium(IV) complex featuring comparable structural motifs has shown to display a KIE of 49 for the hydrogen abstraction reaction of dihydroanthracene.\cite{229,230}

Even though this review mainly focuses on molecular systems, we will now briefly discuss atom tunneling on surfaces. Hydrogen atoms were frequently observed to tunnel in surface processes.\cite{231,232} It was
shown that the motion of hydrogen on Cu(001), Pd/Cu(111), Ru(0001), W(110), and Ni(100) surfaces is enhanced by tunneling at low temperature. Even the motion of CO on a Cu(111) surface was shown to occur below 6 K using scanning tunneling microscopy (STM), with a temperature-independent hopping rate.

In the field of heterogenous catalysis, the CO oxidation and the dissociative H2O desorption as well as the OH dissociation on various metal (111) surfaces were shown to be affected by tunneling. The dissociation of CH4 on Pt(111) and Ni(111) was found to involve thermally assisted tunneling. Further, the dissociation and recombination rates of H2 on Ni(100) and the NH formation on a Ru(0001) surfaces and the following successive H-addition reactions – important in the process of NH3 formation – are found to be accelerated by tunneling especially at lower temperatures. Even oxygen tunneling was observed in the dissociative adsorption on an Ag(111) and on Pt(111) surfaces. Heterogenous catalysis, however, often employs high temperatures where tunneling is less important.

### 3.5 Heavy-Atom Tunneling

All atoms in a molecule are generally involved to some extent in the tunneling motion, see Figure 2. Thus, heavy-atom tunneling happens in the reactions mentioned previously as well 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 absolute reaction rate constants due to heavy atom tunneling is often rather small, it leads to heavy-atom KIEs like 12C/13C being detectable by, for example, mass spectrometry.

In the Bergmann cyclization, carbon atom tunneling accelerates the reaction rate by 38–40% at 30°C as obtained by DFT and CASSCF calculations. In the Roush allylboration of p-anisaldehyde, multidimensional tunneling involving heavy atoms is necessary to explain the experimental 12C/13C KIEs at −78°C, a temperature commonly used in organic synthesis. At this temperature the reaction is accelerated by a factor of 1.36 by heavy atom tunneling, which cannot be observed directly by experiments. Thus, the 12C/13C KIEs are a suitable probe to investigate the agreement of experimental and theoretical methods. Oxygen tunneling is found in the ring-opening reaction of cyclic O3 to its usual (open) form. This rearrangement is observed even below 150 K. In this temperature regime, the reaction rate constants are calculated to be almost constant with a 16O/18O-KIE of up to 10 for the reaction of 18O3.

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

A noteworthy case is the carbon tunneling in the automerization of the antiaromatic cyclobutadiene and its derivates which probably is among the first evidences for heavy atom tunneling in chemistry. \[262\-266\] Tunneling in other anti- or non-aromatic systems like 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 heavy atom tunneling at low temperature. \[136\-268\] Reactions of strained organic molecules often involve unusually strong heavy atom tunneling: a high activation energy due to 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 instance, in the Cope rearrangement of semibullvalene \[276\] or for the ring opening reaction of cyclopropylcarbinyl radical \[277\-281\] heavy atom tunneling is prominent. In the former case, \[^{12}\text C/^{13}\text C\text{-KIEs of more than 5 at 40 K are predicted.}^{276}\] In the latter one, 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. Note-worthy features, when considering reactions and reaction rates in the interstellar medium, are the low particle density and the strong radiation fields and generally the low temperature. Although more than 170 molecular species were detected so far (not including isomers and isotopologues), all of them except fullerenes are smaller than 14 atoms. In diffuse clouds temperatures 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 instance induced by photons or cosmic rays, or via tunneling.

The de Broglie wavelength of particles increases with decreasing momentum and, thus, with decreasing temperature. Consequently, at the temperatures predominant in 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 pre-reactive 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 with decreasing temperature. In combination with atom tunneling the increasing attempt frequency
can even lead to an increase of the rate constant at decreasing temperature. Experimental evidence for this counterintuitive effect exists in a few cases, for example in the gas-phase reactions

$$\text{H}_2 + \text{NH}_3^+ \rightarrow \text{NH}_2^+ + \text{H}$$ \[283\]

and

$$\text{CH}_3\text{OH} + \text{OH} \rightarrow \text{CH}_3\text{O} + \text{H}_2\text{O}.$$ \[284\]

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. \[288\]

For example, the surface reaction of hydrogen addition to CO, a key step in the formation of methanol in space, is governed by tunneling, leading to strong H/D-KIEs. \[289–290\] Also for the hydrogenation of formaldehyde leading to methoxy radical, tunneling is important. \[291\]

Many small molecules are found to be heavily deuterated in space. \[292–294\] For some of them, like methanol \[295\] and formaldehyde, \[291\] this can be explained by tunneling: the lighter protium can be abstracted by a hydrogen atom to form H2 while deuterium remains bound to the COH\textsubscript{x} fragment. Subsequent barrier-less recombination with another protium or deuterium atom leads to deuterium enrichment, see Scheme 4.

![Scheme 4: Reaction network for the deuteration of methanol. The abstraction of protium is facilitated via a tunneling mechanism, the abstraction of deuterium not.](image)

Although tunneling also takes place in reactions involving only non-hydrogen atoms, like O + CO → CO\textsubscript{2}, it was shown that in this case tunneling sets in at a too low temperature to be of astrochemical importance. \[296\]

One model to simulate H\textsubscript{2} formation on carbonaceous dust grains, the hydrogenation of benzene, was studied by quantum chemistry. \[297\] Here, tunneling contributes to the reaction rate of the first hydrogen chemisorption while the addition of the second hydrogen atom is barrier-less. \[297–299\] 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\textsubscript{2} and OH on water surfaces even at 10 K, \[13\] even though the gas phase reaction exhibits a barrier of 17.5 kJ mol\textsuperscript{-1}. For further reactions on water surfaces enhanced by atom tunneling, we refer to reference \[300\]
4 Conclusions

Quantum mechanical tunneling of atoms, despite it being known for almost 90 years, still provides challenging and surprising results as it influences chemical reactions. While it is dominant at low temperature and for reactions involving atoms with low masses, hydrogen transfer reactions are often accelerated at room temperature and above by the tunnel effect. Tunneling causes strong KIEs, 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 reaction rate constant. 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. It causes a splitting of the vibrational energy levels. In contrast to that, thermal reaction rates are typically influenced by non-resonant tunneling. Atom tunneling was 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. While 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 the recent years, new and exciting findings can be expected for the future as well.

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TOC graphic

The quantum mechanical tunnel effect is increasingly found to influence many chemical reactions. While atom-tunneling can only be detected indirectly in experiment, computational investigations allow a direct observation. Here, we review cases in which the tunnel effect changes reaction paths and branching ratios, enables chemical reactions in an astrochemical environment and influences biochemical processes.