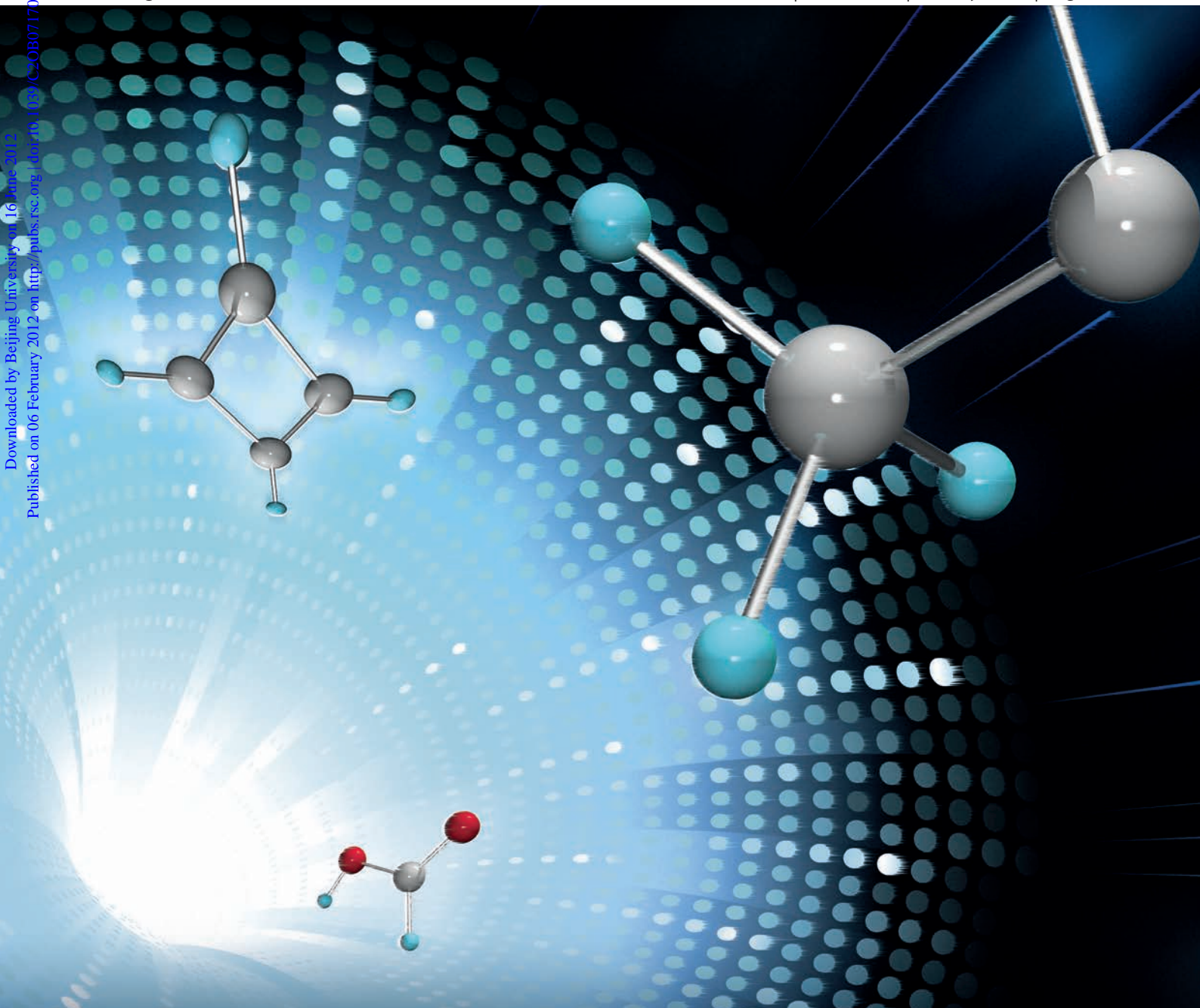


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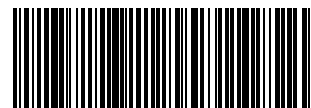
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Peter R. Schreiner *et al.*

Tunnelling control of chemical reactions – the organic chemist's perspective



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Tunnelling control of chemical reactions – the organic chemist’s perspective

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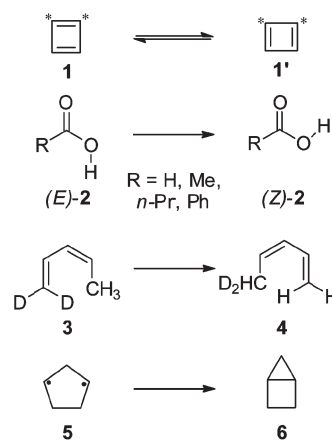
Even though quantum mechanical tunnelling has been appearing recurrently mostly in theoretical studies that emphasize its decisive role for many chemical reactions, it still appears suspicious to most organic chemists. Recent experiments in combination with powerful computational approaches, however, have demonstrated that tunnelling must be included to fully understand chemical reactivity. Here we provide an overview of the importance of tunnelling in organic chemical reactions.

Introduction

A peculiar property of quantum mechanical particles is their ability to overcome potential energy barriers despite of a lack of energy to surmount them. This effect is commonly referred to as quantum mechanical tunnelling (QMT) and is directly related to the inherent wave character of particles, allowing them to penetrate their surrounding potential energy barriers. While investigations on the origin and impact of QMT are widespread in the physics literature (it is, *inter alia*, responsible for the α -decay in some heavy atoms as well as for electrical flows in semiconductor systems), QMT tends to have the image of not being particularly relevant for ‘real’ chemistry: One finds over 40 times as many publications with the keyword “electron tunnelling” than with “atom tunnelling”. While this is in part due to the electron’s ability to tunnel much more effectively owing to its significantly

smaller mass compared to atoms, it also reflects the neglect of this important effect in chemistry.

One question, therefore, is why chemists have chosen to underrate tunnelling as a viable path to rationalize the rates of



Scheme 1 Tunnelling in some organic compounds.

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chemical reactions, especially when light atoms (mostly hydrogens, Scheme 1) are involved.

Transition state theory (TST) was introduced independently in 1935 by Eyring,¹ as well as Evans and Polanyi.² TST revolutionized the prevalent understanding of chemical reactivity and selectivity, and both groups noted the latent influence of QMT on chemical reactions by pointing out that their theory was mainly based on a picture given by classical mechanics. Non-classical barrier penetration *via* QMT was thus not taken into account and Eyring noted that “*the barriers are so flat near the top that tunnelling may be neglected without appreciable error*” but also that “*Tunnelling may occasionally play some role in the motion*”. Stating that “*light masses, such as hydrogen and deuterium [...] will result in the appearance of tunnelling effects [...]*” Evans and Polanyi were even more specific in assigning a distinct role to QMT. At first, TST did not receive broad recognition until Woodward and Baer simplified the theoretical concept pictorially to explain the kinetic *endo* selectivity of a particular Diels–Alder reaction.³ This didactic reduction helped establish TST as an important tool for chemistry, and the notion of thermodynamic *vs.* kinetic control was born, but tunnelling as a controlling factor for chemical reactions was left out (Fig. 1).

Tunnelling probabilities $\kappa(\varepsilon)$ can be evaluated using the Wentzel–Kramers–Brillouin (WKB) formalism with one-dimensional barrier penetration integrals $\theta(\varepsilon)$ along the intrinsic reaction path:

$$\kappa(\varepsilon) = \frac{1}{1 + e^{2\theta(\varepsilon)}}$$

$$\theta(\varepsilon) = \int_{s_1}^{s_2} \sqrt{2[V(s) - \varepsilon]} ds$$

in which ε is the collision energy, s_1 and s_2 are the classical turning points where $V(s) = \varepsilon$, and atomic units are assumed throughout. The square root in the expression for $\theta(\varepsilon)$ affects $V(s)$, which also contains the mass of the tunnelling particle



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of the Organic Institute in Giessen in 2002. His awards received include the Dirac Medal (2003) and the ADUC Prize (1999). He currently serves as Editor-in-Chief of WIREs-Computational Molecular Sciences, as an editor for the Journal of Computational Chemistry and the Beilstein Journal of Organic Chemistry, and as an advisory board member for several organic chemistry journals.

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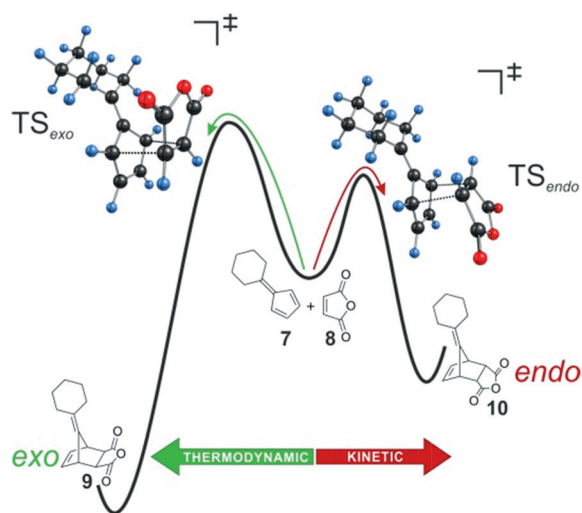


Fig. 1 Woodward and Baer's graphical representation of the Diels–Alder reaction's *endo* selectivity.

since a mass weighted coordinate system is used. The barrier width given by the integral scales linearly and is more important than the activation barrier, which scales with its square root. For this reason, QMT can play a special role in chemical reactions with high but narrow activation barriers. A detailed mathematical analysis and approaches to tunnelling computations will be presented elsewhere.⁴

The history of tunnelling

Following the discovery of radioactivity and the finding that its first order decay constants do not depend on pressure, temperature or chemical environment, the first explanation of the tunnelling effect went hand in hand with the quantum mechanical interpretation of the α -decay by Gamow in 1928.⁵ While the vast majority of work concerning tunnelling focuses on electrons as the tunnelling particles, the effect itself was initially noticed for He-atoms, and thus for an atomic mass that is chemically relevant.

The most familiar example for atom tunnelling is probably the inversion of NH_3 through a planar transition structure (TS, Fig. 2);⁶ its narrow 6 kcal mol^{-1} barrier is highly susceptible to tunnelling. The resulting vibrational splitting is the basis for the so-called ammonia maser,⁷ the predecessor of the laser. From a chemical point of view, the low NH_3 inversion barrier results in rapid racemization of chiral amines at ambient conditions and tunnelling can further promote the inversion, especially at low temperatures and for secondary amines.

The situation is conceptually different for tetrahedral carbon compounds, as inversion of methane through the non-planar C_s -symmetric TS demands more energy (about $117 \text{ kcal mol}^{-1}$)⁸ than breaking the first C–H bond ($110.3 \text{ kcal mol}^{-1}$).^{9,10} By analogy to NH_3 , one could still consider that the reaction does not directly involve the TS, but rather takes the shortcut through the barrier so that racemization occurs *via* QMT.^{11,12} In 1927, and thus long before the term *tunnelling* was established, Hund discussed this regarding the

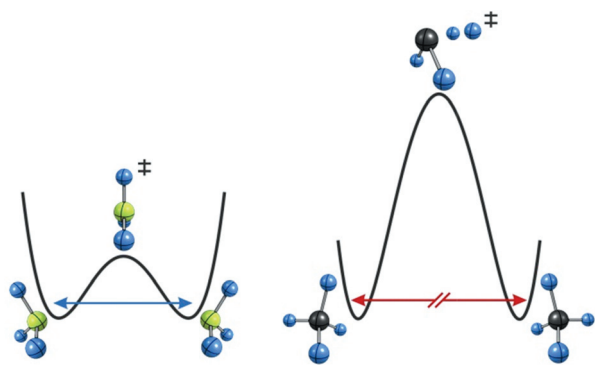


Fig. 2 The inversion has a strong tunnelling contribution in NH_3 , but not so for methane.

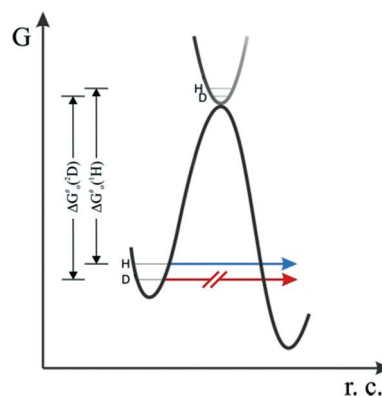


Fig. 4 Isotope exchange influences the over barrier- and the barrier-penetration processes.

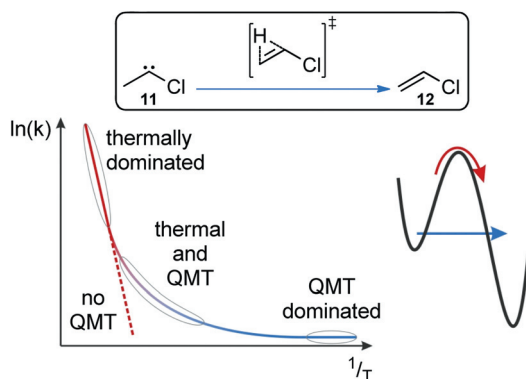


Fig. 3 If there is a QMT contribution, one can only slow the reaction to the QMT limit.

configurational stability of enantiomeric pure natural products such as amino acids. He excluded tunnelling contributions to their racemization, concluding that the respective half-lives are within millions of years, and thus in the range of geological ages.^{13,14}

Why tunnelling has been neglected in the past

The bottom line of TST is that reactants must have a certain energy to surmount an activation barrier. This concept allows the explanation of chemical reactivity and selectivity in an intuitive way, and this is why selectivity is strictly associated with the term kinetic control. Asymmetric synthesis is entirely built on this concept: While the products are thermodynamically equal, the two diastereomeric transition structures are associated with different activation barriers, whereby a difference of 3 kcal mol⁻¹ already entails an ee of 95% at ambient conditions.¹⁵ Modern highest-level computational methods are capable of capturing such small energy differences, even though computational precision remains difficult, *e.g.*, in a biochemical context where large systems have to be considered. It is contradictory that chemists are generally taken aback by the computational expense demanded by tunnelling computations, whereas the expense of doing highest-level energy computations in a biochemical context is not an obstacle, as these studies are done and widely

spread in the literature, so why—for the same reason—should tunnelling computations be rare?

Owing to its temperature independence, QMT's significance on the overall reaction rate dominates in the low temperature regime (Fig. 3). At higher temperatures it mixes with the classical over barrier rate, as indicated in Fig. 3, resulting in seemingly lowered activation barriers derived by Arrhenius plots. This behaviour is, *e.g.*, known from the [1,2]H-shift in methylchlorocarbene (**11**) to vinyl chloride (**12**): The activation barrier was computed¹⁶ to be 11.4 kcal mol⁻¹ and thereby strongly overrates the experimental¹⁷ value of 4.9 kcal mol⁻¹. Precise computational values can thus only be obtained when taking QMT into account.¹⁸ Hence, the approach of describing a chemical reaction as a process that is determined by a reactant evolving *over* an energetic barrier is only adequate if QMT can be neglected with certainty.

In many instances, QMT is only visible indirectly, *e.g.*, from a deviation between theoretical and experimental rate constants, strong kinetic isotope effects (KIE) as well as temperature dependent pre-exponential factors that result in a curvature of the Arrhenius plot in the low temperature regime. As KIEs, pre-exponential factors and computed rate constants are not routinely determined, it is fair to say that the occurrence of QMT is somewhat concealed, as it appears suspect to unravel the deviation from a theoretical concept by introducing another one. As a consequence, organic chemists generally view the idea of tunnelling with some scepticism. QMT still experiences lack of attention and Einstein's rule of making everything “*as simple as possible, but not simpler*” is violated: The oversimplified TST concept is given too much credit, because some of its failures have not been readily apparent so far. Based on the multiple recent challenges to TST by experimental as well as highly accurate theoretical results, it is obvious that the established interpretation of TST has to be at least critically reconsidered.¹⁹

Light and heavy atom tunnelling

Kinetic isotope effects

TST treats chemical kinetics in terms of a multidimensional potential energy hypersurface (PES), wherein reactants and products are connected by TSs. In the case of the minima (reactants and products), the curvatures of the energy profiles are positive

everywhere with respect to every possible coordinate. A TS, on the other hand, is characterized by having one negative curvature along a certain line through the PES connecting reactants and products; this is the so-called reaction coordinate (Fig. 4). The negative curvature entails a considerable difference between the two distinctive quantum corrections for the minima and for the TS, respectively: The positive value results in a real number—thus called semi-classic—and it can be interpreted as the zero-point vibrational energy correction (ZPVE).

As the reactant follows the reaction coordinate toward the TS, bonds may become looser—or in the case of bond-dissociation even non-existent—resulting in a significant difference in ZPVEs between reactants and TS. Due to the mass dependence of the vibrational energy, isotope exchange results in a difference in activation barriers and thus different reaction rates, which is called the kinetic isotope effect (KIE = $k_{\text{H}}/k_{\text{D}}$). If bonds strengthen as the system approaches the TS, the KIE will be inverse; KIE values in the range of 0.8 to 7.0 can be interpreted in a semi-classical manner.

Due to the negative curvature, the last-mentioned quantum correction is imaginary and thus peculiar; it is the tunnelling correction,²⁰ which affects the rate constant by allowing barrier penetration with its mass dependence leading to a tunnelling KIE. It can reach quite large values, while the classical KIE is restricted to an upper limit of about 7 (at 300 K),²¹ entailing the following relationship found by Swain and Schaad:²²

$$\text{SSE} = \frac{\ln(k_{\text{H}}/k_{\text{T}})}{\ln(k_{\text{D}}/k_{\text{T}})} = 3.26 \quad (1)$$

wherein H, D, and T are the three respective hydrogen isotopes and SSE is the so-called Swain–Schaad exponent. Since KIEs in tunnelling reactions are typically much higher than classical ones, QMT results in exalted SSEs (>3.26), thereby allowing them to be used as tunnelling probes. There are several interpretations of the strong KIE on tunnelling rates: First, a higher mass involves more classical behaviour, resulting in a smaller tendency to penetrate the barrier. Second, as the frequency of the active mode decreases, the tunnelling particle makes fewer attempts to penetrate the barrier at the same time, and third, the lower ZPVE results in a longer tunnelling distance (Fig. 4), since the barrier is broader at its bottom.

Primary and secondary KIEs merge into each other, if the reaction coordinate is given by a vibrational mode that includes coupled movement of several atoms, and the same reason makes it impossible to strictly distinguish between light- and heavy atom tunnelling. In the semi-classical approximation, the tunnelling path is the trajectory of a molecule along an active vibrational mode and as some frequencies are considered as characteristic for a certain functional group and are reduced to the movement of a small number of atoms rather than the whole molecule, the same approximation can also be used for tunnelling. This way it is possible to roughly distinguish between light- and heavy QMT.

Hydrogen tunnelling in carboxylic acids

There are some systems for which the reaction coordinate is approximately given by H-atom movements only. One is the

simplest carboxylic acid, formic acid (**2a**), which features two isomers by rotation of its OH unit. Stabilized with an intramolecular hydrogen bond, *Z*-**2a** is favoured by almost 4 kcal mol⁻¹, and is effectively the only observable conformer at ambient conditions. By means of vibrational overtone pumping of matrix-isolated, monomeric **2a** with a quantum yield in the range of 0.2–0.3,²³ Räsänen *et al.* succeeded in the isomerization to the *E*-isomer. Surprisingly, it converted back to the more stable *Z*-isomer with a half-life of a few minutes at cryogenic temperatures in solid Ar²⁴ and QMT turned out to facilitate the interconversion through the barrier of about 8 kcal mol⁻¹. The authors even managed the selective excitation of guest molecules at several different matrix sites and furthermore found solvation effects on the tunnelling rate due to phonon coupling: Heavier noble gas atoms slightly stabilize *E*-**2a** toward the tunnelling decay, with the effect of H₂ as matrix material being between that of Ne and Ar.²⁵ This shows how sensitive the tunnelling rate is, as noble-gas matrices at cryogenic temperatures are typically considered as chemically inert environments.

The observed tunnelling in cold matrices solely occurs from the vibrational ground state, thereby exceeding the rate of the thermal reaction by 13 and 15 orders of magnitude in Ar and Ne, respectively.²⁶ *O*-Deuteration extends the half-life of *E*-**2a** in a Ne matrix from ~5 s to 13.5 d, which corresponds to a primary KIE of more than five orders of magnitude. In contrast, *C*-deuteration results in a greater tunnelling rate, and thus an inverse secondary KIE.²⁷ By analogy, acetic acid (**2b**)²⁸ and propionic acid (**2c**)²⁹ showed similar tunnelling characteristics and computations indicated that the over barrier reaction does not significantly contribute to the reaction rate for temperatures below 100 K, but will outrun QMT at ambient conditions.³⁰ In addition, these systems provided the first experimental evidence for tunnelling from vibrationally excited states, as excitation energies below the isomerization barrier already yielded the high energy conformer (Fig. 5).³¹

Compared to the aliphatic carboxylic acids, the computed half-life for the tunnelling process in benzoic acid (**2d**) and its derivatives is about five orders of magnitude smaller.³² Hammett relationships for deuterium tunnelling revealed that σ -electron donors (CH₃, ^tBu) increase, while σ -acceptor groups (NO₂, Cl) decrease the half-life of *d*₁-**2d**. This was the first study of a linear free energy relationship for a tunnelling process.

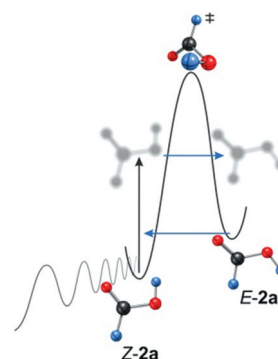
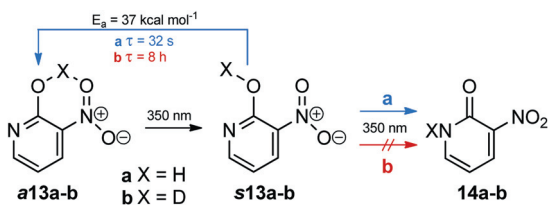
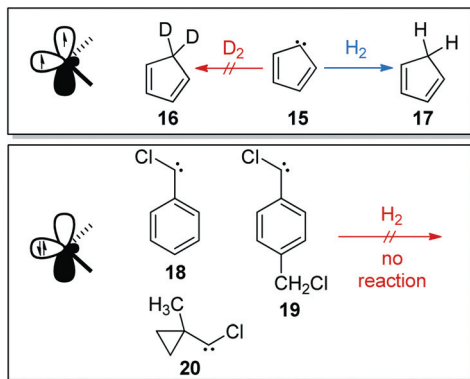


Fig. 5 Even pumping with IR energies below the activation barrier yields the high-energy conformer of formic acid.



Scheme 2 Isomers of the 2-hydroxy-3-nitropyridine system.

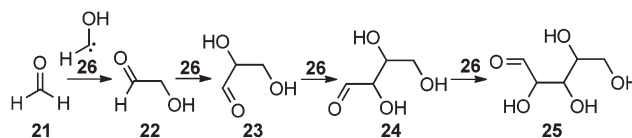


Scheme 3 Tunnelling controlled reactions of H_2 with carbenes in the matrix. Triplet carbenes (top) react *via* tunnelling, whereas various singlet chlorocarbenes (bottom) do not, thereby opposing the expected reactivity.

Conceptually similar to the carboxylic acids, 2-hydroxy-3-nitropyridine (**13**, Scheme 2) revealed fast rotational hydrogen tunnelling.³³ Upon irradiation with $\lambda > 350$ nm, the minimum *anti* configuration of the enol (**a13a**) undergoes photo-induced isomerization to the *syn* configuration (**s13a**), which in turn undergoes photo-induced keto–enol tautomerism so that finally all of the starting material can be transformed to **14a** and **s13a** can only be detected during irradiation. If the exposure is insufficient, **s13a** converts back to **a13a** by a tunnelling reaction with a half-life of 32 s. *O*-Deuteration stabilizes **s13b** and thereby not only stretches its tunnelling half-life to 8 h, but also blocks the second photo-reaction to the respective keto product **14b**. Since the photon energy of **s13a** to **14a** is below the isomerization barrier, the authors suggest tunnelling to occur from an electronically activated state.³³

Tunnelling in hydrogen abstractions

Singlet- and triplet methylene both add H_2 , yet by two considerably different pathways: While the singlet carbene undergoes a concerted and almost barrierless addition, triplet methylene reacts *via* an abstraction–recombination mechanism involving a higher reaction barrier.³⁴ One might expect that this reactivity also holds for higher methylene homologues. This is, however, not the case if QMT controls the reactivity:³⁵ Despite a higher activation barrier, triplet carbene **15** does react with H_2 at low temperatures in a tunnelling reaction which can be suppressed upon deuteration. In contrast, the singlet halocarbenes **18–20** do not react (Scheme 3), thereby opposing the reactivity derived from parent methylene.



Scheme 4 Concept of a hydroxycarbene mediated formose reaction.

A thoroughly discussed example for hydrogen atom tunnelling is given by the 1,5[H]-shift in *cis*-1,3-pentadiene (**3**, Scheme 1). Already experimentally studied 45 years ago,³⁶ the system turned out to show a tunnelling contribution,³⁷ but at first the role of QMT could not be elucidated clearly. On the one hand, the geometrical change of the molecule during the reaction seemed much too large for tunnelling to be involved. On the other hand, the observed KIE, especially if extrapolated to room temperature, could not be explained without a QMT contribution. Attempts to find direct experimental evidence for tunnelling, *i.e.*, a curvature in the Arrhenius plot, failed, even when investigating a large temperature range of 77–185 °C.³⁸ Using sophisticated computational methods, Borden *et al.* indicated that a major part of the reaction proceeds by tunnelling and that it should be visible for **3**,³⁹ as well as for related 5-methyl-1,3-cyclopentadiene.⁴⁰ Dewar *et al.* finally suggested⁴¹ the reaction to occur by vibrationally assisted tunnelling (VAT) and this theory was further supported by Truhlar *et al.*,³⁷ stating that for a given set of conditions, the overall reaction rate given by VAT results from a compromise between lower Boltzmann population at higher and smaller tunnelling rates at lower energy levels. The concept of VAT is ground breaking, because it sheds new light on nonclassical barrier penetration; QMT contributions cannot be generally left out on the basis of barrier shapes and high masses of the involved particles, as one has to consider tunnelling from excited states.

Hydroxycarbenes—the missing link

As mentioned earlier, QMT experienced lack of attention in the context of chemical reactions, mainly because its effects seem to be somewhat imperceptible. There was no unambiguous example for QMT to clearly manifest itself as a *control element* in chemical reactions until the discovery of hydroxymethylene (**26**) in 2008:⁴² The little molecule represents a high-energy isomer and thus an activated form of formaldehyde (**21**),⁴³ the parent adduct of water and a carbon atom, so that **26** can be regarded as the monomer of all carbohydrates.

Electron donation from the O-atom strongly enforces the electronic singlet state for **26**, indicated by a large singlet–triplet energy separation of 37.6 kcal mol^{−1} at the AE-CCSD(T)/cc-pCVQZ level of theory.⁴² Its strong singlet character renders the carbene centre of **26** highly nucleophilic, so that the carbene can undergo a barrierless addition reaction with its isomer **21**,⁴⁴ and higher carbonyl compounds, finally resulting in the formation of sugars. The respective polymerization of **21** in aqueous solutions has been known for 150 years,⁴⁵ but the mechanism of the so-called formose reaction has still not been unravelled.^{43,45} Long before its spectroscopic discovery, **26** was thus awarded a special role in the photocatalytic formation of carbohydrates,⁴⁶ as well as for the formation of sugars in space (Scheme 4).⁴⁷ The first

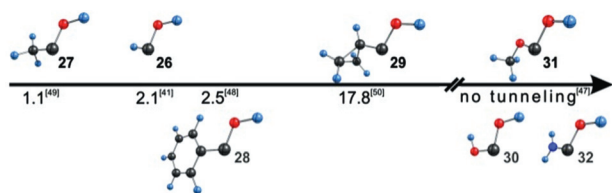


Fig. 6 Half-lives (in Ar at 11 K) of experimentally characterized hydroxycarbenes.

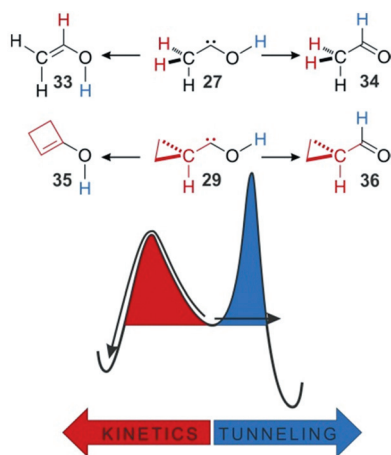
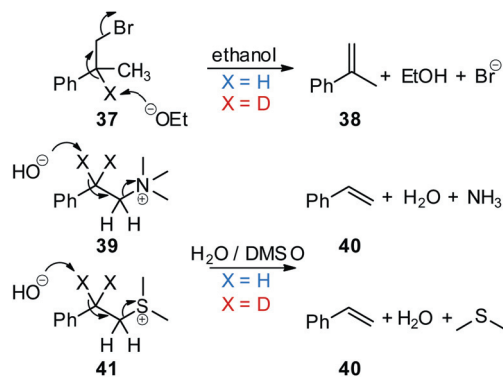


Fig. 7 Tunnelling control of chemical reactions.

experimental characterization of **26** through thermal extrusion of CO₂ from glyoxylic acid⁴² revealed that trapping **26** at cryogenic temperatures (11–20 K) does not stop the isomerization reaction to formaldehyde, but brings it to a tunnelling controlled limit with a half-life of 2 h in Ar, Kr and Xe matrices, whereas the half-life stretches by factor three in an N₂ matrix. The tunnelling process could be monitored by means of IR spectroscopy, as the decrease in carbene concentration, as well as the corresponding increase in formaldehyde concentration over time was clearly visible. Further research on other hydroxycarbenes^{48–51} revealed that the tunnelling rate strongly depends on the substituents' electron donor abilities: While the alkyl substituted hydroxycarbenes feature half-lives of about 2 h, the cyclopropyl moiety in **29** entails a prolonged half-life of almost 18 h because of the donating overlap between the Walsh orbital and the carbene's empty *p*-orbital. Finally, all currently characterized hetero-substituted hydroxycarbenes do not undergo tunnelling^{48,52} and for all hydroxycarbenes, QMT shuts down upon *O*-deuteration (Fig. 6).

The discovery of **27**⁵⁰ and **29**⁵¹ shed new light on the tunnelling effect in a conceptual way: Until now, QMT has only been considered and utilized as a *correction* on the semi-classical rate constant whereas in the case of **27** and **29**, it even inverts the reactivity of the systems. Chemical intuition led by TST implies low temperature to entail kinetic control, *i.e.*, only the reaction path with the lowest barrier is accessible. Yet, neither system undergoes these reactions: both favour the through-barrier route to their thermodynamic products **34** and **36**, respectively (Fig. 7). That is, the tunnelling path does not necessarily follow the kinetic direction but provides a choice: *tunnelling control* ensues.



Scheme 5 Systems that were used for investigations of C/H-tunnelling.

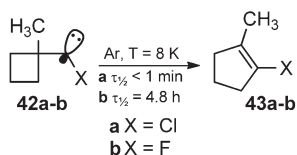
Carbon tunnelling

Cyclobutadiene (**1**) is a fascinating molecule and the smallest possible closed-shell neutral antiaromatic system, which is the reason why **1** has a distorted (*D*_{2h}) rather than a square shape (*D*_{4h}) structure in its electronic ground state. Before **1** was directly characterized, trapping reactions revealed a negative activation entropy for its automerization reaction through the antiaromatic transition state⁵³ and since negative activation entropies are known to be an indication for tunnelling,⁵⁴ QMT was proposed to drive the reaction.⁵⁵ This proposal came at a time where even light atom tunnelling was considered a rare case and heavy atom tunnelling was supposed to not play a role in chemistry. However, the distances that the four carbons that move during the reaction is less than 0.2 Å, resulting in a very narrow barrier, whose height is estimated to be in the range of 8–15 kcal mol⁻¹, thereby allowing QMT; various computations predicted a very high tunnelling rate.⁵⁶ Structure **1** is accessible by photochemical cleavage of various precursors,⁵⁷ and the proposed tunnelling mechanism was confirmed experimentally utilizing NMR spectroscopy on ¹³C labelled **1** in an Ar matrix at 25 K.⁵⁸

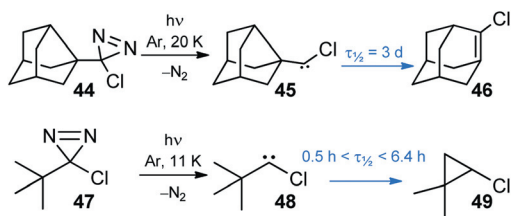
Thus far we have not discussed examples where a chemical reaction is solely driven by QMT at ambient conditions. Even if a reaction is accelerated by tunnelling, the visible overall reaction rate is still a mixture of the classical and QMT parts. For a high QMT contribution one needs to focus on a concerted reaction with a high barrier and study the system over a large temperature range in order to obtain precise Arrhenius parameters that can reveal QMT. These requirements are met by several E₂ reactions (Scheme 5).

Kinetic studies of the deprotonation of 1-bromo-2-phenylpropane (**37**)⁵⁹ with ethoxide in ethanol indicated that deuteration entails an increase in the Arrhenius reaction barrier by 1.8 kcal mol⁻¹; an extraordinarily strong KIE that can only be explained by accounting for QMT.²¹

The elimination reactions of **39** and **41** showed that the solvent composition (DMSO and H₂O) affects the KIE, most likely by influencing the force constants and thus the barrier width.^{60,61} Experiments with the respective β-¹³C-**39** compound allowed breaking down the overall isotope effect into a semi-classic and a QMT part. The authors showed that heavy atom movement is coupled to the reaction coordinate and lowers the *k*_H/*k*_D values;⁶¹ the whole system tunnels rather than just the directly involved proton.⁶² Motions of non-transferred atoms can



Scheme 6 Tunnelling controlled ring insertion of a carbene.



Scheme 7 C-atom tunnelling in carbene rearrangements.

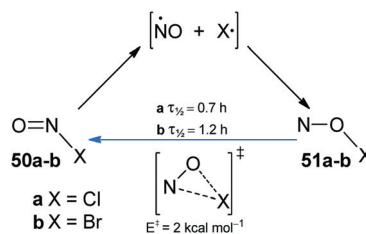
thus be coupled to the migration of the transferred hydrogen atom, corresponding to a heavy-atom 2° KIE.⁶³

Elimination reactions were the first systems for utilizing early semi-empirical tools from Bell *et al.* to determine the role of tunnelling contributions.⁶⁴ The proton was treated as a charged particle moving in the field of two rigid electron distributions, each surrounding a carbon and an oxygen nucleus, respectively, with their electron distributions represented by Slater orbitals. The basicity of the oxygen atom was computationally varied by changing its partial charge. After the model was augmented to take Pauli repulsion into account, it turned out to yield reasonable values for experimentally known KIEs. The KIEs arise from different tunnelling contributions of ^1H and ^2D species and the computational results were in agreement with the experiments.

QMT attracts special attention if it drives a reaction that would not be possible without it. Such an example for heavy atom tunnelling has recently been shown by Zuev *et al.*, namely the ring insertion of carbenes **42a–b** into the strained cyclobutyl moiety (Scheme 6).⁶⁵ Whereas the tunnelling rate could be determined for the fluoro-substituted carbene (**42b**), it was immeasurably fast for the chloro-substituted system (**42a**), thereby reflecting the different barrier heights of 3.1 and 6.5 kcal mol⁻¹ for **42a** and **42b**, respectively.

A similar example is given by the noradamantylcarbene system (Scheme 7), where the unsubstituted carbene could not be characterized and computations predict fast rearrangement to adamantene over a barrier of only 0.4 kcal mol⁻¹.⁶⁶ Chloro substitution (**45**) raises this barrier up to 5.3 kcal mol⁻¹, but still does not stop the isomerization to **46**, which occurs at 23 K in solid argon with a half-life of 3 d through heavy atom tunnelling.⁶⁷ The authors support QMT with computations and the fact that the longest distance travelled by any of the carbons was only 0.44 Å.

Photolysis of matrix isolated **47** yielded halocarbene **48**, which vanished in the course of several hours with a half-life that could not be determined exactly, because of strong matrix site effects. The temperature independence of the rate from 10 to 30 K and the carbene's short lifetime at room temperature indicate a remarkable speedup of seven orders of magnitude. This



Scheme 8 N/O-tunnelling in isonitrosyl halides.

increase in reaction rate is inconsistent with a classical Arrhenius behaviour and the authors suggested that QMT plays a decisive role.⁶⁸

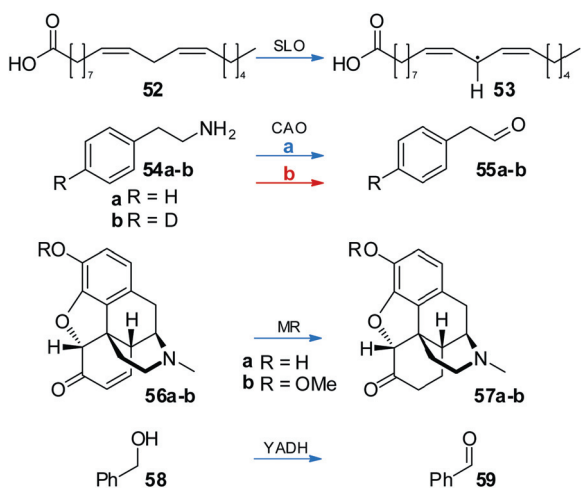
Heteroatom tunnelling

Maier *et al.* reported the isomerization of matrix isolated nitrosyl halides (**50a–b**) to the respective isonitrosyl halides (**51a–b**). The absence of a vibrational fine structure of the intense UV band lead the authors to suggest that irradiation of **50a–b** at first results in fragmentation and subsequent recombination of the two radicals inside the matrix cage finally yields the isomers **51a–b** (Scheme 8).⁶⁹

With a reaction barrier of ~ 2 kcal mol⁻¹ the isonitrosyl halides (**51a–b**) should be stable under matrix conditions, however, the bromo- and chloro compounds vanished in the dark with temperature independent half-lives of about one hour. The authors hesitantly acknowledged a QMT contribution to the isomerization, but they were reluctant to clearly propose it as a driving force in the context of the heavy halogen atoms. According to our M06-2X/6-311++G(d,p) computations, the reaction coordinate involves only very little halogen atom motions; the imaginary frequency of the TS corresponds to an internal rotation of the N–O moiety adjacent to an almost stationary halogen atom. These systems feature an example for heteroatom tunnelling through a low barrier. The fluoro compound could not be characterized which—we suppose here—is probably due to a further increased tunnelling rate: Our CVT/ZCT computations are consistent with the experimental half-lives of **51a–b**, as well as with the non-observation of the fluoro compound, that our computations indicate a tunnelling rate of more than factor 10^3 times greater compared to **51b**.

Biological systems

The classical picture of enzyme catalysis solely relies on altering the enthalpic and entropic reaction profiles, such as lowering the activation barriers or locating the reactants closer to one other. Many biologically relevant reactions involving transfer of a hydrogen over a barrier of only a few kcal mol⁻¹ appear to involve H-atom tunnelling.⁷⁰ In this context, one has to consider that QMT can play a crucial role in enzymatic activity and not only altering the barrier height, but also its shape and thus the tunnelling rate, may be a key to catalytic activity.⁷¹ Recognizing this, it is not surprising that QMT plays a crucial role in several enzyme catalyzed reactions (Scheme 9). In the context of asymmetric reactions one may wonder whether tunnelling control



Scheme 9 Some enzyme reactions that show tunnelling control.

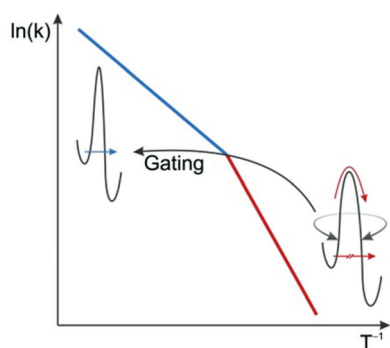


Fig. 8 The concept of “gating” assumes that low-energy vibrational modes of the enzyme are populated and narrow the barrier width.

could also entail enantioselection. In the case of a prochiral molecule tunnelling to a chiral product, the two existing pathways could be influenced independently by a chiral environment. While it is not possible to generate a chiral noble gas matrix, enzymes in a sense represent such an environment. If one considers an enzyme's activity exerted not only on the barrier height but also on its width, chiral properties of enzymes may favour one of two possible tunnelling pathways and thereby lead to enantioselection.

Klinman *et al.* were the first to report the occurrence of H-atom tunnelling in the yeast alcohol dehydrogenase (YADH) oxidation of **58** to **59** by nicotinamide adenine dinucleotide (NAD⁺), as indicated by extraordinarily large KIEs⁷² that could not be explained without taking atom tunnelling into account.⁷³ This work opened the door for further studies on enzyme kinetics involving tunnelling so that shortly thereafter it could be shown that the oxidation/hydrolysis of **54a** to **55a** catalyzed by copper amine oxidase (CAO), also involves tunnelling.⁷⁴ Further investigations by Murakawa *et al.* revealed that conformational flexibility has a strong influence on the tunnelling rate: Small modifications on the substrate can easily suppress tunnelling,⁷⁵ as reaction of **54b** catalyzed by the same enzyme does not involve QMT.

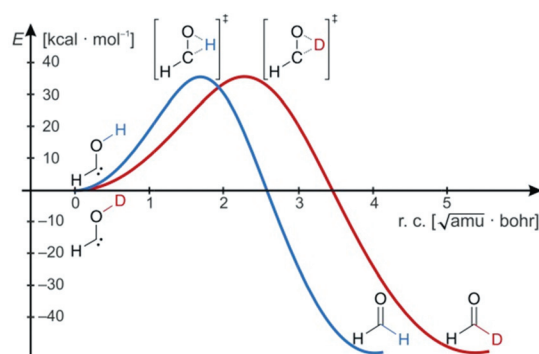


Fig. 9 Influence of the mass of the tunnelling particle on the barrier width.

Another milestone in this area was the discovery of a temperature dependent tunnelling rate by Klinman *et al.*, revealing that an increasing tunnelling contribution is measurable for the dehydrogenase catalyzed ethanol oxidation above 30 °C, but it vanishes as the temperature is lowered to 5 °C.⁷⁶ A concept to explain this behaviour is known as *vibrational gating* and is based on the assumption that the enzyme framework features low-frequency molecular vibrations⁷⁷ that have a contracting effect on the barrier width, leading to a temperature dependent KIE (Fig. 8). This behaviour was found for a variety of enzymes, such as alcohol dehydrogenase (ADH) as well as soybean lipoxygenase (SLO),^{78–81} and for morphinone reductase (MR).⁸² The temperature dependence of the KIE indicates that the system in its ground state is not “tunnelling ready” and needs to be slightly activated in order to facilitate the tunnelling process.⁸³ This concept of a pre-tunnelling state was explicitly discussed by Limbach *et al.*, concluding that thermal activation combined with QMT plays a major role for light- and heavy atom motions.⁸⁴ While higher quantum states of the more rigid, fundamental vibrational modes are generally not populated at room temperature, large molecules, such as enzymes, involve low frequency modes that can be populated at biologically relevant temperatures. The pre-tunnelling state can also be achieved by photoactivation, as Scrutton *et al.* found for the enzyme prochlorophyllide oxidoreductase.⁸⁵ Recent work⁸⁶ also revealed a possible pressure dependence of the tunnelling rate, thereby completing the dichotomy to the classic physical understanding of the effect, which does not suggest dependence on the physical parameters of the system.

Tunnelling computations

Regarding tunnelling computations, we will only briefly outline the Wentzel–Kramers–Brillouin formalism, which is a simple way of computing tunnelling half-lives (*vide supra*):⁴ In this model, the tunnelling problem is typically treated in one dimension: A certain vibrational mode of the reactant is considered the reaction mode; displacing the involved atom(s) leads to the TS—where the value of the reaction mode becomes imaginary—and finally down to the product. Such an energy profile can be computed with the Hessian-based predictor corrector algorithm⁸⁷ as, *e.g.*, implemented in Gaussian09.⁸⁸ The ZPVE correction for each point is given by the frequencies projected along the

reaction path; this mathematical operation leads to the disappearance of the reactive vibrational mode, because the frequency now represents the reaction coordinate of the system. The isotope effect is taken into account as the mass is part of the reaction coordinate: Whereby isotope exchange does not affect the PES, doubling the mass of the migrating particle results in stretching the effective distance by a factor of $\sqrt{2}$ (Fig. 9).

The barrier penetration integral $\theta(\epsilon)$ (*vide supra*), the area restricted by the curve and the horizontal line between the reactant and the curve, is directly connected to the tunnelling probability by $\kappa(\epsilon) \approx e^{-2\theta(\epsilon)}$. Multiplying $\kappa(\epsilon)$ with the reaction mode frequency yields the rate constant. Since $\theta(\epsilon)$ scales linearly with the width, but only as square root of the height, it is possible for QMT to lever out the rules of chemical selectivity that are based on classical kinetics.

Even though the results of the WKB approximation applied to reaction profiles that were obtained at the M06-2X/6-311++G-(d,p) level were in excellent agreement with the experimental values for our hydroxycarbenes, the approximation still has a serious disadvantage: The tunnelling path is assumed to exactly match the minimum energy path, which is a caveat, since the tunnelling pathway might favour the penetration of a higher, but narrower barrier: Accurate tunnelling computations call for an optimization of the barrier penetration tendency with respect to the reaction coordinate, rather than only the path of the least energy. The deviation between tunnelling and minimum energy path can be recovered by multidimensional tunnelling corrections.^{89,90} Clearly, there are still methodological challenges to be overcome to allow routine and very exact tunnelling computations.

Conclusions

The classic pictorial understanding of chemical reactivity has been moulded by the early work of Woodward and Baer, who emphasized, building on the theoretical foundations of Eyring as well as Evans and Polanyi, that the decisive factors for selectivity in a chemical reaction are the heights of the activation barriers for the various reaction paths. Since then, chemical selectivity has strictly been associated with the term *kinetic control*. However, the appearance of QMT and its interpretation far beyond mere corrections to reaction rates, has led to the formulation of *tunnelling control*. Such situations are particularly obvious if *no* reaction occurs through thermal activation and the product can only form through a tunnelling pathway.⁹¹

High and narrow activation barriers are particularly prone to QMT and they provide a direct assessment of the chemical relevance of tunnelling as a physical phenomenon. For instance, the isomerizations of matrix-isolated alkyl or aryl hydroxycarbenes are only possible through QMT as the thermal reactions are entirely blocked at the very low temperatures of the experiment. Tunnelling control is not restricted to these conditions, as QMT rates in chemical reactions can in fact show temperature dependence and thus are also relevant at ambient conditions. In some cases of heavy atom tunnelling, thermal activation is even needed to populate higher vibrational levels wherein the barrier penetration tendency exceeds the ground state's value by many orders of magnitude.⁹² The concept of tunnelling from

vibrationally excited states reveals the strong significance of QMT for reactions catalyzed by enzymes.

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- 91 Such conditions are typically given by noble gas matrices at cryogenic temperatures, wherein the chemical environment still effects the tunnelling rate, as it can be altered by changing the matrix material. These matrix effects still have to be considered as a minor perturbation: Resembling each other by influencing the rates of any tunnelling processes, they do not influence the outcome of a chemical reaction, such as the distribution of different tunneling products.
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