Chem Soc Rev

IR-induced and tunneling reactions in cryogenic matrices: the (incomplete) story of a successful endeavor

Journal:	*Chemical Society Reviews*
Manuscript ID	CS-SYN-10-2021-001026.R1
Article Type:	Synopsis
Date Submitted by the Author:	28-Dec-2021
Complete List of Authors:	Fausto, Rui; University of Coimbra, Department of Chemistry Ogruc Ildiz, Gulce; Istanbul Kultur Universitesi - Atakoy Kampusu, Department of Physics; University of Coimbra Department of Chemistry, Department of Chemistry Manaia Nunes, Cláudio ; University of Coimbra, Department of Chemistry
Note: The following files were submitted by the author for peer review, but cannot be converted to PDF. You must view these files (e.g. movies) online.	
Permissions_for_reproduction_of_Figures.zip	

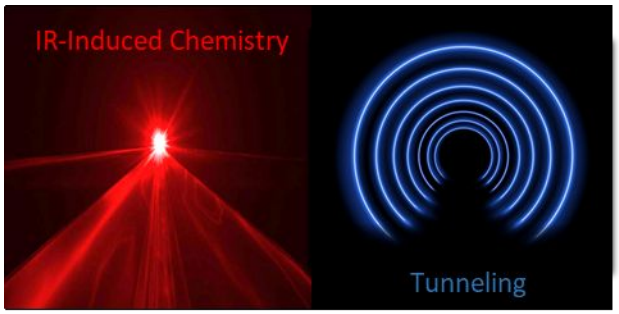
SCHOLARONE™
Manuscripts

TABLE OF CONTENTS ENTRY

IR-induced and tunneling reactions in cryogenic matrices: the (incomplete) story of a successful endeavor

Rui Fausto, Gulce O. Ildiz and Cláudio M. Nunes

IR-induced reactions in cryogenic matrices and related tunneling-driven processes are surveyed, highlighting the entanglement between the two types of processes.



REVIEW ARTICLE

IR-induced and tunneling reactions in cryogenic matrices: the (incomplete) story of a successful endeavor

Received 28th December 2021,
Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

Rui Fausto,*[a] Gulce O. Ildiz [a,b] and Cláudio M. Nunes[a]

In this article, IR-induced and tunneling-driven reactions observed in cryogenic matrices are described in a historical perspective, the entangling of the two types of processes being highlighted. The story of this still ongoing fascinating scientific endeavor is here presented following closely our own involvement in the field for more than 30 years, and thus focuses mostly on our work. It is, by this reason, also an incomplete story. Nevertheless, it considers a large range set of examples, from very selective IR-induced conformational isomerizations to IR-induced bond-breaking/bond-forming reactions and successful observations of rare heavy atom tunneling processes. As a whole, this article provides a rather general overview of the major progresses achieved in the field.

Keywords: IR-induced chemistry, tunneling-driven reaction, Infrared spectroscopy in cryogenic matrices

Introduction and background perspective

The first reported IR-induced reaction was described by Hall and Pimentel almost 60 years ago [1]. In that pioneer experiment, the authors isolated nitrous acid in an argon matrix and used broadband infrared excitation in the νOH stretching wavenumber region (3650-3200 cm^{-1}) to induce changes in the relative populations of the two conformers of the molecule (Figure 1). The conformational changes were found to depend on the specific wavenumber range applied to irradiate the sample, which could be chosen by using appropriate infrared bandpass filters. In their article, Hall and Pimentel pointed out that *"the [observed] IR-induced isomerization of nitrous acid can be considered to be a new type of photochemical reaction"* and stressed the fact that the *"study of this reaction [was] possible only because of the unique potentialities of the matrix isolation technique"* [1]. They appropriately concluded that *"perhaps the most important [result] in this work is the implied high efficiency of intramolecular energy transfer among the vibrational degrees of freedom of a vibrationally excited molecule"* [1].
Very interestingly, at the time, the discovery of Hall and Pimentel was not received so enthusiastically by the scientific community as it could be expected considering its highly innovative character. The main reason for that was the lack of selectivity of the observed process. In fact, upon broadband excitation both conformers were being simultaneously excited, so that their final populations resulted from the attainment of a photostationary state. A photostationary state is a function of the applied excitation wavenumber range and, in that way, some control of the system can be achieved. Nevertheless, it was clear that to accomplish full control of this type of reactions and make the approach useful for application to other systems, selective excitation of a single specific conformer had to be made possible.

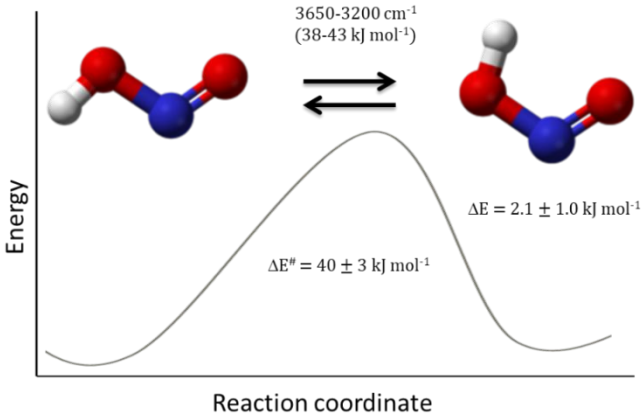


Figure 1. Potential energy profile for interconversion between the two conformers of nitrous acid, whose relative populations could be changed by bandpass-filtered broadband IR excitation of the matrix isolated compound. Adapted from ref. 1. Copyright 1963 American Institute of Physics.

This problem was only solved 34 years later, when infrared narrowband tunable light sources became more easily available. In 1997, Pettersson, Lundell, Khriahtchev and Räsänen, at the University of Helsinki, published a major breakthrough study [2] where the selective conformational isomerization of formic acid isolated in an argon matrix was successfully induced by narrowband excitation with a laser-based IR tunable light source. The most stable ***Z*** conformer of formic acid (O=C–O–H dihedral: 0°) was initially trapped in the

[a] CQC-IMS, Department of Chemistry, University of Coimbra, 3004-535 Coimbra, Portugal.
[b] Department of Physics, Faculty of Sciences and Letters, Istanbul Kultur University, 34158 Bakirkoy, Istanbul, Turkey.
* Corresponding author (e-mail: rfausto@ci.uc.pt).

cryogenic matrix from the gas phase, and subsequently converted into the higher energy ***E*** conformer (O=C–O–H dihedral: 180°) upon matrix irradiation at the wavenumber of the νOH stretching first overtone of the ***Z*** form (6934 cm^{-1}) [2]. This first investigation was followed by others where the ***Z*** → ***E*** conformational conversion of formic acid was investigated in further details [3-10]. In those studies, isotopically labelled formic acid and different types of matrices were used.

Our group had the chance to join those pioneer investigations since the very beginning. The studies were promptly expanded to other simple carboxylic and dicarboxylic acids, like acetic, oxalic, fumaric, maleic and malonic acids [7,11-15]. From our fruitful collaboration with the Helsinki group (and also in result of the work of other groups participating in this adventure) some general conclusions emerged, which became the basis for the subsequent more elaborated studies on more complex systems, like amino acids, nucleic acid bases, halogenated carboxylic acids, α-hydroxyl, α-keto and α,β-unsaturated carboxylic acids, aromatic and other cyclic carboxylic acids, and phenol derivatives [16-47], among others.

One very interesting early observation was that the IR excitation of a matrix isolated compound can be selective to the nature of the matrix sites occupied by the molecules [5]. In a matrix, molecules might be trapped in different local environments (matrix sites). Molecules in different matrix sites feel different intermolecular potentials due to the different interactions with the matrix atoms, this leading to slightly different intramolecular potentials. Therefore, the vibrational spectra of identical molecules trapped in different sites differ slightly. In practice, this leads to observation of bands in the spectrum of a given compound that appear split. It shall be noticed that not all bands have to show matrix splitting, since this depends upon the degree of perturbation of the intramolecular potential associated to each vibrational coordinate in result of the intermolecular interactions. In general, vibrational coordinates associated with more polar groups are more affected by the matrix medium and the corresponding bands appear more frequently split due matrix effects. For simple carboxylic acids, this is the case of, for example, the νOH and νC=O stretching modes. For formic acid, it was found that the molecules may occupy two main sites in an argon matrix, which give rise to νOH fundamental bands at 3548.2 (site 1) and 3550.5 cm^{-1} (site 2) [5]. The corresponding 1st overtone bands are observed at 6930.3 and 6934.8 cm^{-1} [5]. As shown in Figure 2, excitation of molecules trapped in a given matrix site at the wavenumber of the corresponding νOH 1st overtone results in the ***Z*** → ***E*** conformational conversion, without affecting in a measurable way the structure of the site. This means that, besides being selective to the molecular species (e.g., a given conformer of a given molecule), the reactions resulting from vibrational excitation are also selective regarding the local matrix trapping environment. As it will be shown later in this article, such selectivity is also kept when the energy delivered to the reactant conformer is substantially higher than that corresponding to excitation to a νOH stretching 1st overtone, i.e., when excitation is performed, for example, at the characteristic wavenumbers of higher-order overtones of this vibration.

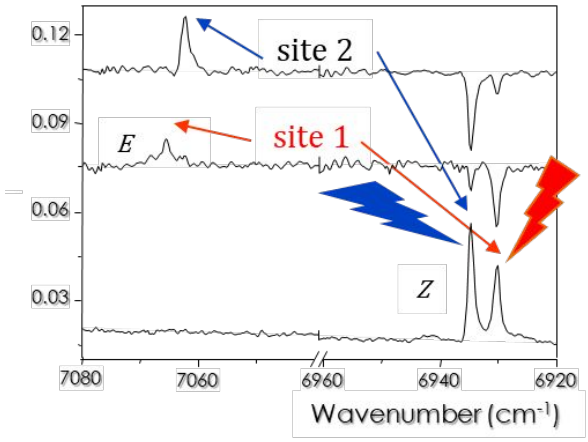


Figure 2. Results of narrowband IR irradiation at the νOH 1st overtone wavenumbers of the ***Z*** conformer of formic acid molecules isolated in two different matrix sites in an argon matrix, leading to its conversion into the ***E*** isomer. The bottom spectrum is that of the as-deposited matrix, while the middle and upper spectra are difference spectra obtained by subtracting the bottom spectrum to those obtained after the performed irradiations. Adapted from ref. 5. Copyright 2003 Elsevier.

Another fascinating observation resulting from the very first series of studies with narrowband selective vibrational excitation was that the mechanism of energy redistribution from the excited coordinate to the reactive coordinate (in the case of the conformational isomerization of formic acid this latter is the low energy C–O torsional coordinate) is not strictly statistical, implying that there are preferred channels which maximize the efficiency of the process. One simple proof for this is the observation of very similar efficiencies in the IR-induced isomerization processes of molecules having significantly different numbers of potentially competitive acceptor low-energy coordinates, e.g. formic acid and cytosine [2,6,45]. The existence of such funnel-like preferential energy relaxation channels was demonstrated for the case of matrix isolated formic acid using time-resolved IR spectroscopy [48].

In the context of the present article, however, the most relevant observation extracted from the initial studies on IR-induced processes in cryogenic matrices was the fact that the conformational isomerization reactions may take place even when the energy deposited in the excited coordinate stays below that of the barrier separating the reactant conformer from the product. This was first observed for formic acid [6], and immediately after for acetic acid [49], but it is a rather general phenomenon. As shown in Figure 3, the quantum yields for the ***Z*** → ***E*** conformational conversion in both formic and acetic acids reduce by only one to two orders of magnitude once the excitation energy stays below but close to that corresponding to the energy barrier of the reaction, and only diminish considerably when the excitation is performed at an energy far from that of the energy barrier. The significant quantum yields of the reaction for excitation at energies below the barrier are easily explained taking into account its occurrence *via* the quantum mechanical tunneling (QMT) mechanism. Vibrational

 This journal is © The Royal Society of Chemistry 20xx

Please do not adjust margins

excitation followed by intramolecular energy relaxation takes the molecule to a vibrational state of the reactive coordinate in which both the effective height and width of the reaction barrier reduce, so that the tunneling probability becomes high. These reactions are designated as vibrationally-assisted QMT-driven reactions.

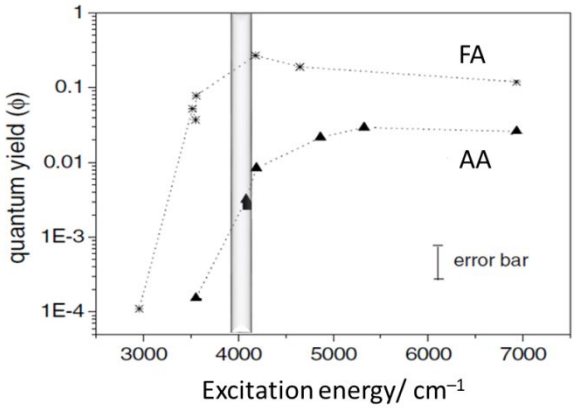


Figure 3. Quantum yields for the ***Z*** → ***E*** conformational isomerization for formic acid (FA) and acetic acid (AA) as a function of the excitation energy. The excitations were performed at the indicated wavenumbers, which correspond to observed bands in the IR spectrum of the reactant ***Z*** conformer of the two acids. The shadowed region in the figure shows the range of energies predicted for the ***Z*** → ***E*** energy barrier for the two molecules using different methods. Adapted from ref. 49. Copyright 2004 American Institute of Physics.

It is worth noticing that the quantum yields for the reaction of acetic acid were found to be systematically lower than those observed for formic acid [49], a result that is in agreement with the existence in the former molecule of an alternative energy relaxation channel efficiently competing with the reactive channel (as already mentioned, the torsion around the C–O bond that leads to the ***Z*** → ***E*** conformational conversion). Such secondary relaxation channel has as final acceptor coordinate the low-energy internal rotation of the methyl group of acetic acid [49].

An additional observation resulting from the studies performed on the simple carboxylic acids first investigated was that the higher energy ***E*** conformers (formed upon vibrational excitation of the most stable ***Z*** conformers) spontaneously decay back to the original species in the dark *via* a tunneling-driven process. For formic acid isolated in argon, such tunneling process has a rate of ca. 2 x 10^{-3} s^{-1}, which corresponds to a half-life of the ***E*** form of a few minutes [5]. The nature of the mechanism involved in these reactions was since the very beginning proved unequivocally through experiments with isotopically labelled formic and acetic acids [5,6,49], and this has been confirmed later for other types of molecules containing the carboxylic group (e.g., amino acids and halogenated carboxylic acids [16-19,35-41]). The relevance of spontaneous QMT decay of higher-energy conformers produced *in situ* in matrices (using either vibrational or electronic excitation of suitable precursors) has also been demonstrated for other types of conformational isomerizations involving movement of hydrogen atoms, for example in derivatives of nucleic acid bases and phenols [30,42-47].

As noticed above, the matrix isolation method provides optimal conditions for direct observation of QMT. The very low work temperatures characteristic of a matrix isolation experiment (typically of a few Kelvin) prevent occurrence of any spontaneous over-the-barrier reaction that has an associated barrier higher than a few kJ mol^{-1}. Under these conditions, observation of a spontaneous reaction usually implies that it takes place by tunneling. Since tunneling from the ground vibrational state implies that the reaction product has a lower energy than the reactant, it is easy to understand why vibrational excitation is particularly suitable to allow for observation of tunneling reactions: in one side, one can shift the state of the reactant to a higher vibrational state and open the gate for tunneling to products otherwise inaccessible and, on the other side, a higher energy species can be first generated as a result of the vibrational excitation of the reactant followed by energy relaxation, and subsequently undergo a tunneling-driven reaction to the final product. In the latter case, the final product can either be the original reactant, as in the cases described above for formic and acetic acids, or a completely different species, as it will be here shown later. In this way, in a certain perspective one can state that IR-induced chemistry and QMT are, under matrix isolation conditions, very often entangled processes. The interesting point is that one can take advantage of this intertwining to strategically play with the structure of molecules, as it will be demonstrated in the next sections.

It shall also be highlighted at this point that recent studies of QMT in cryogenic matrices have been providing evidence that this phenomenon shall not be considered only as a complementary mechanism to kinetics and thermodynamics in explaining chemical reactivity. QMT can in fact even determine the reactivity of a chemical species, superseding the classical rules of thermodynamics and kinetics and emerging as a new paradigm in chemical reactivity [50,51]. Figure 4 exemplifies how this can be conceived. In the top panel of the figure, a potential energy profile for two competitive reactions of **A**, to give products **B** and **C**, is presented. **B** corresponds to the thermodynamically driven product of lowest energy, while **C** is the result of kinetical control, generated *via* a lower energy transition state. Tunneling can also be considered to take place for generation of both **B** and **C**, and in matrix isolation conditions even dominate or occur exclusively (depending on the barrier heights and widths), but whatever the situation would be in this case tunneling does not lead to a new product. On the other hand, the potential energy profile shown in the bottom panel of Figure 4 is considerably more interesting, and it is exemplified for a real example [50,52]. In this case, the 1,2-methyl shift product of rearrangement of *tert*-butylchloro-carbene is both the thermodynamics and kinetics determined product, since it has the lowest energy among the possible products and can be reached *via* the lowest energy transition state. However, after *in situ* generation of the reactant carbene in a cryogenic N_2 matrix (at 11 K), this putative product was not experimentally observed [52]. Instead, the C–H bond insertion

cycloalkane product was observed, which results from tunneling control, since though being higher the barrier leading to its formation is considerably narrower than that corresponding to the formation of the alkene species resulting from the 1,2-methyl shift. Another paradigmatic example of tunneling control of chemical reactivity has been reported recently by Shreiner, involving the rearrangement of matrix isolated methylhydoxycarbene [50,51].

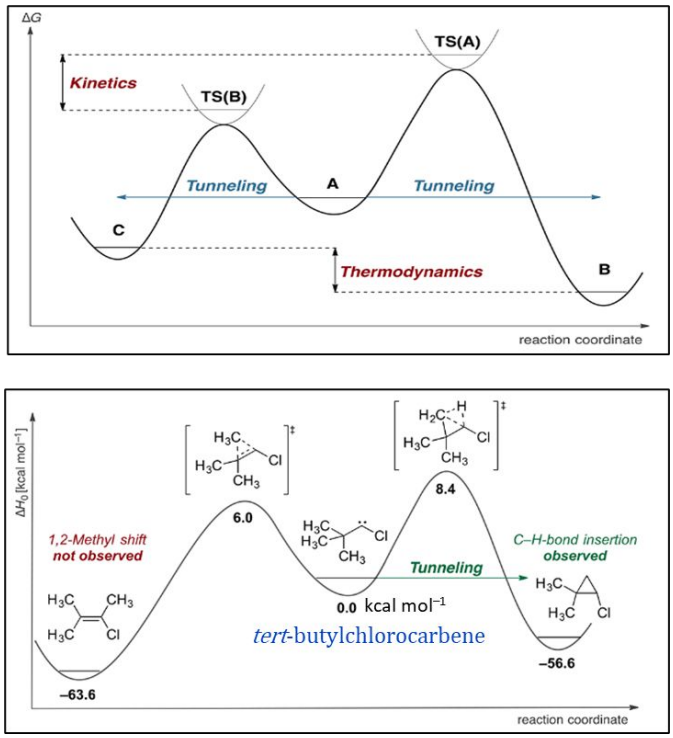


Figure 4. *Top*: Potential energy profile showing a trivial case where two possible products resulting either from the kinetics or thermodynamics control are expected to be obtained. *Bottom*: potential energy profile where the reaction proceeds through the higher, but narrower energy barrier, yielding a product that is neither kinetically nor thermodynamically favored (the given example corresponds to the reactivity of *in situ* generated *tert*-butylchlorocarbene in a N_2 matrix). The original data was shown in ref. 52, but the authors apparently did not notice they were observing a reaction resulting from tunneling control, fact that was later pointed out by Schreiner [50]. Adapted from ref. 50. Copyright 2017 American Chemical Society.

Before starting to provide relevant examples to illustrate the progress on the investigation of IR-induced and tunneling-driven reactions observed in cryogenic matrices in a historical perspective, which will be the subject of the next sections of this article, it appears appropriate to present here the main reasons why vibrationally-induced chemistry is so appealing. The main reason for this is because a laser can be tuned to the vibrational frequency of a specific bond and used to deposit sufficient energy to cleave that bond while leaving the remaining part of the molecule practically undisturbed. This is a very much different situation compared to thermally- or UV-induced processes, where extensive changes are made to the structure of the whole molecule. Using a simple comparison, IR-induced processes are the equivalent of a laparoscopic surgery, where the target organ is reached with minimum damage of the body, in opposition to a strongly invasive open-abdominal surgery, which in this comparison is the equivalent of both thermal and UV-induced reactions. Additionally, IR excitation may be used to change the structure of the molecule, in a very specific and localized way, to open new reaction channels, as illustrated, for example, in the decomposition reaction of diazomethane depicted in Figure 5. In this case, selective vibrational excitation of the νCNN anti-symmetric stretching fundamental of the molecule was performed [53], which took the molecule to a vibrational state where the path to the cleavage of the CN bond *via* δCH_2 bending became accessible.

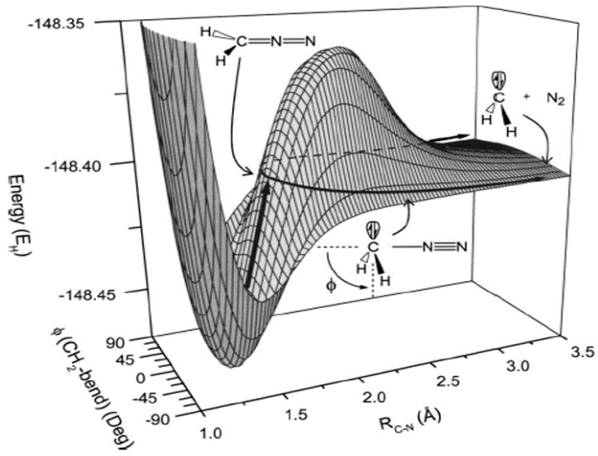


Figure 5. Potential energy surface illustrating the opening of the dissociation channel *via* δCH_2 bending, upon vibrational excitation of the νCNN anti-symmetric stretching of diazomethane. The reaction was carried out in the gas phase and fs pumping was used to prevent statistical redistribution of energy (ps time scale). Adapted from ref. 53. Copyright 2003 American Institute of Physics.

Another interesting possibility opened by IR-induced chemistry results from the fact that conformers can be produced in a very selective way, including conformers of high-energy otherwise not accessible to experimentation. This allows for conformationally selective chemistry to be investigated. The UV-induced photodegradation of formic acid is a good example of conformationally dependent reactivity of a compound [4], but other examples have also been reported [54-57]. Formic acid has only two conformers and they were found to have distinct preferential photodegradation pathways (Figure 6). After isolation in a cryogenic matrix of the most stable ***Z*** conformer, UV irradiation results mostly in the production of CO + H_2O. On the other hand, *in situ* generation of the higher energy ***E*** conformer, upon vibrational excitation of the initially deposited ***Z*** form, allowed for the investigation of its photochemistry, which was shown to preferentially yield H_2 + CO_2 [4].

In the next sections, the major developments resulting from the above-mentioned initial experiments on IR-induced chemistry and interconnected tunneling-driven reactions will be presented, following closely our involvement in the field for more than 30 years. We will focus mostly on our own work, but many other groups have also been given outstanding

 This journal is © The Royal Society of Chemistry 20xx

Please do not adjust margins

contributions to the field, and this has been highlighted in our sequence of reviews published in the RSC Series *Photochemistry* [58-65]. The story here presented is necessarily an incomplete story. Nevertheless, it considers a large range of examples, from very selective IR-induced conformational isomerizations to successful observations of rare heavy atom tunneling processes, and it provides a rather general overview of most of the major progresses achieved in the field.

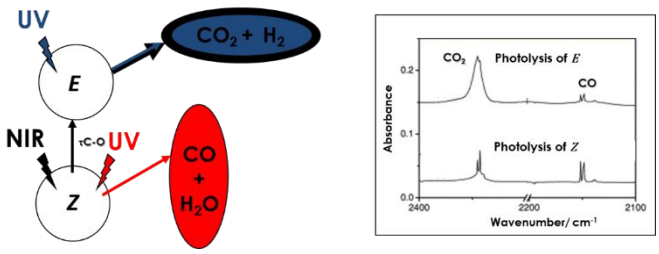


Figure 6. Schematic representation of the conformationally dependent photodegradation of formic acid, and IR spectra illustrating the formation of the representative products CO and CO_2. Adapted from ref. 4. Copyright 2002 American Chemical Society.

From simple 2-states systems to complex multi-states systems: on the route of generalization

The first IR-induced studies focused on simple molecules exhibiting two conformational states, with particular emphasis on formic and acetic acids [2-6,49]. Our already classic study on propionic acid (in collaboration with the Helsinki group) [66] appeared as a landmark in the field, bringing the technique to the investigation of a molecule with a larger number of relevant conformers.

Propionic acid has two conformers of low energy, where the carboxylic group is in the *Z* conformation (***Z-syn*** and ***Z-skew*±**), and two conformers of higher energy, where the carboxylic group is in the *E* conformation (***E-syn*** and ***E-skew*±**). Figure 7 shows the structures of the conformers and the energy barriers for their interconversion, as predicted theoretically.

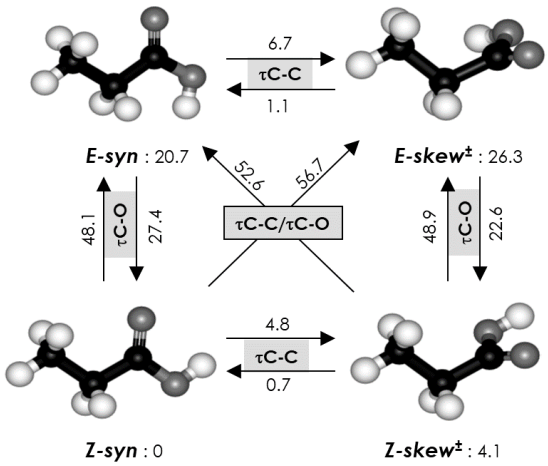


Figure 7. Conformers of propionic acid and their predicted energy differences and interconversion barriers (kJ mol⁻¹). Adapted from ref. 66. Copyright 2005 American Chemical Society.

Considering their high relative energy, the *E* conformers have a negligible population in gas phase, so that it could be expected that only the two *Z* conformers should be observed experimentally. Interestingly, it was found that the most stable ***Z-syn*** conformer was exclusively present in the as-deposited matrices of the compound [66]. The absence of the ***Z-skew*±** conformer in the initially prepared matrices is, however, easy to understand. This conformer is separated from the most stable form by a very small energy barrier (0.72 kJ mol^{-1}, as predicted at the MP2/6-311++G(2d,2p) level [66]). This barrier is then easily surpassed at the time the molecules, initially in a hot gaseous beam, land onto the optical substrate (a CsI window cooled to 15 K) during deposition of the matrix. Consequently, the higher-energy ***Z-skew*±** conformer converts into the most stable ***Z-syn*** form. This phenomenon (known by conformational cooling effect) is well-known and has been observed many times in matrix isolation experiments for molecules with conformers separated by energy barriers of only a few kJ mol^{-1} [67-69].

The fact that just the ***Z-syn*** conformer is present in the as-deposited matrices of propionic acid is interesting, since this allows for the study of its properties and reactivity in an easy way. The vibrational excitation of this conformer at the wavenumber of its νOH stretching 1st overtone (6960 cm^{-1}) was found to generate both the high-energy ***E-syn*** conformer, *via* rotation around the C–O bond, and the ***Z-skew*±** conformer, through rotation about the C_α–C bond. The latter conformer, once produced *in situ*, is rather stable under matrix isolation conditions at the lowest temperatures used (8 K), because now no energy is available to efficiently surpass the ***Z-skew*± → *Z-syn*** barrier. On the other hand, the ***E-syn*** conformer decays quickly back to the ***Z-syn*** conformer by tunneling, since this reaction involves only motion of the light carboxylic hydrogen atom (this is in fact a similar process to those observed in formic and acetic acids described above). Hence, not just the ***E-syn*** and ***Z-skew*±** conformers could be prompted identified and characterized vibrationally [66], but these experiments opened the possibility for the study of their specific reactivities. Since the initially produced ***Z-skew*±** conformer is stable under the experimental conditions used, a subsequent IR-irradiation at the wavenumber of its νOH stretching 1st overtone (6950 cm^{-1}) could be undertaken. In result of such irradiation, this conformer was converted into the highest-energy ***E-skew*±** conformer, thus generating the last of the 4 conformers of propionic acid (this conformer also decays in the dark, by QMT, to the most stable conformer) [66].

The whole series of experiments performed on propionic acid is summarized in Figure 8 and illustrates well the power of the coordinated use of IR-induced chemistry and tunneling to manipulate chemical structures. The next example deals with an even more complex chemical system and shows how IR-excitation can be coupled not just with QMT but also with UV-excitation in a strategic way to achieve selective structural manipulations. The target compound in those studies was the nucleic acid base cytosine, and the investigations were performed within the scope of a broader program of research developed in collaboration with the group of Nowak and

Lapinski, from the Institute of Physics of the Polish Academy of Sciences, Warsaw.

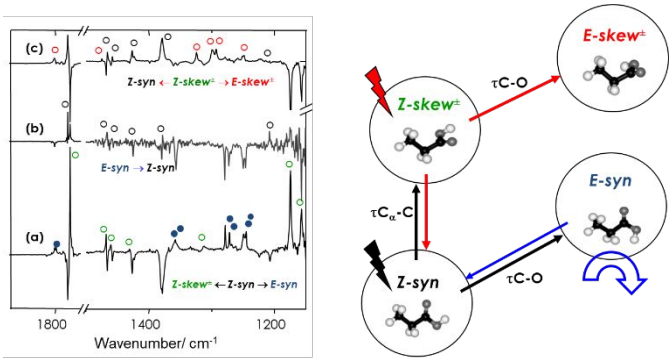


Figure 8. Schematic representation of the IR-induced and QMT experiments on propionic acid (*right*) and IR spectra showing the results (*left*): (a) spectral changes upon excitation of the 2νOH mode of ***Z-syn*** conformer; (b) dark decay of ***E-syn***; (c) spectral changes upon excitation of the 2νOH mode of the ***Z-skew±*** conformer. Difference spectra (a) and (c) were obtained by subtracting the spectra recorded before pumping from those recorded under pumping. Difference spectrum (b) was obtained by subtracting the spectra recorded under pumping from that recorded after a few minutes in the dark. Adapted from ref. 66. Copyright 2005 American Chemical Society.

Cytosine has five main isomeric species: the two lowest energy amino-hydroxy conformers (**AH1**, **AH2**, with **AH2** being ~3 kJ mol^{-1} higher in energy than **AH1**), the amino-oxo form (**AO**) that has an intermediate energy (ca. 5 kJ mol^{-1} above the most stable **AH1** form), and two higher energy imino-oxo isomers (**IO1**, **IO2**) with energies 7 and 12 kJ mol^{-1} above **AH1**. These species are represented in Figure 9, which also summarizes the sequence of experiments we successfully undertook to change the relative amounts of the five forms in a cryogenic matrix [45-47].

Upon deposition of cytosine in an argon matrix, the signatures of all the five isomers of cytosine depicted in Figure 9 were detected [45-47]. UV irradiation at 300 nm resulted in conversion of the **AO** form into the remaining species. In this way, the population of the minor imino-oxo isomers could be strongly enhanced. Subsequent irradiation at 311 nm led to interconversion between the **IO1** and **IO2** isomers. This is a typical reaction progressing toward a photostationary state and, when performed immediately after the irradiation at 300 nm that converts **AO** into both **IO1** and **IO2**, results in effective conversion of **IO1** into the higher energy **IO2** isomer. This UV irradiation does not change the populations neither of **AO** nor of the **AH1** and **AH2** isomers. On the other hand, when the matrix is let in the dark, the **AH2** form spontaneously decays by QMT to the most stable **AH1** form, in a reaction obeying to a dispersive-type kinetics [47] with an average time constant of ca. 36.5 h.

Selective interconversions between the two amino-hydroxy conformers could be achieved by IR excitation. Irradiation at 7013 cm^{-1} (νOH 1st overtone of **AH1**) led to conversion of this form into **AH2**, whereas irradiation at 7034 cm^{-1} (νOH 1st overtone of **AH2**) induced the opposite transformation [45].

It is worth mentioning that these studies were the first ever reported where IR-induced conformational isomerizations were successfully achieved for a large heterocyclic molecule under matrix isolation conditions. In polyatomic molecules containing more than 10 atoms, the higher density of vibrational states could *a priori* be expected to strongly affect the pathways of vibrational energy redistribution, and hence the efficiency of the IR-induced conformational isomerizations. Nevertheless, the results proved that for cytosine the process occurs with an efficiency that is similar to those observed for small molecules like formic and acetic acid, and this was a clear experimental evidence of the existence of preferred channels for vibrational energy redistribution.

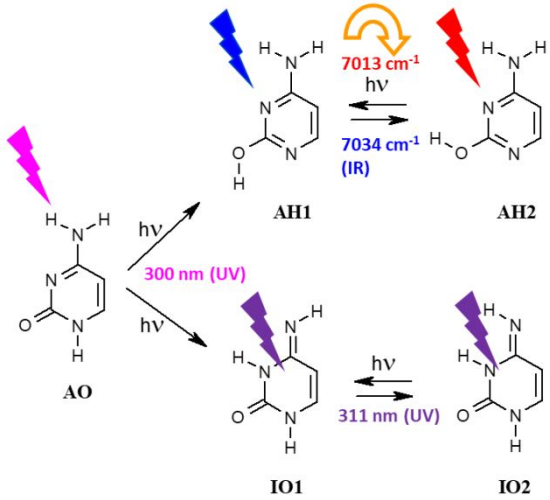


Figure 9. IR- and UV- induced and QMT reactions of matrix isolated cytosine. Adapted from ref. 46. Copyright 2011 Royal Society of Chemistry.

Another relevant development in the field was the use of selective IR excitations to generate rare high-energy dimers of carboxylic acids, showing that the method could also be applied for weakly bonded species. Formic and acetic acids are the paradigmatic examples of this type of studies. For both molecules a large number of unusual dimers was generated in cryogenic matrices upon vibrational excitation of more common dimeric species, and subsequently characterized structurally and spectroscopically [70,71]. The most interesting dimers of these two carboxylic acids that have been produced this way have at least one of their molecular units in the intrinsically less stable carboxylic *E* conformation. Since both ***E*** formic and acetic acid monomers are unstable in a cryogenic matrix, the *E* units of the dimer have to be generated *in situ*. Two different strategies have been applied: in the first, the ***E*** monomer of the acid is first produced by vibrational excitation of the ***Z*** form, and then the matrix is annealed to a higher temperature, allowing for molecular diffusion and formation of the dimers containing the *E* units (very interestingly, the ***E*** conformers were found to diffuse in the warmed matrices more efficiently than the ***Z*** forms, which facilitated the generation of *E* containing dimers [70,71]); in the second approach, the *Z-Z* dimers are first prepared from the ***Z*** monomer by warming the matrix and then the dimers are subjected to IR irradiation to convert them into dimers containing an *E* structural unit [70,71].

This journal is © The Royal Society of Chemistry 20xx

Please do not adjust margins

Figure 10 illustrates this last case, for acetic acid. In this example, note the selective character of the IR-induced process. Upon irradiation at the specific wavenumber of the νOH 1st overtone of the free OH group of the *Z-Z* dimer **D2 *Z-Z***, this species was converted to the **D2 *Z-E*** dimer, without any change taking place either for the ***Z*** monomer or for the *Z-Z* centrosymmetric dimer **D1 *Z-Z*** present in the matrix.

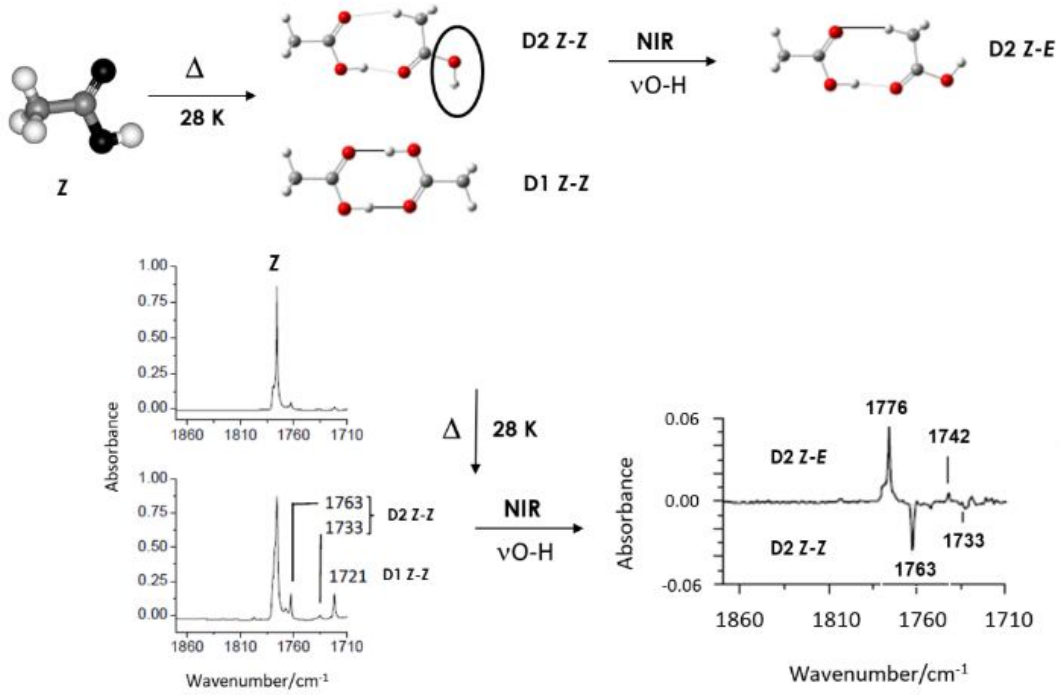


Figure 10. IR-induced selective generation of a *Z-E* dimer of acetic acid in a cryogenic matrix. The matrix was first annealed to 28 K to generate *Z-Z* dimers **D1 *Z-Z*** and **D2 *Z-Z*** and then irradiated at the νO-H first overtone of the free OH bond of **D2 *Z-Z***, generating **D2 *Z-E***. Adapted from ref. 71. Copyright 2015 American Institute of Physics.

Vibrational excitation *via* higher-order overtones: opening the gate to higher energy processes

One limitation to the generalization of vibrational excitation as a tool for inducing chemical reactivity is the relatively small range of energies accessible. If excitation is undertaken using a fundamental vibration, in the most favorable case of pumping of the νOH stretching mode, the energy introduced in the molecule is in the range of only 30–45 kJ mol^{-1} (3000-3600 cm^{-1}). First overtone excitation expands the range of energy to 75-87 kJ mol^{-1} (6300–7300 cm^{-1}), and this is enough energy to allow inducing quite efficiently many types of conformational isomerization processes. We asked ourselves about the possibility of using higher-order overtones to introduce even more energy in the molecules. If possible, excitation using the 2nd overtone of a νOH stretching mode would allow to expand the range of processes energetically accessible to those having barriers as large as ca. 130 kJ mol^{-1}. Though conceptually the idea is simple, there were some important questions to verify: *(i)* in order to choose the wavenumber to use for the excitation, the position of the 2nd overtone has to be determined, so that the corresponding band has to be experimentally observed; is this possible using the conventional detectors for near-IR?; *(ii)* for the processes to be efficient, the IR absorption cross section of the mode to excite has to be as large as possible; is that of the νOH 2nd overtone large enough?; *(iii)* since the width of the 2nd overtone bands can be expected to be larger than those of the fundamental bands or 1st overtones, can selectivity still be kept in a way that this can be useful in practical terms?; *(iv)* considering the higher energy introduced in the molecule, can the process still be selective also regarding the matrix site, or will it affect the nature of the sites?

We noticed that for reliable observation of 2nd overtone bands of matrix isolated species the detection system of the FTIR spectrometer used for studies involving excitation of fundamentals or 1st overtones had to be improved. A thermoelectrically cooled indium gallium arsenide (InGaAs) detector was then installed in our equipment. With this detector, the bands due to νOH stretching 2nd overtones are in general detectable. We also found that by appropriate choice of the excitation conditions (in particular the laser power), the absorption cross section of these vibrations is enough to guarantee efficiency of the IR-induced processes. For excitation, a continuous wave diode tunable near-IR laser system Toptica DLC TA PRO (spectral range: 10500–10100 cm^{-1}; fwhm < 1 MHz, up to 3 W) was purchased and, in a typical experiment, irradiation shall be carried on during 20 min with at least 120 mW of power.

Three structurally related molecules, hydroxyacetone, glycolic acid and glycolamide, were chosen as targets of the first

experiments [72]. In all these cases, we were able to successfully induce conformational isomerizations upon excitation of the νOH 2nd overtone. Figure 11 summarizes the results obtained for glycolamide, where the conversion of the **Tt** conformer into the **Cc** form is demonstrated. Interestingly, the process was shown to be site selective, allowing us to conclude that despite the higher energies involved compared to excitation of fundamentals and 1st overtone modes no measurable disturbance of the matrix sites takes place also upon excitation of the νOH 2nd overtone.

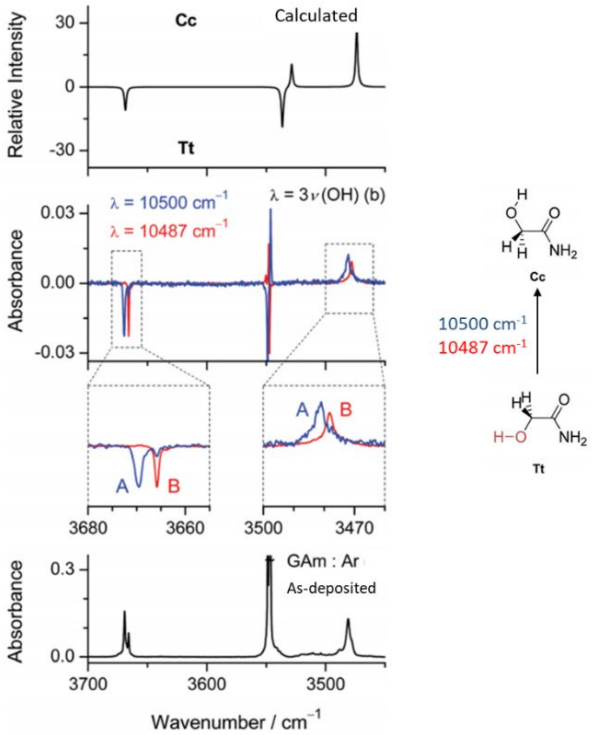


Figure 11. IR-induced conformational isomerization in glycolamine (GAm) in an argon matrix, as result of excitation of the νOH 2nd overtone (3ν(OH)). Note the site selectivity of the process (A and B designate the two sites). Adapted from ref. 72. Copyright 2019 Royal Society of Chemistry.

We also noticed that, as anticipated, the widths of the νOH 2nd overtone bands are in general larger than those of the bands ascribed to fundamental and 1st overtone modes (FWHM ~6 cm^{-1} *vs* ~3 cm^{-1} for acid OH group of most stable conformer of glycolic acid [72]). Nevertheless, they still allow for selective excitation to be performed in many cases, since the spacing between the absorption wavenumbers of the different conformers also tend to increase for the higher order overtones. Higher-order overtone (v = 6) excitation Raman studies on matrix isolated formic acid have been reported by Olbert-Majkut, Ahokas, Lundell and Pettersson, in studies where the ***E*** conformer was produced upon vibrational excitation of the ***Z*** conformer using visible light (532.0 nm, or 18797 cm^{-1}, provided by a continuous laser highly-focused at the sample and a power level up to 260 mW). The laser light was used simultaneously for pumping and to collect the Raman spectra [73,74]. Interestingly, the authors suggested that much higher overtone states can also be used, opening the gate for UV-region vibrational overtone induced reactions [73]. We had not yet attempted to use excitations at overtones above the second in a systematic way in our laboratory. Indeed, we performed only a very preliminary series of experiments using visible light excitation of matrix isolated formic acid, with a ns pulsed light pumping source (at 532 nm) and IR spectroscopy probing to detect the formation of the ***E*** conformer, but these experiments resulted unsuccessful. One of the reasons for that was, much probably, the irradiation power at the sample provided by our irradiation system, which is much less than the 260 mW used in the Raman experiments of Olbert-Majkut and coworkers [73,74]. The feasibility and appropriateness of excitations to higher than the second overtone as a general strategy is not yet proved, at least when IR spectroscopy is used as probing technique, and this is a field that shall be considered still open to investigation.

The concept of vibrational antenna: remote control of molecular structures

The first reported IR-induced structural transformations were limited to changes in the close proximity of the excited fragment of the molecule. Most of times, excitation of the νOH stretching mode was used to modify the orientation of the hydroxyl hydrogen atom itself, as in the case of the *Z* → *E* conformational conversion of carboxylic acids. Less frequently, internal rotation around a C–C bond vicinal to the excited hydroxyl group was observed, as in the cases of propionic acid and glycolamine described above [66,72], but also in other compounds like glycolic acid and hydroxyacetone, for example [25,72]. From the comparison of the quantum yields for the *Z* → *E* conformational conversion in formic and acetic acids, it could also be indirectly concluded that excitation of the νOH stretching mode also induced internal rotation of the methyl group around the C–C bond in the latter compound [49], as described in the introduction section.

In 2015, we reported the first example of an IR-induced conformational isomerization of a fragment in a molecule that was remotely located from the excited group [75]. The target compound of these studies was 6-methoxy indole, which has two conformers of similar energy. By excitation of the νNH stretching 1st overtone of the conformers, we were able to selectively interconvert them (Figure 12) [75]. The processes involve a structural transformation of a methoxy group located four bonds apart from the excited vibrational antenna and were found to be very efficient. Since this pioneer investigation, the concept of remote vibrational antenna has been explored in our group in several other systems, like the thiol forms of thioacetamide, kojic acid or *E*-glutaconic acid [76-78], for example. We have also shown that different antennas can be used in an interchangeable way to induce conformational changes in the same molecular fragment, as demonstrated in our studies on conformational changes of an aldehyde group

 This journal is © The Royal Society of Chemistry 20xx

Please do not adjust margins

connected to a 2*H*-azirine ring *via* vibrational excitation of hydroxy or amino antennas [79].

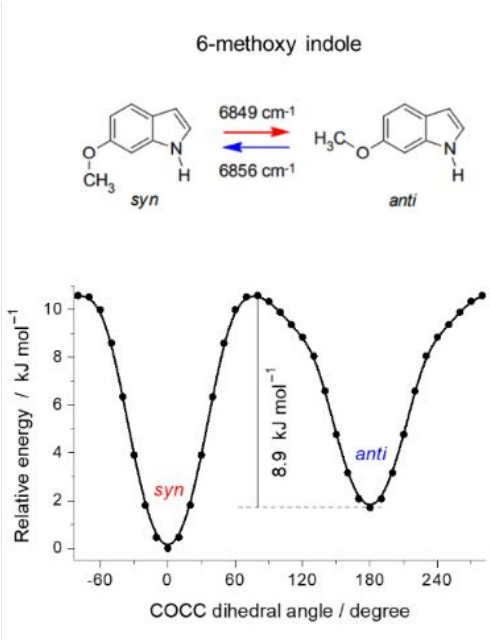


Figure 12. IR-induced conformational isomerization of the methoxy group in 6-methoxy indole using a remotely located NH vibrational antenna. Adapted from ref. 75. Copyright 2015 American Chemical Society.

IR-induced bond-breaking/bond-forming reactions

More recently, we were able to use vibrational excitation to cleave and form covalent bonds. The first example was reported in 2020 and considered the bidirectional thiol↔hydroxy tautomerization in thiotropolone [80].

Thiotropolone has two tautomers, the thiol and the hydroxy forms, each one having two conformers. As shown in Figure 13, the *syn*-hydroxy (***s*-OH-TT**) form is the most stable species, followed by the *syn*-thiol isomer (***s*-SH-TT**; 7.5 kJ mol^{-1} higher in energy than the most stable form), the *anti*-thiol form (***a*-SH-TT**; 17.1 kJ mol^{-1}), and the *anti*-hydroxy isomer (***a*-OH-TT**; 51.6 kJ mol^{-1}). In a freshly deposited argon matrix of the compound, only the ***s*-OH-TT** form is present. IR irradiation at the wavenumber of the νCH stretching 1st overtone (5940 cm^{-1}) or the combination mode at 5980 cm^{-1} of this isomer led to its conversion into the ***a*-SH-TT** form [80] (Figure 14). The reaction involves the cleavage of the O–H bond and the formation of an S–H bond. Very interestingly, the observed product is not the ***s*-SH-TT** form, which could be expected to be the direct product of the reaction, but ***a*-SH-TT**. The data shown in Figure 15 allows to understand the reasons for this observation.

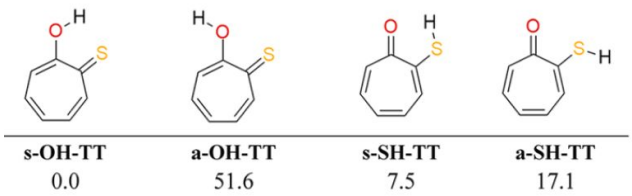
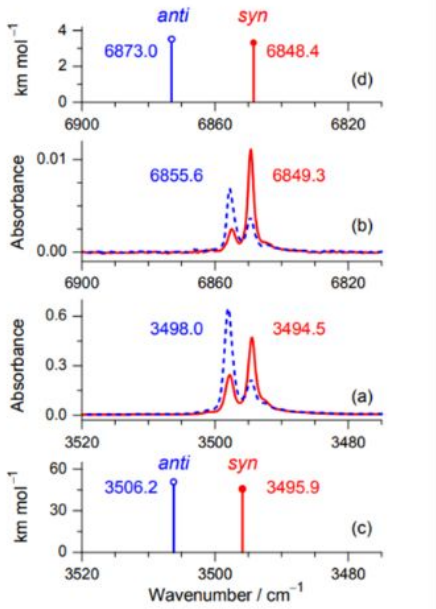


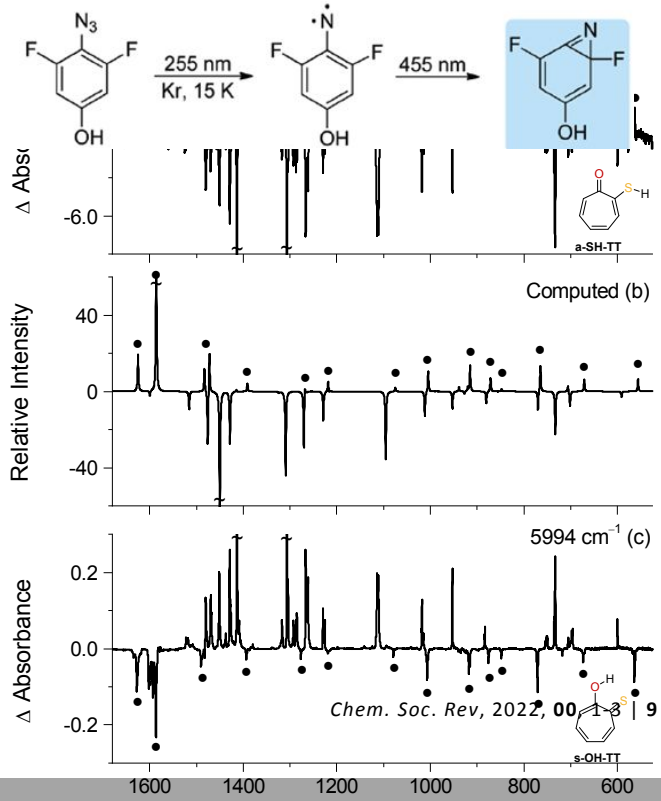
Figure 13. Tautomers of thiotropolone and respective conformers and CBS-QB3 calculated relative energies (in kJ mol^{-1}). Adapted from ref. 80.

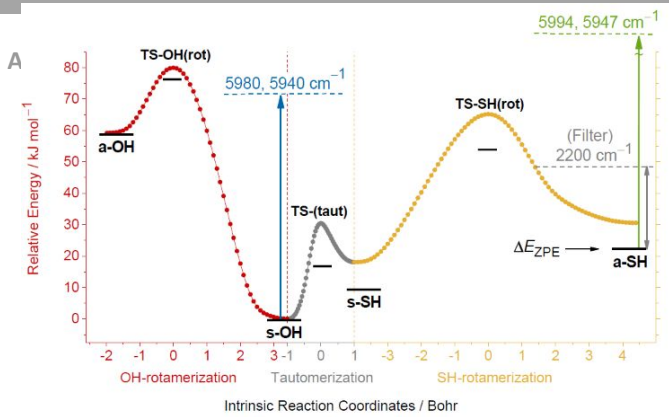


Copyright 2020 American Chemical Society.

Figure 14. Difference IR spectra showing the observed IR-induced bidirectional tautomerizations of matrix isolated thiotropolone. (a) and (c), experimental difference spectra: (a) irradiation at 5940 cm^{-1}; (c) irradiation at 5994 cm^{-1}. Bands marked with circles (●) are due to ***a*-SH-TT**, which is produced by irradiation at 5940 cm^{-1} (a) and consumed by irradiation at 5994 cm^{-1} (c). (b) Simulated difference IR spectrum based on B3LYP/6-311+G(2d,p) vibrational data. Adapted from ref. 80. Copyright 2020 American Chemical Society.

Figure 15. Potential energy profile showing the a priori possible reaction pathways for interconversion between the different tautomers (and respective conformers) of thiotropolone (B3LYP/6-311+G(2d,p) results).





The horizontal bars at each stationary point (minima and transition states; TS) show the corresponding computed ZPE-corrected relative energy value. Adapted from ref. 80. Copyright 2020 American Chemical Society.

Upon excitation of ***s*-OH-TT** at 5980 or 5940 cm^{-1}, ~71 kJ mol^{-1} are introduced in the molecule. Such energy is below the transition state (TS) for OH-rotamerization (~76 kJ mol^{-1}), justifying the non-observation of the ***s*-OH-TT** → ***a*-OH-TT** process, but well above the TS for tautomerization to ***s*-SH-TT** (~17 kJ mol^{-1}) and also clearly above the TS for production of the observed ***a*-SH-TT** product (~53 kJ mol^{-1}). The important fact here is that, contrarily to ***a*-SH-TT**, which is stable once it is produced, the ***s*-SH-TT** form cannot persist, tautomerizing promptly back to ***s*-OH-TT** by spontaneous QMT because of a low (~9 kJ mol^{-1}) and thin (~0.63 Å) barrier separating these two species. With such barrier, the occurrence of extremely fast QMT is expected, making ***s*-SH-TT** a fleeting species even at cryogenic conditions (estimated $\tau_{1/2}$ ~1 × 10^{-11} s applying the Wentzel–Kramers–Brillouin model [80]). These data unequivocally justify the experimental capture and identification of the thiol ***a*-SH-TT** form and not of ***s*-SH-TT** form upon vibrational excitation of ***s*-OH-TT**.

The observed tautomerization of ***a*-SH-TT** back to ***s*-OH-TT** was also successfully induced upon irradiation at the wavenumber of the νCH stretching 1st overtone (5947 cm^{-1}) or the combination mode at 5990 cm^{-1} of this isomer (see Figure 14). In this case, the energy deposited in the molecule (~71 kJ mol^{-1}) is high enough to activate the SH-rotamerization to ***s*-SH-TT** (~33 kJ mol^{-1}), which rapidly tautomerizes by tunneling to ***s*-OH-TT**.

Globally, these results demonstrate that the hydroxyl → thiol and thiol → hydroxyl tautomerizations in thiotropolone, which imply cleavage of an OH or SH bond and formation of and SH or OH bond, respectively, were both promoted by vibrational excitation of the corresponding reactant tautomeric species, generalizing the use of IR-induced chemistry also to covalent bond-breaking/bond-forming processes. More recently, we have shown that IR-induced bond-breaking/bond-forming reactions can also be successfully promoted for neat solid samples at low temperature [81].

Another advance in the field of IR-induced chemistry was our recent demonstration that bond-breaking/bond-forming reactions can likewise be induced by vibrational excitation of an antenna remotely located in relation to the molecular reaction site [82]. This generalization of the use of remote vibrational antennas to promote chemical reactions involving cleavage and formation of covalent bonds opened the gate for a wider application of IR-induced chemistry, in particular in organic chemistry.

The selected reactant molecule was a fluoro-substituted benzazirine bearing an OH vibrational antenna (2,6-difluoro-4-hydroxy-2*H*-benzazirine; Figure 16). This species was produced *in situ* in a low temperature (15 K) krypton matrix by UV (455 nm) irradiation of the corresponding nitrene, which was also generated *in situ* by photolysis (255 nm) of the azide precursor (Figure 16).

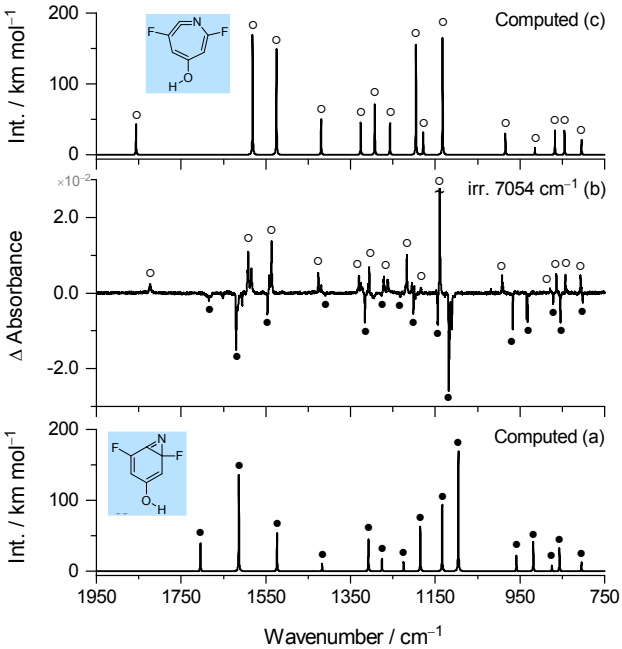
Figure 16. *In situ* generation of the 2,6-difluoro-4-hydroxy-2*H*-benzazirine from the corresponding azide precursor isolated in a krypton matrix (15 K). Two successive irradiations were performed, at different wavelengths, the first giving rise to the nitrene species and the second converting this latter into the desired benzazirine. Adapted from ref. 82. Copyright 2021 Royal Society of Chemistry.

As shown in Figure 17, IR irradiation of the benzazirine through the remotely located OH vibrational antenna (via its νOH 1st overtone at 7054 cm^{-1}) led to its transformation into the cyclic ketenimine 3,7-difluoro-5-hydroxy-1-aza-1,2,4,6-cycloheptatetraene, with breaking of a C–C bond and extensive rearrangement of the electronic π-bonding system. It is worth noticing that both the benzazirine and the photoproduced ketenimine were found to be present in the matrix in a single conformer, the ***syn*** and ***anti*** forms, respectively, while two conformers of each molecule exist (no IR bands ascribable to the alternative conformers of these molecules were observed experimentally [82]). The explanation for this can be rationalized based on Figure 18 and involves again reactions taking place through the QMT mechanism.

This journal is © The Royal Society of Chemistry 20xx

Please do not adjust margins

The OH-rotamerization barrier converting the non-observed ***anti*** conformer of the benzazirine to the observed most stable



syn conformer is only 7.5 kJ mol^{-1}, whereas the barrier of conversion of the non-observed less stable ***syn*** conformer of the ketenimine to the observed most stable ***anti*** form is 14.6 kJ mol^{-1} [82]. These low energy barriers allow for fast OH-rotamerization QMT to take place, precluding observation of the higher-energy forms of the two molecules. In consonance with this interpretation, tunneling calculations using the Wentzel–Kramers–Brillouin model [82] estimated very short half-lives for both the ***anti***-benzazirine [$t_{1/2}$ ~10^{-7} s] and ***syn***-ketenimine [$t_{1/2}$ ~10^{-4} s]. In this regard, it is then likely that the IR vibrational excitation of the ***syn***-benzazirine induces ring-expansion to the ***syn***-ketenimine, which then undergoes fast QMT OH-rotamerization to the observed ***anti***-ketenimine form.

Figure 17. Experimental IR difference spectrum (b) showing the result of the IR-induced conversion of the studied benzazirine into the corresponding cyclic ketenimine, *via* 1st stretching overtone of the remotely located OH vibrational antenna, and calculated spectra of the benzazirine (a) and ketenimine (c). Adapted from ref. 82. Copyright 2021 Royal Society of Chemistry.

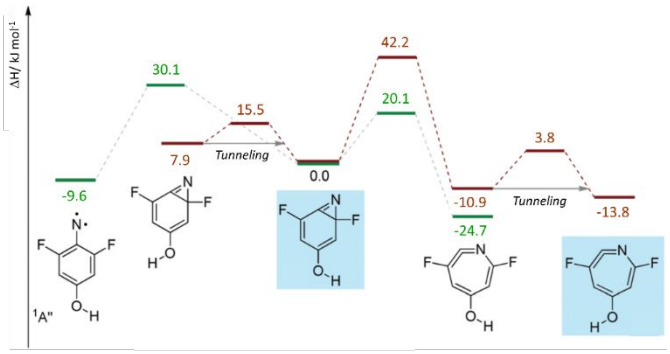


Figure 18. Reaction pathways, computed at CCSD(T)/cc-pVTZ//B3LYP/6-311+G(2d,p)+ZPVE (red) and MRMP/cc-pVTZ//CASSCF(8,8)/ccpVTZ +ZPVE (green) levels of theory for interconversion between the different species relevant for the understanding of the observed IR-induced conversion of the studied benzazirine into the corresponding cyclic ketenimine, *via* 1st stretching overtone of the remotely located OH vibrational antenna. 1A'' = open-shell singlet state. Adapted from ref. 82. Copyright 2021 Royal Society of Chemistry.

In summary, in our study [82], we demonstrated that the selective IR vibrational excitation of a remote antenna allows inducing a bond-breaking/bond-forming reaction in an organic molecule, in an efficient way. This accomplishment paves the way for developing a general approach to guide a variety of molecular structure manipulations using IR-light and creates unprecedented opportunities for highly-selective transformations, in ways not attainable by thermal or electronic excitation processes.

Switching on H-tunneling through IR-induced conformational control

In one of our most recent investigations [83], we demonstrated the feasibility of using IR-induced chemistry as a switch to control H-atom tunneling. This was outlined with a triplet 2-hydroxyphenylnitrene generated in an N_2 matrix at 10 K by UV-irradiation of an azide precursor. The ***anti*** conformer of the nitrene, where the OH moiety points to the opposite side of the nitrogen atom, could be selectively converted into the ***syn*** conformer upon vibrational excitation at the wavenumber of its νOH stretching 1st overtone (6976 cm^{-1}). By this way, the hydroxyl hydrogen atom moves closer to the vicinal nitrene center, triggering spontaneous H-tunneling to a singlet 6-imino-2,4-cyclohexadienone (Figure 19). The reaction was monitored by IR spectroscopy using a long-pass filter blocking IR light above 1580 cm^{-1} to exclude the absorption of photons above the OH-rotamerization barrier of the nitrene (~1700 cm^{-1} as calculated at the B3LYP/6-311+G(2d,p) level [83]) (Figure 20). Computations reveal that such fast H-tunneling occurs through crossing the triplet-to-singlet potential energy surfaces [83], establishing in this way a rare model for a nonadiabatic H-atom QMT. Note that the alternative conceivable mechanism for the reaction of the ***syn*** triplet nitrene that considers the occurrence of H-atom QMT on the triplet surface to the triplet 6-imino-2,4-cyclohexadienone, followed by intersystem crossing, could be safely excluded [83]. Indeed, the height (~98.2 kJ mol^{-1}) of the barrier for the reaction in the triplet surface is incompatible with the occurrence of a very fast QMT reaction and with the elusive nature of the ***syn*** triplet nitrene (according to Wentzel–Kramers–Brillouin calculations, its half-life time would be 1.14 × 10^3 s, if tunneling occurred in the triplet surface [83]).

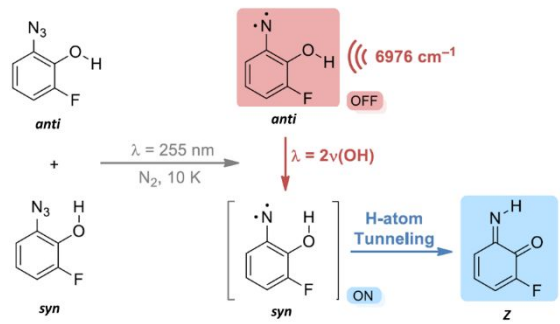
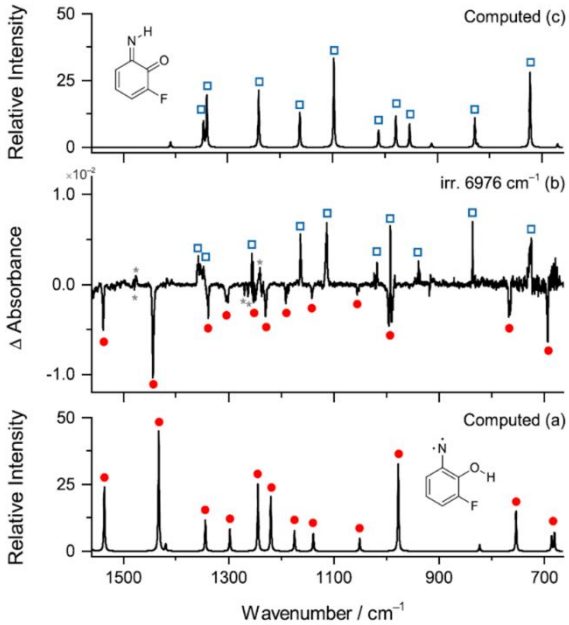


Figure 19. IR-switch for the H-atom tunneling reaction of triplet 2-hydroxyphenylnitrene generated in an N_2 matrix from the azide precursor. Adapted from ref. 83. Copyright 2021 American Chemical Society.

This study provides an exciting novel strategy to attain control over tunneling, opening new avenues for directing chemical transformations. These results are also important as a



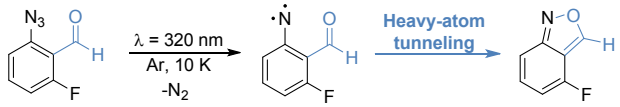
contribution to the understanding of enzyme-catalyzed reactions, since it has been suggested that enzymatic C–H transfer reactions rely on the dynamic sampling of enzyme-substrate conformations to tune the donor–acceptor distance conductive to QMT [84,85].

Figure 20. (a) B3LYP/6-311+G(2d,p) computed IR spectrum of triplet *anti*-3-fluoro-2-hydroxyphenylnitrene. (b) Experimental difference IR spectrum showing changes resulting from irradiation at 6976 cm^{-1}. (*) indicate minor changes in the population of conformers of the azide precursor of the nitrene. (c) B3LYP/6-311+G(2d,p) computed IR spectrum of (*Z*)-2-fluoro-6-imino-2,4-cyclohexadienone. Adapted from ref. 83. Copyright 2021 American Chemical Society.

Heavy-atom QMT

As emphasized in the Introduction section of this article, examples of QMT-driven reactions involving the motion of light hydrogen atoms are relatively abundant and this phenomenon has been recognized to play an important role in organic chemistry, biochemistry, and catalysis [86-90]. Because the tunneling probabilities decrease exponentially with the square root of the moving mass, atoms heavier than hydrogen were for long assumed to behave essentially classically [90]. However, recent evidence indicates that heavy-atom QMT can have significant implications for many chemical reactions [91,92]. About a dozen of examples of direct spectroscopic observation of carbon-atom QMT occurring under matrix isolation conditions have been reported [92-96]. In recent investigations, we have also discovered a new and distinctive case of a heavy-atom QMT reaction involving the displacement of both nitrogen and oxygen atoms [97].

The 2-formyl-3-fuorophenylazide precursor, which was designed to achieve stabilization of the *syn*-aldehyde conformation, allows generation of the corresponding triplet *syn*-2-formylarylnitrene upon UV-irradiation under cryogenic conditions. Once produced, this nitrene species was observed to spontaneously cyclize to the corresponding singlet 2,1-benzisoxazole (Figure 21). The experimental IR spectrum of the consumed and produced species is well reproduced by the B3LYP/6-311+G(2d,p) computed IR spectra, providing unequivocal identification for the occurrence of such cyclization



reaction (Figure 22). The reaction kinetics was measured in the dark in an argon matrix at 10, 15 and 20 K, and rate constants of ~1.4×10^{-3} s^{-1} were obtained. The observation of a fast and temperature-independent cyclization rate at those low temperatures provided convincing evidence for the occurrence of a heavy-atom QMT cyclization [97].

Figure 21. Summary of the heavy-atom QMT cyclization of a triplet *syn*-2-formylarylnitrene to a singlet 2,1-benzisoxazole, which involves the displacement of nitrogen and oxygen atoms. Adapted from ref. 97 with permission from John Wiley and Sons. Copyright 2020 WILEY-VCH Verlag GmbH & Co. KGaA, Weinheim.

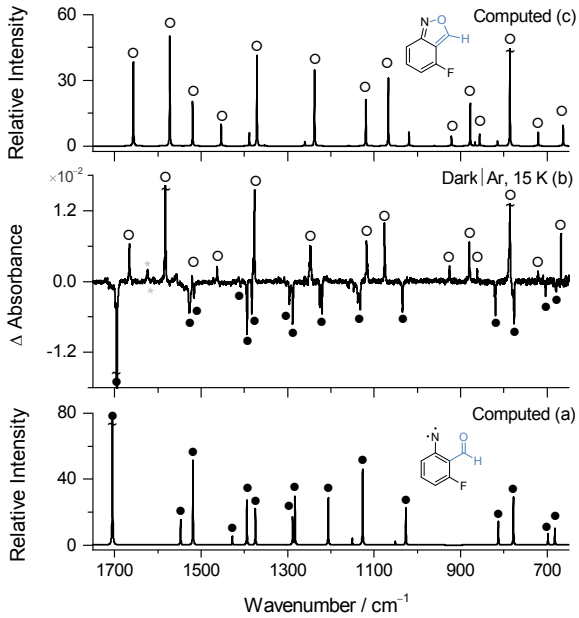


Figure 22. B3LYP/6-311+G(2d,p) computed IR spectrum of (a) triplet *syn*-2-formyl-3-fluorophenyl-nitrene and (c) singlet 3-fluoro-2,1-benzisoxazole. Experimental difference IR spectrum showing changes after keeping the sample at 15 K (Ar matrix) in the dark for 40 min, subsequent to the generation of triplet nitrene by UV-irradiation of the corresponding azide precursor. Adapted from ref. 97 with permission from John Wiley and Sons. Copyright 2020 WILEY-VCH Verlag GmbH & Co. KGaA, Weinheim.

A reaction mechanism involving heavy-atom QMT on the triplet surface was excluded, because the triplet state of the product

 This journal is © The Royal Society of Chemistry 20xx

Please do not adjust margins

is energetically higher than the triplet state of the reactant. A minimum energy crossing point (MECP) between the triplet nitrene and singlet benzisoxazole surfaces was found at ~50 kJ mol^{-1}. Such large reaction energy requirement is clearly prohibitive to be achieved by a classical process at the cryogenic temperatures of the experiment. On the other hand, a spin-forbidden heavy-atom QMT rate calculated by nonadiabatic transition state theory (NA-TST) using the weak coupling (WC) model, at the MRMP(10,10)//CASSCF(10,10) or M06-2X levels of theory, provides a qualitative agreement with the experimental values, supporting the exclusive existence of a mechanism of heavy atom tunneling through crossing triplet and singlet potential energy surfaces [97]. To the best of our knowledge, the WC formulation of nonadiabatic-TST was for the first time successfully applied in this study to calculate vibrational ground state QMT reactions rates.

We also recently unveiled a new reactivity paradigm in this area by demonstrating that a well-defined chemical starting material spontaneously decay at cryogenic temperatures into two different products *via* two competitive heavy-atom QMT processes [98]. After generation of 4-amino-2*H*-benzazirine in an argon matrix (3–18 K), this species was observed to concomitantly undergo spontaneous ring-opening to a triplet nitrene and ring-expansion to a cyclic ketenimine (Figure 23). The process was monitored by IR spectroscopy, which allows the identification of these two products by comparison with their IR spectra signature (obtained during UV-irradiation experiments starting from an azide precursor), and the identification of the consumed benzazirine with the support of its B3LYP/6 311+G(2d,p) computed IR spectrum (Figure 24). The reaction kinetic was measured at 3, 10 and 18 K, and rate constants of ~5.5 × 10^{-5}, ~6.0 × 10^{-5} and ~7.0 × 10^{-5} s^{-1}, respectively, were obtained. The observed triplet nitrene : cyclic ketenimine product ratio was ~15:85 (3 K), ~18:82 (10 K) and ~17:83 (18 K). The evidence that the reaction rate is nearly constant upon increasing of the temperature by a factor of five and that the product rate practically did not change confirmed that the observed benzazirine transformations were due to two independent and competitive heavy-atom tunneling reactions [98].

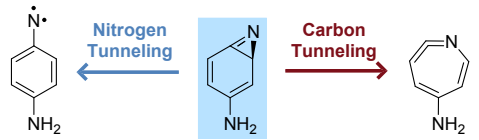


Figure 23. Summary of the competitive heavy-atom QMT ring-open versus ring-expansion of 4-amino-2*H*-benzazirine to triplet nitrene and cyclic ketenimine, respectively. Adapted with permission from ref. 98. Copyright 2019 American Chemical Society.

The ring-opening mechanism of 4-amino-2*H*-benzazirine should involve the formation of the corresponding open-shell singlet (OSS) nitrene, followed by fast ISC to triplet nitrene ground state. Due to the need of using multi-configurational methods to correctly described OSS nitrenes, such transformation was computed at NEVPT2(8,8)//CASSCF(8,8) level and an energy barrier of ~10.5 kJ mol^{-1} was estimated. The ring-expansion mechanism of 4-amino-2*H*-benzazirine to the corresponding cyclic ketenimine was found to be most reliably computed at the CCSD(T)//B3LYP level, and an energy barrier of ~30.5 kJ mol^{-1} was estimated (Figure 25). According to the classic TST, even such low energy barriers are prohibitive at the cryogenic temperatures of the experiment. Moreover, the formation of cyclic ketenimine as major product, having a higher energy barrier than the minor nitrene product, contradicts the rules inferred from classic TST. Therefore, it becomes clear that a thermal over-the-barrier process cannot explain the observed transformation but only the occurrence of heavy-atom QMT dominated by tunneling control. Indeed, computed tunneling probabilities through those two barriers (applying the Wentzel-Kramers-Brillouin formalism), predict the existence of two competitive reactions of the benzazirine, in line with the experimental observations. Computations also show that for the tunneling of the benzazirine to the nitrene the nitrogen atom in the three-membered ring is clearly the heavy-atom with the largest displacement, whereas for the tunneling of the benzazirine to the ketenimine the two carbon atoms in the three-membered ring have by far the largest displacement [98]. Therefore, they support a case for the existence of competitive nitrogen *vs.* carbon QMT reactions occurring simultaneously with 4-amino-2*H*-benzazirine as the reactant species.

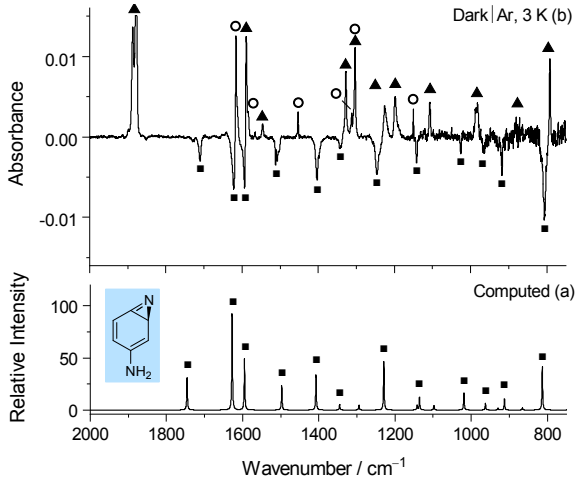


Figure 24. (a) B3LYP/6-311+G(2d,p) computed IR spectrum of 4-amino-2*H*-benzazirine. (b) Experimental difference IR spectrum showing changes after keeping the sample at 3 K (argon matrix) in the dark for 24 h. The downward bands are due to the consumption of 4-amino-2*H*-benzazirine (squares) and the upward bands due to the formation of the corresponding triplet nitrene (circles) and cyclic ketenimine (triangles). Adapted with permission from ref. 98. Copyright 2019 American Chemical Society.

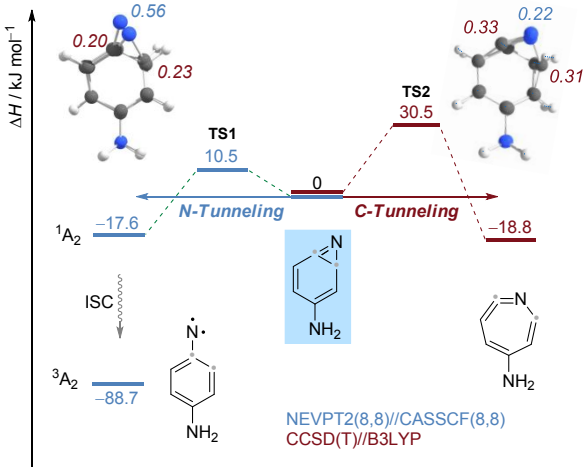


Figure 25. (a) Computed reactions pathways for the transformation of 4-amino-2*H*-benzazirine at NEVPT(8,8)/6-311+G(2d,p)//CASSCF(8,8)6-311+G(2d,p)+ZPVE (blue), and CCSD(T)/cc-pVTZ//B3LYP/6-311+ G(2d,p) +ZPVE (red), $^1A_2$ = open-shell singlet state, $^3A_2$ = triplet ground state. Top left and right images show the structural overlap of the turning point geometries and the most significant tunneling distances of the individual atoms (arc lengths in Å in *italic*) involved in N and C-tunneling, respectively. Adapted with permission from ref. 98. Copyright 2019 American Chemical Society.

Conclusion and Outlook

Along the previous sections, we have surveyed the major progresses in the field of IR-induced and tunneling-driven chemistry for matrix isolated species. As mentioned in the Introduction section, we focused essentially on our own contributions to develop vibrationally induced chemistry as a powerful tool to manipulate molecular structures in a highly selective way, and to use and control QMT as a tool to explore the reactivity of organic molecules in an unprecedented way. Figure 26 provides a timeline graph that summarizes these major achievements in a historical perspective.

We have showed that using tunable narrowband IR-light and matrix isolation conditions, it is possible to manipulate the structure and reactivity of chosen molecular species in a very selective way. This methodology has been applied successfully to trigger conformational isomerizations in a different range of organic compounds, including weakly-bonded (dimeric) species. Noteworthy, the feasibility to produce high-energy conformers of different species by vibrational excitation, which otherwise are not accessible to experimentation, opened the gate to new fascinating investigations such as conformational selective chemistry or the synthesis of unusual high-energy crystals composed by rare conformers.

From the first cases studied, where the IR-induced conformational isomerizations comprised changes in the moiety where the vibrational excitation was applied or in an adjacent bond, we and others expanded the scope of the technique to consider also reversible interconversions between conformers by vibrational excitation of a group (having the role of an antenna) remotely located from the fragment undergoing conformational changes. Moreover, we have demonstrated that different antennas can be used in an interchangeable way to trigger conformational isomerizations of the same remote molecular fragment.

Our recent demonstration that vibrational excitation can be used to induce bond-breaking/bond-forming reactions for matrix-isolated organic molecules established a new domain in vibrationally-driven chemistry. Furthermore, envisioning a generalized strategy to guide a variety of chemical reactions using IR light, we demonstrated as proof-of-principle the triggering of an electrocyclic reaction by vibrational excitation of an antenna remotely located in relation to the reaction center. We expect that future studies using target molecules with more than one vibrational antenna and more than one possible reaction coordinates will give fundamental answers regarding the relation between the nature of the excited mode and the activated reactions. By introducing vibrational energy in a molecule in an amount above the threshold required to induce different transformations, the possibility to activate a higher-energy pathway, so that it can effectively compete with a lower-energy one, is a problem currently under study in our laboratories. Such investigations can be expected to strongly expand the power of IR-induced processes for more practically oriented uses and provide important hints regarding intramolecular vibrational energy redistribution in different types of molecular systems.

Up until quite recently, all IR-induced processes carried out for matrix isolated species resorted on the vibrational excitation of fundamental vibrations or first overtones (or combination modes) of favorable stretching modes, such as that of an OH group. A significant progress was achieved when we demonstrated that selective vibrational excitation of second overtone modes, 3ν(OH), also successfully triggers conformational isomerizations in the target molecules. Such approach allows to introduce much more energy in a molecule [~120 kJ mol^{-1} for 3ν(OH) *vs.* ~80 kJ mol^{-1} for 2ν(OH)] and, therefore, offer prospects to control the manipulation of chemical species stable even at temperatures close to room temperature. In conjugation with our recent breakthrough on inducing bond-breaking/bond-forming reactions by infrared vibrational excitation and the demonstration of the feasibility of such approach also to neat solid conditions, we might foresee the development of this methodology to achieve the activation of drugs *in vivo* or the switch of materials in optical and electronic devices in a highly controlled and selective way, not attainable by thermal and electronic excitation.

We have also shown here that IR-induced processes in cryogenic matrices are frequently entangled with tunneling-driven reactions. Several investigations on direct spectroscopic observation of spontaneous conformational isomerizations of high-energy conformers (produced by vibrational excitation of lower energy forms) at cryogenic temperatures have provided important data to improve our knowledge of fundamental principles of the QMT phenomenon. Interestingly, some studies have unrevealed the occurrence of vibrationally-assisted QMT processes, by showing that conformational isomerizations can take place even when the vibration excitation energy introduced in the target conformer is below that corresponding to the isomerization energy barrier. As described in details above, more recently, we have demonstrated how to switch on H-atom QMT by IR-induced conformation control. To the best of our knowledge, such approach represented the first ever achievement of the control of tunneling by means of external radiation. We can expect future advances in such new conceptual strategy to harness the control of QMT, which will be likely to inspire progress in the fields of enzymatic catalysis and quantum switches, and to provide new avenues for directing chemical transformations.

Contributing to a paradigm shift, we and others have been reported direct spectroscopic observation of heavy-atom QMT reactions in cryogenic matrices, in this way demonstrating that this phenomenon can have much more significant implications in chemical reactivity than previously thought. Although most examples comprise carbon-atom QMT, we have also discovered

 This journal is © The Royal Society of Chemistry 20xx

Please do not adjust margins

a distinctive case of a heavy-atom QMT reaction involving the displacement of both nitrogen and oxygen atoms. One can expect that future studies will extend the limits of observed QMT to even heavier elements, such as fluorine. Besides, we have also unraveled a new, fascinating reactivity pattern, by demonstrating a unique case of two competitive heavy-atom QMT reactions (nitrogen *vs.* carbon) occurring simultaneously from a well-defined chemical starting material, leading to two different products. This paradigmatic example offers an excellent opportunity to investigate how electronic effects imposed internally by different substituents or externally by different media can tune the selectivity of a QMT reaction. Electronic effects will most likely affect QMT differently than an over-the-barrier process, rationalized by classical TST, and, therefore, new fundamental understanding will likely emerge from such studies. Due to the recent progress witness on the field of QMT reactions, we foresee their entrance in synthetic organic chemistry and synthetic planning disciplines for the very near future. In this way, new reactivity paradigms and synthetic strategies will likely emerge under more conventional laboratory conditions, opening new avenues for the design of new molecules.

This is the story of a still ongoing endeavor, and by this reason necessarily an incomplete (but opportune) story. We can only expect that this survey can stimulate others to contribute to the development of the field and inspire young scientists to follow our steps in this captivating adventure. But, as pointed out in the beginning of this article, this story is also incomplete in the sense that many others have also been given very important contributions to the development of the research areas here addressed. To all of them we have to pay our respect and acknowledge for their invaluable efforts.

2021 -Nunes, Pereira, Viegas, Pinho e Melo & Fausto described the first example of an IR-induced bond-breaking-bond-forming reaction through use of a remotely located vibrational antenna.
-Together with Shreiner, we reported the case of conformational control of tunneling in triplet 2-hydroxyphenylnitrene.

2020 -Our group reported the bidirectional IR-induced bond-breaking-bond-forming tautomerization of thiotropolone.
-We presented the case of heavy atom tunneling through crossing triplet and singlet potential energy surfaces: cyclization of a triplet 2-formylarylnitrene to a singlet 2,1-benzisoxazole.

2019 -Use of higher order overtones to induce conformational isomerizations with IR detection, by Nunes, Reva Fausto.
-With the group of Schreiner, we reported the first case of competitive heavy-atom tunneling (N *vs.* C).

2014-2015 -IR-induced production of rare dimers of formic and acetic acids by Räsänen's and our groups.
-Our group introduces the concept of "remote vibrational antenna".

2010-2011 -In collaboration with the Nowak's group we reported the first studies on the conformational isomerization of cytosine.
-Schreiner introduced the concept of tunneling control of chemical reactivity.

2008-2009 -Olbert-Majkut, Ahokas, Lundell & Pettersson reported use of higher-order overtones in the visible range to induce conformational isomerizations in formic acid and its dimers, with simultaneous Raman probing.

2005 -Maçôas, Khriachtchev, Pettersson, Fausto & Räsänen reported the IR and tunneling rotamerizations in propionic acid.

2003 -Tunneling assisted IR-induced conformational isomerization in formic acid was described by our group in collaboration with Räsänen's group.

2002 -IR-induced conformational isomerization studies on dicarboxylic acids reported by our group in collaboration with Räsänen's group.

2000-2001 -Dissipative tunneling in formic acid was reported by Pettersson, Maçôas, Khriachtchev, Lundell, Räsänen & Fausto.
-Conformational dependent photochemistry of formic acid was reported by Khriachtchev, Maçôas, Pettersson & Räsänen.

1997 -Pettersson, Lundell, Khriachtchev & Räsänen introduced narrowband tunable IR light to selectively promote the conformational isomerization of formic acid.

1993 -Kulbida & Fausto used monochromated IR light of a globar source to induce conformational isomerization in matrix isolated dichloroacetic acid.

1963 -Hall & Pimentel reported the first IR-induced conformational isomerization for matrix isolated nitrous acid.

Figure 26. Timeline showing some of the most relevant keystones in the field of IR-induced and related tunneling-driven chemistry for matrix isolated organic molecules.

Author Contributions

All authors contributed equally to the article.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

This work was supported by Projects POCI-01-0145-FEDER-028973 and PTDC/QUI-QFI/1880/2020, funded by National Funds *via* the Portuguese Foundation for Science and Technology (FCT), the first being also funded by FEDER, *via*

Portugal 2020 – POCI. The Coimbra Chemistry Centre – Institute of Molecular sciences (CQC-IMS) is supported by FCT through projects UIDB/QUI/0313/2020 and UIDP/QUI/0313/2020 and LA/P/0056/2020 (national funds). C.M.N. acknowledges FCT for an Auxiliary Researcher grant. All our co-workers that have participated in the studies mentioned in this article are acknowledged. The acknowledgements are also extended to all members of the groups with whom we have collaborated and that have also participated in this endeavor.

References

1. R. T. Hall and G. C. Pimentel, Isomerization of Nitrous Acid: An Infrared Photochemical Reaction, *J. Chem. Phys.*, **38** (1963) 1989.
2. M. Pettersson, J. Lundell, L. Khriachtchev and M. Räsänen, IR Spectrum of the Other Rotamer of Formic Acid, *cis*-HCOOH, *J. Am. Chem. Soc.*, **119** (1997) 11715.
3. M. Pettersson, E. M. S. Maçôas, L. Khriachtchev, J. Lundell, M. Räsänen and R. Fausto, *Cis→trans* Conversion of Formic Acid by Dissipative Tunneling in Solid Rare Gases: Influence of Environment on the Tunneling Rate, *J. Chem. Phys.*, **117** (2002) 9095.
4. L. Khriachtchev, E. M. S. Maçôas, M. Pettersson and M. Räsänen, Conformational Memory in Photodissociation of Formic Acid, *J. Am. Chem. Soc.*, **124** (2002) 10994.
5. E. M. S. Maçôas, J. Lundell, M. Pettersson, L. Khriachtchev, R. Fausto and M. Räsänen, Vibrational Spectroscopy of *cis*- and *trans*-Formic Acid in Solid Argon, *J. Mol. Spectrosc.*, **219** (2003) 70.
6. M. Pettersson, E. M. S. Maçôas, L. Kriachtchev, R. Fausto and M. Räsänen, Conformational Isomerization of Formic Acid by Vibrational Excitation at Energies below the Torsional Barrier, *J. Am. Chem. Soc.*, **125** (2003) 4058.
7. S. Lopes, A. V. Domanskaya, R. Fausto, M. Räsänen and L. Khriachtchev, Formic and Acetic acids in a Nitrogen Matrix: Enhanced Stability, *J. Chem. Phys.*, **133** (2010) 144507
8. S. V. Ryazantsev and V. I. Feldman, Radiation-induced Transformations of Matrix-isolated Formic Acid: Evidence for the HCOOH → HOCO + H Channel, *Phys. Chem. Chem. Phys.*, **17** (2015) 30648.
9. S. Lopes, R. Fausto and L. Khriachtchev, Formic Acid in Deuterium and Hydrogen Matrices, Mol. Phys., 117 (2019) 1587.
10. A. Aerts, P. Carbonnière, F. Richter and A. Brown. Vibrational States of Deuterated *trans*- and *cis*-Formic Acid: DCOOH, HCOOD, and DCOOD, *J. Chem. Phys.*, **152** (2020) 024305.
11. E. M. S. Maçôas, L. Khriachtchev, R. Fausto and M. Räsänen, Photochemistry and Vibrational Spectroscopy of the *trans* and *cis* Conformers of Acetic Acid in Solid Argon, *J. Phys. Chem. A*, **108** (2004) 3380.
12. E. M. S. Maçôas, R. Fausto, M. Pettersson, L. Khriachtchev and M. Räsänen, Infrared Induced Rotamerization of Oxalic Acid Monomer in an Argon Matrix, *J. Phys. Chem. A*, **104** (2000) 6956.
13. E. M. S. Maçôas, R. Fausto, J. Lundell, M. Pettersson, L. Khriachtchev and M. Räsänen, Conformational Analysis and Near-Infrared-Induced Rotamerization of Malonic Acid in an Argon Matrix, *J. Phys. Chem. A*, **104** (2000) 11725.
14. E. M. S. Maçôas, R. Fausto, J. Lundell, M. Pettersson, L. Khriachtchev and M. Räsänen, A Matrix Isolation Spectroscopic and Quantum Chemical Study of Fumaric and Maleic Acid, *J. Phys. Chem. A*, **105** (2001) 3922.
15. R. Fausto and E. M. S. Maçôas, Photochemical Reactivity of Matrix-Isolated Monomeric Carboxylic Acids, *J. Mol. Struct.*, **563/564** (2001) 29.
16. R. F. G. Apóstolo, R. R. F. Bento, G. Tarczay and R. Fausto, The First Experimental Observation of the Higher-Energy *trans* Conformer of Trifuoroacetic Acid, *J. Mol. Struct.*, **1125** (2016) 288.
17. R. F. G. Apóstolo, R. R. F. Bento and R. Fausto, Narrowband IR-Induced In Situ Generation of the High-Energy *trans* Conformer of Trichloroacetic Acid Isolated in Solid Nitrogen and its Spontaneous Decay by Tunneling to the Low-Energy *cis* Conformer, *Croat. Chem. Acta*, **88** (2015) 377.
18. R. F. G. Apóstolo, G. Bazsó, G. O. Ildiz, G. Tarczay and R. Fausto, Near-Infrared *In Situ* Generation of the Higher-Energy *trans* Conformer of Tribromoacetic Acid: Observation of a Large-Scale Matrix-Site Changing Mediated by Conformational Conversion, *J. Chem. Phys.*, **148** (2018) 044303.
19. G. Bazsó, S. Góbi and G. Tarczay, Near-Infrared Radiation Induced Conformational Change and Hydrogen Atom Tunneling of 2-Chloropropionic Acid in Low-Temperature Ar Matrix, *J. Phys. Chem. A*, **116** (2012) 4823.
20. S. Lopes, T. Nikitin and R. Fausto, Propiolic Acid in Solid Nitrogen: NIR- and UV-Induced *cis* → *trans* Isomerization and Matrix-Site-Dependent *trans* → *cis* Tunneling, *J. Phys. Chem. A*, **123** (2019) 1581.
21. N. Kuş and R. Fausto, Near-infrared and Ultraviolet Induced Isomerization of Crotonic Acid in N_2 and Xe Cryomatrices: First Observation of Two High-energy *trans* C–O Conformers and Mechanistic Insights, *J. Chem. Phys.*, **141** (2014) 234310.
22. I. D. Reva, S. Stepanian, L. Adamowicz and R. Fausto, Combined FTIR Matrix Isolation and Ab Initio Studies of Pyruvic Acid: Proof for Existence of the Second Conformer, *J. Phys. Chem. A*, **105** (2001) 4773.
23. S. G. Stepanian, I. D. Reva, E. D. Radchenko, M. T. S. Rosado, M. L. T. S. Duarte, R. Fausto, and L. Adamowicz, Matrix-Isolation Infrared and Theoretical Studies of the Glycine Conformers, *J. Phys. Chem. A*, **102** (1998) 1041.
24. I. D. Reva, S. Jarmelo, L. Lapinski and R. Fausto, IR-Induced Photoisomerization of Glycolic Acid in Low Temperature Matrices, *J. Phys. Chem. A*, **108** (2004) 6982.
25. A. Halasa, L. Lapinski, I. Reva, H. Rostkowska, R. Fausto and M. J. Nowak, NIR-Laser-Induced Generation of Three Rare

 This journal is © The Royal Society of Chemistry 20xx

Please do not adjust margins

Conformers of Glycolic Acid, *J. Phys. Chem. A*, **118** (2014) 5626.

26. D. Gerbig and P. R. Schreiner, Hydrogen-Tunneling in Biologically Relevant Small Molecules: The Rotamerizations of α-Ketocarboxylic Acids, *J. Phys. Chem. B*, **119** (2015) 693.
27. N. Kuş and R. Fausto, Effects of the Matrix and Intramolecular Interactions on the Stability of the Higher-energy Conformers of 2-Fluorobenzoic Acid, *J. Chem. Phys.*, **146** (2017) 124305.
28. L. Lapinski, I. Reva, H. Rostkowska, R. Fausto and M. J. Nowak, Conformational Transformation in Squaric Acid Induced by Near-IR Laser Light, *J. Phys. Chem. A*, **117** (2013) 5251.
29. A. Halasa, L. Lapinski, I. Reva, H. Rostkowska, R. Fausto and M. J. Nowak, Three Conformers of 2-Furoic Acid: Structure Changes Induced with Near IR Laser Light, *J. Phys. Chem. A*, 119 (2015) 1037.
30. L. L. G. Justino, I. Reva and R. Fausto, Thermally- and Vibrationally-Induced Conformational Isomerizations, Infrared Spectra and Photochemistry of Gallic Acid in Low-Temperature Matrices, *J. Chem. Phys.*, **145** (2016) 014304.
31. S. Amiri, H. P. Reisenauer and P. R. Schreiner, Electronic Effects on Atom Tunneling: Conformational Isomerization of Monomeric Para-Substituted Benzoic Acid Derivatives, *J. Am. Chem. Soc.*, **132** (2010) 15902.
32. S. Nishino and M. Nakata, Intramolecular Hydrogen Atom Tunneling in 2-Chlorobenzoic Acid Studied by Low-temperature Matrix-isolation Infrared Spectroscopy, *J. Phys. Chem. A*, **111** (2007) 7041.
33. A. Halasa, I. Reva, L. Lapinski, M. J. Nowak and R. Fausto, Conformational Transformations in Thiazole-2-Carboxylic Acid Induced by Selective Near-IR and UV Narrowband Laser Light, *J. Phys. Chem. A*, **120** (2016) 2078.
34. P. R. Schreiner, J. P. Wagner, H. P. Reisenauer, D. Gerbig, D. Ley, J. Sarka, A. G. Császár, A. Vaughn and W. D. Allen, Domino Tunneling, *J. Am. Chem. Soc.*, **137** (2015) 7828.
35. N. Kuş, A. Sharma, I. Peña, M. C. Bermúdez, C. Cabezas, J. L. Alonso and R. Fausto, Conformers of β-Aminoisobutyric Acid Probed by Jet-Cooled Microwave and Matrix Isolation Infrared Spectroscopic Techniques, *J. Chem. Phys.*, **138** (2013) 144305.
36. C. M. Nunes, L. Lapinski, R. Fausto and I. Reva, Near-IR Laser Generation of a High-energy Conformer of L-Alanine and the Mechanism of Its Decay in a Low Temperature Nitrogen Matrix, *J. Chem. Phys.*, **138** (2013) 125101.
37. G. Bazsó, G. Magyarfalvi and G. Tarczay, Tunneling Lifetime of the ttc/VIp Conformer of Glycine in Low-Temperature Matrices, *J. Phys. Chem. A*, **116** (2012) 10539.
38. G. Bazsó, E. E. Najbauer, G. Magyarfalvi and G. Tarczay, Near-Infrared Laser Induced Conformational Change of Alanine in Low-Temperature Matrixes and the Tunneling Lifetime of Its Conformer VI, *J. Phys. Chem. A*, **117** (2013) 1952.
39. G. Bazsó, G. Magyarfalvi and G. Tarczay, Near-infrared Laser Induced Conformational Change and UV Laser Photolysis of Glycine in Low-temperature Matrices: Observation of a Short-lived Conformer, *J. Mol. Struct.*, **1025** (2012) 33.
40. E. E. Najbauer, G. Bazsó, R. Apóstolo, R. Fausto, M. Biczysko, V. Barone and G. Tarczay, Identification of Serine Conformers by Matrix-Isolation IR Spectroscopy Aided by Near-Infrared Lased Induced Conformational Change and 2D Correlation Analysis, *J. Phys. Chem. B*, **119** (2015) 10496.
41. E. E. Najbauer, G. Bazsó, S. Góbi, G. Magyarfalvi and G. Tarczay, Exploring the Conformational Space of Cysteine by Matrix Isolation Spectroscopy Combined with Near-infrared Laser Induced Conformational Change, *J. Phys. Chem. B*, **118** (2014) 2093.
42. A. J. Lopes Jesus, C. M. Nunes, I. Reva, S. M. V. Pinto and R. Fausto, The Effects of Entangled IR-Radiation and Tunneling on the Conformational Interconversion of 2-Cyanophenol, *J. Phys. Chem. A*, **123** (2019) 4396.
43. A. J. Lopes Jesus, I. Reva, C. M. Nunes, J. P. L. Roque, S. M. V. Pinto and R. Fausto, Kinetically Unstable 2-Isocyanophenol Isolated in Cryogenic Matrices: Vibrational Excitation, Conformational Changes and Spontaneous Tunneling, *Chem. Phys. Lett.*, **747** (2020) 137069.
44. L. Lapinski, I. Reva, H. Rostkowska, R. Fausto and M. J. Nowak, Near-IR-Induced, UV-Induced and Spontaneous Isomerizations in 4-Methylcytosine and 5-Fluorocytosine, *J. Phys. Chem. B*, **118** (2014) 2831.
45. L. Lapinski, M. J. Nowak, I. Reva, H. Rostkowska and R. Fausto, NIR-Laser-Induced Selective Rotamerization of Hydroxy Conformers of Cytosine, *Phys. Chem. Chem. Phys.*, **12** (2010) 9615.
46. L. Lapinski, I. Reva, M. J. Nowak and R. Fausto, Five Isomers of Monomeric Cytosine and Their Interconversions Induced by Tunable UV Laser Light, *Phys. Chem. Chem. Phys.*, **13** (2011) 9676.
47. I. D. Reva, M. J. Nowak, L. Lapinski and R. Fausto, Spontaneous Tunneling and NIR/IR Induced Interconversion between the Amino-Hydroxy Conformers of Cytosine, *J. Chem. Phys.*, **136** (2012) 064511.
48. R. Fausto, L. Khriachtchev and P. Hamm, Conformational Changes in Cryogenic Matrices, in Physics and Chemistry at Low Temperatures, (Ed. L. Khriachtchev), Jenny Stanford Publishing, Boca Raton, FL (USA), 2011, Chapter 3. pp. 51-84.
49. E. M. S. Maçôas, L. Khriachtchev, M. Pettersson, R. Fausto and M. Räsänen, Rotational Isomerism of Acetic acid Isolated in Rare-gas Matrices: Effect of Medium and Isotopic Substitution on IR-Induced Isomerization Quantum Yield and *cis* → *trans* Tunneling Rate, *J. Chem. Phys.*, **121** (2004) 1331.
50. P. R. Schreiner, Tunneling Control of Chemical Reactions: The Third Reactivity Paradigm, *J. Am. Chem. Soc.*, **139** (2017) 15276.
51. P. R. Schreiner, H. P. Reisenauer, D. Ley, D. Gerbig, C.-H. Wu and W. D. Allen, Methylhydroxycarbene: Tunneling Control of a Chemical Reaction, *Science*, **332** (2011) 1300.
52. P. Zuev and R. S. Sheridan, Tunneling in the C-H Insertion of a Singlet Carbene: *tert*-butylchlorocarbene, *J. Am. Chem. Soc.*, **116** (1994) 4123.

53. L. Windhorn, J. S. Yeston, T. Witte, W. Fuß, M. Motzkus, D. Proch, and K.-L. Kompa, Getting Ahead of IVR: A Demonstration of Mid-infrared Induced Molecular Dissociation on a Sub-Statistical Time Scale, *J. Chem. Phys.*, **119** (2003) 641.
54. S. Jarmelo and R. Fausto, Entropy Effects in Conformational Distribution and Conformationally Dependent UV-Induced Photolysis of Serine Monomer Isolated in Solid Argon, *J. Mol. Struct.*, **786** (2006) 175.
55. A. Borba, A. Gómez-Zavaglia and R. Fausto, Conformational Cooling and Conformationally Selective Aggregation in Dimethyl Sulfite Isolated in Solid Rare Gases, *J. Mol. Struct*., **794** (2006) 196.
56. A. M. Ismael, M. L. S. Cristiano, R. Fausto and A. Gómez-Zavaglia, Tautomer Selective Photochemistry in 1-(Tetrazol-5-yl)ethanol, *J. Phys. Chem. A*, **114** (2010) 13076.
57. M. Pagacz-Kostrewa, I. Reva, R. Bronisz, B. M. Giuliano, R. Fausto and M. Wierzejewska, Conformational Behavior and Tautomer Selective Photochemistry in Low Temperature Matrices: The Case of 5-(1H-tetrazol-1-yl)-1,2,4-triazole, *J. Phys. Chem. A*, **115** (2011) 5693.
58. R. Fausto and A. Gómez-Zavaglia, Light Induced Reactions in Cryogenic Matrices, in Specialistic Reports in Photochemistry, (Ed. Angelo Albini), Royal Society of Chemistry, London (UK), Vol. 37 (2009), Chapter 3. pp. 72-99.
59. R. Fausto and A. Gómez-Zavaglia, Light Induced Reactions in Cryogenic Matrices, in Specialistic Reports in Photochemistry, (Ed. Angelo Albini), Royal Society of Chemistry, London (UK), Vol. 38 (2010), Chapter 2. pp. 37-66.
60. R. Fausto and A. Gómez-Zavaglia, Light Induced Reactions in Cryogenic Matrices, in Specialistic Reports in Photochemistry, (Ed. Angelo Albini), Royal Society of Chemistry, London (UK), Vol. 39 (2011), Chapter 1. pp. 1-27.
61. R. Fausto and A. Gómez-Zavaglia, Light Induced Reactions in Cryogenic Matrices. Highlights 2011-2012, in Specialistic Reports in Photochemistry, (Ed. A. Albini and E. Fasani), Royal Society of Chemistry, London (UK), Vol. 41 (2013), Chapter 2. pp. 12-58.
62. R. Fausto, A. Borba and A. Gómez-Zavaglia, Light Induced Reactions in Cryogenic Matrices. Highlights 2013-2014, in Specialistic Reports in Photochemistry, (Ed. A. Albini and E. Fasani), Royal Society of Chemistry, London (UK), Vol. 43 (2015), Chapter 2. pp. 20-82.
63. R. Fausto, T. Nikitin and A. Gómez-Zavaglia, Light Induced Reactions in Cryogenic Matrices. Highlights 2015-2016, in Specialistic Reports in Photochemistry, (Ed. A. Albini, E. Fasani and S. Protti), Royal Society of Chemistry, London (UK), Vol. 45 (2017), Chapter 1. pp. 22-67.
64. R. Fausto, T. Nikitin and E. M. Brás, Light Induced Reactions in Cryogenic Matrices. Highlights 2017-2018, in Specialistic Reports in Photochemistry, (Ed. A. Albini, E. Fasani and S. Protti), Royal Society of Chemistry, London (UK), Vol. 47 (2019), Chapter 1. pp. 22-67.
65. R. Fausto, T. Nikitin and E. M. Brás, Light Induced Reactions in Cryogenic Matrices. Highlights 2019-2020, in Specialistic Reports in Photochemistry, (Ed. S. Crespi and S. Protti), Royal Society of Chemistry, London (UK), Vol. 49 (2022) Chapter 3. pp. 53-108.
66. E. M. S. Maçôas, L. Khriachtchev, M. Pettersson, R. Fausto and M. Räsänen, Internal Rotation in Propionic Acid: Infrared Induced Isomerization in Solid Argon, *J. Phys. Chem. A*, **109** (2005) 3617.
67. I. D. Reva, S. G. Stepanian, L. Adamowicz and R. Fausto, Missing Conformers: Comparative Study of Conformational Cooling in Cyanoacetic Acid and Methyl Cyanoacetate Isolated in Low Temperature Inert Gas Matrixes, *Chem. Phys. Lett.*, **374** (2003) 631.
68. A. Borba, A. Gómez-Zavaglia and R. Fausto, Conformational Cooling and Conformationally Selective Aggregation in Dimethyl Sulfite Isolated in Solid Rare Gases, *J. Mol. Struct*., **794** (2006) 196.
69. I. D. Reva, A. J. Lopes Jesus, M. T. S. Rosado, R. Fausto, M. E. Eusébio and J. S. Redinha, Stepwise Conformational Cooling Towards a Single Isomeric State in the Four Internal Rotors System 1,2-Butanediol, *Phys. Chem. Chem. Phys.*, **8** (2006) 5339.
70. S. Lopes, R. Fausto and L. Khriachtchev, Formic Acid Dimers in a Nitrogen Matrix, *J. Chem. Phys.*, **148** (2018) 034301.
71. S. Lopes, A. Domanskaya, M. Räsänen, L. Khriachtchev and R. Fausto, Acetic Acid Dimers in a Nitrogen Matrix: Observation of Structures Containing the Higher-Energy Conformer, *J. Chem. Phys.*, **143** (2015) 104307.
72. C. M. Nunes, I. Reva and R. Fausto, Conformational Isomerization Triggered by Vibrational Excitation of a Second Stretching Overtones, *Phys. Chem. Chem. Phys.*, **21** (2019) 24993.
73. A. Olbert-Majkut, J. Ahokas, J. Lundell and M. Pettersson, Investigating Isomerization Reactions in Solid State by Using Simultaneous High Overtone Pumping and Raman Detection, *J. Chem. Phys.*, **129** (2008) 041101.
74. A. Olbert-Majkut, J. Ahokas, J. Lundel and M. Pettersson, Raman Spectroscopy of Formic Acid and its Dimers Isolated in Low Temperature Argon Matrices, *Chem. Phys. Lett.*, **468** (2009) 176.
75. A. J. Lopes Jesus, I. Reva, C. Araujo-Andrade and R. Fausto, Conformational Switching by Vibrational Excitation of a Remote NH Bond, *J. Am. Chem. Soc.*, **137** (2015) 14240.
76. A. Halasa, I. Reva, L. Lapinski, H. Rostkowska, R. Fausto and M.J. Nowak, Conformers of Kojic Acid and Their Near-IR-Induced Conversions: Long-Range Intramolecular Vibrational Energy Transfer, *J. Phys. Chem. A*, **120** (2016) 2647.
77. B. Kovács, N. Kuş, G. Tarczay and R. Fausto, Investigation of Long-Range Intramolecular Vibrational Energy Redistribution by NIR Irradiation Induced Conformational Transformation of E-Glutaconic Acid, *J. Phys. Chem. A*, **121** (2017) 3392.
78. S. Góbi, I. Reva, I. Csonka, C. M. Nunes, G. Tarczay and R. Fausto, Conformational Control over Thiol Forms of

This journal is © The Royal Society of Chemistry 20xx

Please do not adjust margins

Thioacetamide by Selective Excitation of NH Imino Vibrational Antennas, *Phys. Chem. Chem. Phys.*, **21** (2019) 24935.

79. A. J. Lopes Jesus, C. M. Nunes, R. Fausto and I. Reva, Conformational Control over an Aldehyde Fragment by Selective Vibrational Excitation of Interchangeable Remote Antennas, *Chem. Comm.*, **54** (2018) 4778.
80. C. M. Nunes, N. A. M. Pereira, I. Reva, P. S. M. Amado, M. L. S. Cristiano and R. Fausto, Bond-Breaking/Bond-Forming Reactions by Vibrational Excitation: Infrared-Induced Bidirectional Tautomerization of Matrix-Isolated Thiotropolone, *J. Phys. Chem. Lett.*, **11** (2020) 8034.
81. C. M. Nunes, N. A. M. Pereira, I. Reva and R. Fausto, Evidence of IR-Induced Chemistry in Neat Solid: Tautomerization of Thiotropolone by Thermal, Electronic and Vibrational Excitations, *J. Phys. Chem. A*, **125** (2021) 6394.
82. C. M. Nunes, N. A. M. Pereira, L. P. Viegas, T. M. V. D. Pinho e Melo and R. Fausto, Inducing Molecular Reactions by Selective Vibrational Excitation of a Remote Antenna with Near-Infrared Light, *Chem. Comm.*, **57** (2021) 9570.
83. J. P. L. Roque, C. M. Nunes, L. P. Viegas, N. A. M. Pereira, T. M. D. V. Pinho e Melo, P. R. Schreiner and R. Fausto, Switching on H-tunneling Through Conformation Control, *J. Am. Chem. Soc.*, **143** (2021) 8266.
84. J. P. Klinman and A. Kohen, Hydrogen Tunneling Links Protein Dynamics to Enzyme Catalysis, *Annu. Rev. Biochem.*, **82** (2013) 471.
85. J. P. Klinman, An Integrated Model for Enzyme Catalysis Emerges from Studies of Hydrogen Tunneling, *Chem. Phys. Lett.*, **471** (2009) 179.
86. D. Ley, D. Gerbig, P. R. Schreiner, Tunnelling control of chemical reactions – the organic chemist's perspective, *Org. Biomol. Chem.*, **10** (2012) 3781.
87. J. Meisner, J. Kästner, Atom Tunneling in Chemistry, *Angew. Chem. Int. Ed.*, **55** (2016) 5400.
88. E. M. Greer, K. Kwon, A. Greer, C. Doubleday, Thermally activated tunneling in organic reactions, *Tetrahedron*, **72** (2016) 7357.
89. P. R. Schreiner, Quantum Mechanical Tunneling Is Essential to Understanding Chemical Reactivity, *Trends in Chemistry*, **2** (2020) 980.
90. R. P. Bell, The Tunnel Effect in Chemistry, Springer, Boston, 1980.
91. C. Castro, W. L. Karney, Heavy-Atom Tunneling in Organic Reactions, *Angew. Chem. Int. Ed.*, **59** (2020) 8355.
92. C. M. Nunes, I. Reva, R. Fausto, Direct Observation of Tunnelling Reactions by Matrix Isolation Spectroscopy. In Tunnelling in Molecules: Nuclear Quantum Effects from Bio to Physical Chemistry; J. Kästner, S. Kozuch, Eds. The Royal Society of Chemistry: 2021; pp 1– 60.
93. T. Schleif, J. Mieres-Perez, S. Henkel, E. Mendez-Vega, H. Inui, R. J. McMahon, and W. Sander, Conformer-Specific Heavy-Atom Tunneling in the Rearrangement of Benzazirines to Ketenimines, *J. Org. Chem.*, **84** (2019) 16013.
94. T. Schleif, J. Tatchen, J. F. Rowen, F. Beyer, E. Sanchez-Garcia, W. Sander, Heavy-Atom Tunneling in Semibullvalenes: How Driving Force, Substituents, and Environment Influence the Tunneling Rates, *Chem. Eur. J.*, **26** (2020) 10452.
95. T. Schleif, M. P. Merini, W. Sander, The Mystery of the Benzene-Oxide/Oxepin Equilibrium—Heavy-Atom Tunneling Reversed by Solvent Interactions, *Angew. Chem. Int. Ed.*, **59** (2020) 20318.
96. S. Henkel, M. P. Merini, E. Mendez-Vega and W. Sander, Lewis acid catalyzed heavy atom tunneling – the case of 1H-bicyclo[3.1.0]-hexa-3,5-dien-2-one, *Chem. Sci.*, **12** (2021) 11013.
97. C. M. Nunes, L. P. Viegas, S. A. Wood, J. P. L. Roque, R. J. McMahon, R. Fausto, Heavy-Atom Tunneling Through Crossing Potential Energy Surfaces: Cyclization of a Triplet 2-Formylarylnitrene to a Singlet 2,1-Benzisoxazole, *Angew. Chem. Int. Ed.*, **59** (2020) 17622.
98. C. M. Nunes, A. K. Eckhardt, I. Reva, R. Fausto, and P. R. Schreiner, Competitive Nitrogen versus Carbon Tunneling, *J. Am. Chem. Soc.*, **141** (2019) 14340.

REVIEW ARTICLE

IR-induced and tunneling reactions in cryogenic matrices: the (incomplete) story of a successful endeavor

Received 28th December 2021,
Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

Rui Fausto,*[a] Gulce O. Ildiz [a,b] and Cláudio M. Nunes[a]

In this article, IR-induced and tunneling-driven reactions observed in cryogenic matrices are described in a historical perspective, the entangling of the two types of processes being highlighted. The story of this still ongoing fascinating scientific endeavor is here presented following closely our own involvement in the field for more than 30 years, and thus focuses mostly on our work. It is, by this reason, also an incomplete story. Nevertheless, it considers a large range set of examples, from very selective IR-induced conformational isomerizations to IR-induced bond-breaking/bond-forming reactions and successful observations of rare heavy atom tunneling processes. As a whole, this article provides a rather general overview of the major progresses achieved in the field.

Keywords: IR-induced chemistry, tunneling-driven reaction, Infrared spectroscopy in cryogenic matrices

Introduction and background perspective

The first reported IR-induced reaction was described by Hall and Pimentel almost 60 years ago [1]. In that pioneer experiment, the authors isolated nitrous acid in an argon matrix and used broadband infrared excitation in the νOH stretching wavenumber region (3650-3200 cm^{-1}) to induce changes in the relative populations of the two conformers of the molecule (Figure 1). The conformational changes were found to depend on the specific wavenumber range applied to irradiate the sample, which could be chosen by using appropriate infrared bandpass filters. In their article, Hall and Pimentel pointed out that *"the [observed] IR-induced isomerization of nitrous acid can be considered to be a new type of photochemical reaction"* and stressed the fact that the *"study of this reaction [was] possible only because of the unique potentialities of the matrix isolation technique"* [1]. They appropriately concluded that *"perhaps the most important [result] in this work is the implied high efficiency of intramolecular energy transfer among the vibrational degrees of freedom of a vibrationally excited molecule"* [1].
Very interestingly, at the time, the discovery of Hall and Pimentel was not received so enthusiastically by the scientific community as it could be expected considering its highly innovative character. The main reason for that was the lack of selectivity of the observed process. In fact, upon broadband excitation both conformers were being simultaneously excited, so that their final populations resulted from the attainment of a photostationary state. A photostationary state is a function of the applied excitation wavenumber range and, in that way, some control of the system can be achieved. Nevertheless, it was clear that to accomplish full control of this type of reactions and make the approach useful for application to other systems, selective excitation of a single specific conformer had to be made possible.

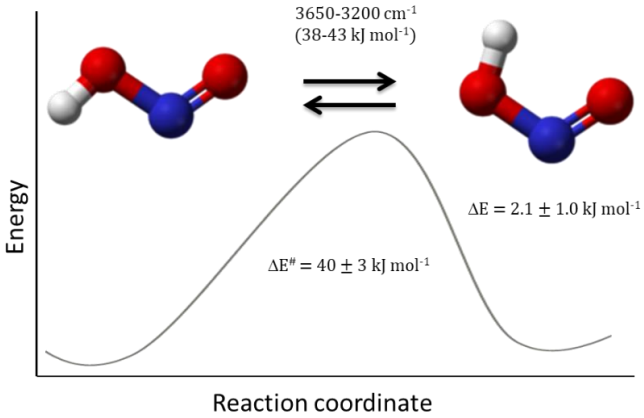


Figure 1. Potential energy profile for interconversion between the two conformers of nitrous acid, whose relative populations could be changed by bandpass-filtered broadband IR excitation of the matrix isolated compound. Adapted from ref. 1. Copyright 1963 American Institute of Physics.

This problem was only solved 34 years later, when infrared narrowband tunable light sources became more easily available. In 1997, Pettersson, Lundell, Khriahtchev and Räsänen, at the University of Helsinki, published a major breakthrough study [2] where the selective conformational isomerization of formic acid isolated in an argon matrix was successfully induced by narrowband excitation with a laser-based IR tunable light source. The most stable ***Z*** conformer of formic acid (O=C–O–H dihedral: 0°) was initially trapped in the

[a] CQC-IMS, Department of Chemistry, University of Coimbra, 3004-535 Coimbra, Portugal.
[b] Department of Physics, Faculty of Sciences and Letters, Istanbul Kultur University, 34158 Bakirkoy, Istanbul, Turkey.
* Corresponding author (e-mail: rfausto@ci.uc.pt).

cryogenic matrix from the gas phase, and subsequently converted into the higher energy ***E*** conformer (O=C–O–H dihedral: 180°) upon matrix irradiation at the wavenumber of the νOH stretching first overtone of the ***Z*** form (6934 cm^{-1}) [2]. This first investigation was followed by others where the ***Z*** → ***E*** conformational conversion of formic acid was investigated in further details [3-10]. In those studies, isotopically labelled formic acid and different types of matrices were used.

Our group had the chance to join those pioneer investigations since the very beginning. The studies were promptly expanded to other simple carboxylic and dicarboxylic acids, like acetic, oxalic, fumaric, maleic and malonic acids [7,11-15]. From our fruitful collaboration with the Helsinki group (and also in result of the work of other groups participating in this adventure) some general conclusions emerged, which became the basis for the subsequent more elaborated studies on more complex systems, like amino acids, nucleic acid bases, halogenated carboxylic acids, α-hydroxyl, α-keto and α,β-unsaturated carboxylic acids, aromatic and other cyclic carboxylic acids, and phenol derivatives [16-47], among others.

One very interesting early observation was that the IR excitation of a matrix isolated compound can be selective to the nature of the matrix sites occupied by the molecules [5]. In a matrix, molecules might be trapped in different local environments (matrix sites). Molecules in different matrix sites feel different intermolecular potentials due to the different interactions with the matrix atoms, this leading to slightly different intramolecular potentials. Therefore, the vibrational spectra of identical molecules trapped in different sites differ slightly. In practice, this leads to observation of bands in the spectrum of a given compound that appear split. It shall be noticed that not all bands have to show matrix splitting, since this depends upon the degree of perturbation of the intramolecular potential associated to each vibrational coordinate in result of the intermolecular interactions. In general, vibrational coordinates associated with more polar groups are more affected by the matrix medium and the corresponding bands appear more frequently split due matrix effects. For simple carboxylic acids, this is the case of, for example, the νOH and νC=O stretching modes. For formic acid, it was found that the molecules may occupy two main sites in an argon matrix, which give rise to νOH fundamental bands at 3548.2 (site 1) and 3550.5 cm^{-1} (site 2) [5]. The corresponding 1st overtone bands are observed at 6930.3 and 6934.8 cm^{-1} [5]. As shown in Figure 2, excitation of molecules trapped in a given matrix site at the wavenumber of the corresponding νOH 1st overtone results in the ***Z*** → ***E*** conformational conversion, without affecting in a measurable way the structure of the site. This means that, besides being selective to the molecular species (e.g., a given conformer of a given molecule), the reactions resulting from vibrational excitation are also selective regarding the local matrix trapping environment. As it will be shown later in this article, such selectivity is also kept when the energy delivered to the reactant conformer is substantially higher than that corresponding to excitation to a νOH stretching 1st overtone, i.e., when excitation is performed, for example, at the characteristic wavenumbers of higher-order overtones of this vibration.

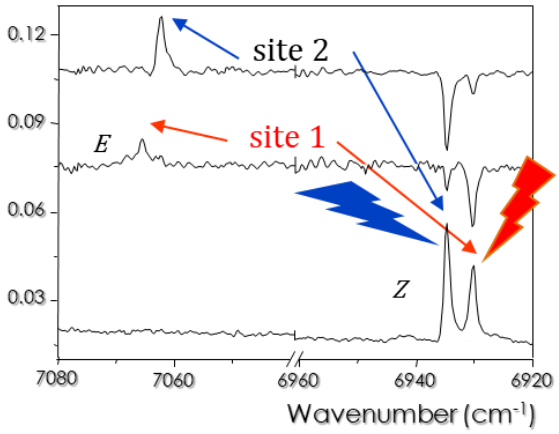


Figure 2. Results of narrowband IR irradiation at the νOH 1st overtone wavenumbers of the ***Z*** conformer of formic acid molecules isolated in two different matrix sites in an argon matrix, leading to its conversion into the ***E*** isomer. The bottom spectrum is that of the as-deposited matrix, while the middle and upper spectra are difference spectra obtained by subtracting the bottom spectrum to those obtained after the performed irradiations. Adapted from ref. 5. Copyright 2003 Elsevier.

Another fascinating observation resulting from the very first series of studies with narrowband selective vibrational excitation was that the mechanism of energy redistribution from the excited coordinate to the reactive coordinate (in the case of the conformational isomerization of formic acid this latter is the low energy C–O torsional coordinate) is not strictly statistical, implying that there are preferred channels which maximize the efficiency of the process. One simple proof for this is the observation of very similar efficiencies in the IR-induced isomerization processes of molecules having significantly different numbers of potentially competitive acceptor low-energy coordinates, e.g. formic acid and cytosine [2,6,45]. The existence of such funnel-like preferential energy relaxation channels was demonstrated for the case of matrix isolated formic acid using time-resolved IR spectroscopy [48].

In the context of the present article, however, the most relevant observation extracted from the initial studies on IR-induced processes in cryogenic matrices was the fact that the conformational isomerization reactions may take place even when the energy deposited in the excited coordinate stays below that of the barrier separating the reactant conformer from the product. This was first observed for formic acid [6], and immediately after for acetic acid [49], but it is a rather general phenomenon. As shown in Figure 3, the quantum yields for the ***Z*** → ***E*** conformational conversion in both formic and acetic acids reduce by only one to two orders of magnitude once the excitation energy stays below but close to that corresponding to the energy barrier of the reaction, and only diminish considerably when the excitation is performed at an energy far from that of the energy barrier. The significant quantum yields of the reaction for excitation at energies below the barrier are easily explained taking into account its occurrence *via* the quantum mechanical tunneling (QMT) mechanism. Vibrational

This journal is © The Royal Society of Chemistry 20xx

Please do not adjust margins

Please do not adjust margins

excitation followed by intramolecular energy relaxation takes the molecule to a vibrational state of the reactive coordinate in which both the effective height and width of the reaction barrier reduce, so that the tunneling probability becomes high. These reactions are designated as vibrationally-assisted QMT-driven reactions.

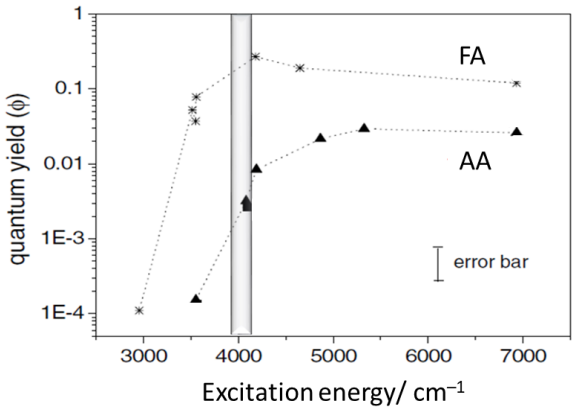


Figure 3. Quantum yields for the ***Z*** → ***E*** conformational isomerization for formic acid (FA) and acetic acid (AA) as a function of the excitation energy. The excitations were performed at the indicated wavenumbers, which correspond to observed bands in the IR spectrum of the reactant ***Z*** conformer of the two acids. The shadowed region in the figure shows the range of energies predicted for the ***Z*** → ***E*** energy barrier for the two molecules using different methods. Adapted from ref. 49. Copyright 2004 American Institute of Physics.

It is worth noticing that the quantum yields for the reaction of acetic acid were found to be systematically lower than those observed for formic acid [49], a result that is in agreement with the existence in the former molecule of an alternative energy relaxation channel efficiently competing with the reactive channel (as already mentioned, the torsion around the C–O bond that leads to the ***Z*** → ***E*** conformational conversion). Such secondary relaxation channel has as final acceptor coordinate the low-energy internal rotation of the methyl group of acetic acid [49].

An additional observation resulting from the studies performed on the simple carboxylic acids first investigated was that the higher energy ***E*** conformers (formed upon vibrational excitation of the most stable ***Z*** conformers) spontaneously decay back to the original species in the dark *via* a tunneling-driven process. For formic acid isolated in argon, such tunneling process has a rate of ca. 2 x 10^{-3} s^{-1}, which corresponds to a half-live of the ***E*** form of a few minutes [5]. The nature of the mechanism involved in these reactions was since the very beginning proved unequivocally through experiments with isotopically labelled formic and acetic acids [5,6,49], and this has been confirmed later for other types of molecules containing the carboxylic group (e.g., amino acids and halogenated carboxylic acids [16-19,35-41]). The relevance of spontaneous QMT decay of higher-energy conformers produced *in situ* in matrices (using either vibrational or electronic excitation of suitable precursors) has also been demonstrated for other types of conformational isomerizations involving movement of hydrogen atoms, for example in derivatives of nucleic acid bases and phenols [30,42-47].

As noticed above, the matrix isolation method provides optimal conditions for direct observation of QMT. The very low work temperatures characteristic of a matrix isolation experiment (typically of a few Kelvin) prevent occurrence of any spontaneous over-the-barrier reaction that has an associated barrier higher than a few kJ mol^{-1}. Under these conditions, observation of a spontaneous reaction usually implies that it takes place by tunneling. Since tunneling from the ground vibrational state implies that the reaction product has a lower energy than the reactant, it is easy to understand why vibrational excitation is particularly suitable to allow for observation of tunneling reactions: in one side, one can shift the state of the reactant to a higher vibrational state and open the gate for tunneling to products otherwise inaccessible and, on the other side, a higher energy species can be first generated as a result of the vibrational excitation of the reactant followed by energy relaxation, and subsequently undergo a tunneling-driven reaction to the final product. In the latter case, the final product can either be the original reactant, as in the cases described above for formic and acetic acids, or a completely different species, as it will be here shown later. In this way, in a certain perspective one can state that IR-induced chemistry and QMT are, under matrix isolation conditions, very often entangled processes. The interesting point is that one can take advantage of this intertwining to strategically play with the structure of molecules, as it will be demonstrated in the next sections.

It shall also be highlighted at this point that recent studies of QMT in cryogenic matrices have been providing evidence that this phenomenon shall not be considered only as a complementary mechanism to kinetics and thermodynamics in explaining chemical reactivity. QMT can in fact even determine the reactivity of a chemical species, superseding the classical rules of thermodynamics and kinetics and emerging as a new paradigm in chemical reactivity [50,51]. Figure 4 exemplifies how this can be conceived. In the top panel of the figure, a potential energy profile for two competitive reactions of **A**, to give products **B** and **C**, is presented. **B** corresponds to the thermodynamically driven product of lowest energy, while **C** is the result of kinetical control, generated *via* a lower energy transition state. Tunneling can also be considered to take place for generation of both **B** and **C**, and in matrix isolation conditions even dominate or occur exclusively (depending on the barrier heights and widths), but whatever the situation would be in this case tunneling does not lead to a new product. On the other hand, the potential energy profile shown in the bottom panel of Figure 4 is considerably more interesting, and it is exemplified for a real example [50,52]. In this case, the 1,2-methyl shift product of rearrangement of *tert*-butylchloro-carbene is both the thermodynamics and kinetics determined product, since it has the lowest energy among the possible products and can be reached *via* the lowest energy transition state. However, after *in situ* generation of the reactant carbene in a cryogenic N_2 matrix (at 11 K), this putative product was not experimentally observed [52]. Instead, the C–H bond insertion

Please do not adjust margins

cycloalkane product was observed, which results from tunneling control, since though being higher the barrier leading to its formation is considerably narrower than that corresponding to the formation of the alkene species resulting from the 1,2-methyl shift. Another paradigmatic example of tunneling control of chemical reactivity has been reported recently by Shreiner, involving the rearrangement of matrix isolated methylhydoxycarbene [50,51].

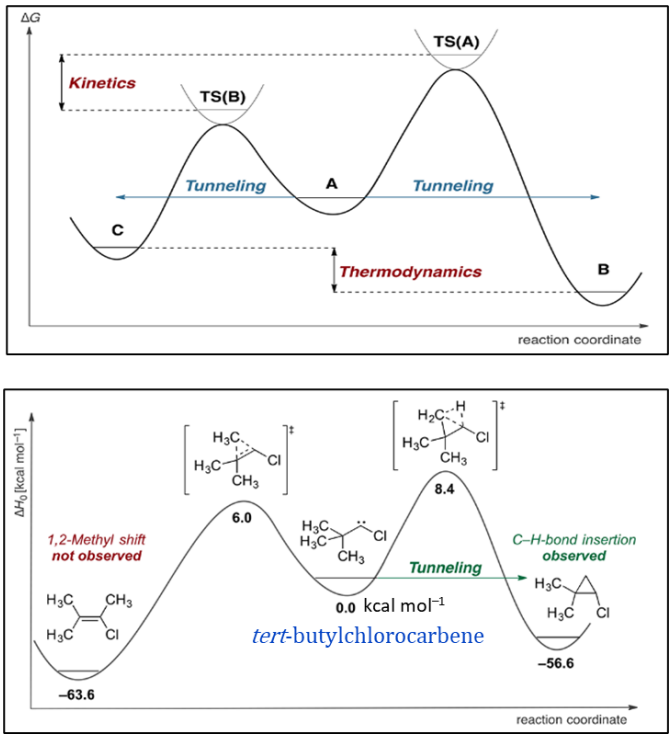


Figure 4. *Top*: Potential energy profile showing a trivial case where two possible products resulting either from the kinetics or thermodynamics control are expected to be obtained. *Bottom*: potential energy profile where the reaction proceeds through the higher, but narrower energy barrier, yielding a product that is neither kinetically nor thermodynamically favored (the given example corresponds to the reactivity of *in situ* generated *tert*-butylchlorocarbene in a N_2 matrix). The original data was shown in ref. 52, but the authors apparently did not notice they were observing a reaction resulting from tunneling control, fact that was later pointed out by Schreiner [50]. Adapted from ref. 50. Copyright 2017 American Chemical Society.

Before starting to provide relevant examples to illustrate the progress on the investigation of IR-induced and tunneling-driven reactions observed in cryogenic matrices in a historical perspective, which will be the subject of the next sections of this article, it appears appropriate to present here the main reasons why vibrationally-induced chemistry is so appealing. The main reason for this is because a laser can be tuned to the vibrational frequency of a specific bond and used to deposit sufficient energy to cleave that bond while leaving the remaining part of the molecule practically undisturbed. This is a very much different situation compared to thermally- or UV-induced processes, where extensive changes are made to the structure of the whole molecule. Using a simple comparison, IR-induced processes are the equivalent of a laparoscopic surgery, where the target organ is reached with minimum damage of the body, in opposition to a strongly invasive open-abdominal surgery, which in this comparison is the equivalent of both thermal and UV-induced reactions. Additionally, IR excitation may be used to change the structure of the molecule, in a very specific and localized way, to open new reaction channels, as illustrated, for example, in the decomposition reaction of diazomethane depicted in Figure 5. In this case, selective vibrational excitation of the νCNN anti-symmetric stretching fundamental of the molecule was performed [53], which took the molecule to a vibrational state where the path to the cleavage of the CN bond *via* δCH_2 bending became accessible.

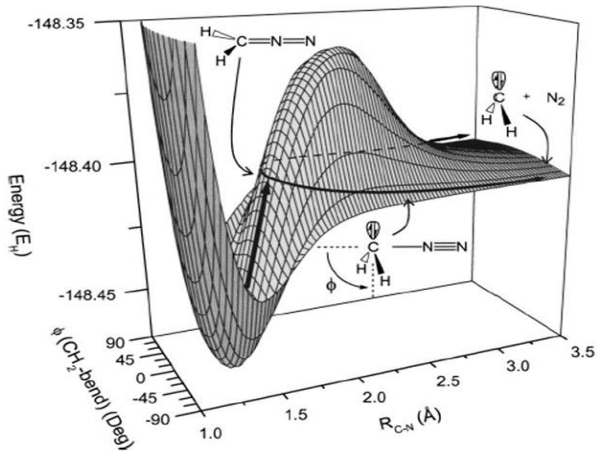


Figure 5. Potential energy surface illustrating the opening of the dissociation channel *via* δCH_2 bending, upon vibrational excitation of the νCNN anti-symmetric stretching of diazomethane. The reaction was carried out in the gas phase and fs pumping was used to prevent statistical redistribution of energy (ps time scale). Adapted from ref. 53. Copyright 2003 American Institute of Physics.

Another interesting possibility opened by IR-induced chemistry results from the fact that conformers can be produced in a very selective way, including conformers of high-energy otherwise not accessible to experimentation. This allows for conformationally selective chemistry to be investigated. The UV-induced photodegradation of formic acid is a good example of conformationally dependent reactivity of a compound [4], but other examples have also been reported [54-57]. Formic acid has only two conformers and they were found to have distinct preferential photodegradation pathways (Figure 6). After isolation in a cryogenic matrix of the most stable ***Z*** conformer, UV irradiation results mostly in the production of CO + H_2O. On the other hand, *in situ* generation of the higher energy ***E*** conformer, upon vibrational excitation of the initially deposited ***Z*** form, allowed for the investigation of its photochemistry, which was shown to preferentially yield H_2 + CO_2 [4].

In the next sections, the major developments resulting from the above-mentioned initial experiments on IR-induced chemistry and interconnected tunneling-driven reactions will be presented, following closely our involvement in the field for more than 30 years. We will focus mostly on our own work, but many other groups have also been given outstanding

This journal is © The Royal Society of Chemistry 20xx

contributions to the field, and this has been highlighted in our sequence of reviews published in the RSC Series *Photochemistry* [58-65]. The story here presented is necessarily an incomplete story. Nevertheless, it considers a large range of examples, from very selective IR-induced conformational isomerizations to successful observations of rare heavy atom tunneling processes, and it provides a rather general overview of most of the major progresses achieved in the field.

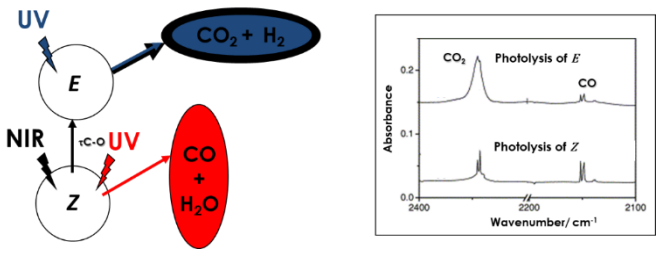


Figure 6. Schematic representation of the conformationally dependent photodegradation of formic acid, and IR spectra illustrating the formation of the representative products CO and CO_2. Adapted from ref. 4. Copyright 2002 American Chemical Society.

From simple 2-states systems to complex multi-states systems: on the route of generalization

The first IR-induced studies focused on simple molecules exhibiting two conformational states, with particular emphasis on formic and acetic acids [2-6,49]. Our already classic study on propionic acid (in collaboration with the Helsinki group) [66] appeared as a landmark in the field, bringing the technique to the investigation of a molecule with a larger number of relevant conformers.

Propionic acid has two conformers of low energy, where the carboxylic group is in the *Z* conformation (***Z-syn*** and ***Z-skew***$^{\pm}$), and two conformers of higher energy, where the carboxylic group is in the *E* conformation (***E-syn*** and ***E-skew***$^{\pm}$). Figure 7 shows the structures of the conformers and the energy barriers for their interconversion, as predicted theoretically.

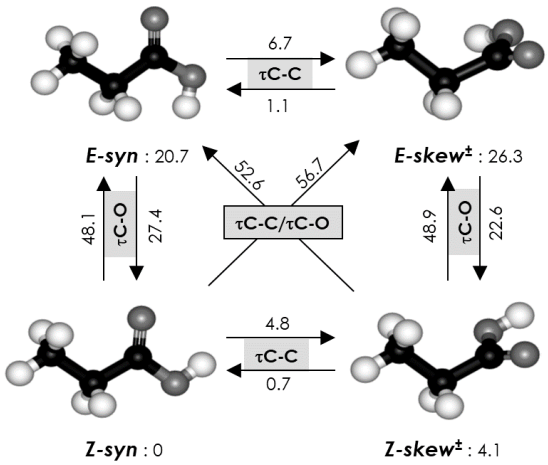


Figure 7. Conformers of propionic acid and their predicted energy differences and interconversion barriers (kJ mol^{-1}). Adapted from ref. 66. Copyright 2005 American Chemical Society.

Considering their high relative energy, the *E* conformers have a negligible population in gas phase, so that it could be expected that only the two *Z* conformers should be observed experimentally. Interestingly, it was found that the most stable ***Z-syn*** conformer was exclusively present in the as-deposited matrices of the compound [66]. The absence of the ***Z-skew***$^{\pm}$ conformer in the initially prepared matrices is, however, easy to understand. This conformer is separated from the most stable form by a very small energy barrier (0.72 kJ mol^{-1}, as predicted at the MP2/6-311++G(2d,2p) level [66]). This barrier is then easily surpassed at the time the molecules, initially in a hot gaseous beam, land onto the optical substrate (a CsI window cooled to 15 K) during deposition of the matrix. Consequently, the higher-energy ***Z-skew***$^{\pm}$ conformer converts into the most stable ***Z-syn*** form. This phenomenon (known by conformational cooling effect) is well-known and has been observed many times in matrix isolation experiments for molecules with conformers separated by energy barriers of only a few kJ mol^{-1} [67-69].

The fact that just the ***Z-syn*** conformer is present in the as-deposited matrices of propionic acid is interesting, since this allows for the study of its properties and reactivity in an easy way. The vibrational excitation of this conformer at the wavenumber of its νOH stretching 1st overtone (6960 cm^{-1}) was found to generate both the high-energy ***E-syn*** conformer, *via* rotation around the C–O bond, and the ***Z-skew***$^{\pm}$ conformer, through rotation about the C_{α}–C bond. The latter conformer, once produced *in situ*, is rather stable under matrix isolation conditions at the lowest temperatures used (8 K), because now no energy is available to efficiently surpass the ***Z-skew***$^{\pm}$ → ***Z-syn*** barrier. On the other hand, the ***E-syn*** conformer decays quickly back to the ***Z-syn*** conformer by tunneling, since this reaction involves only motion of the light carboxylic hydrogen atom (this is in fact a similar process to those observed in formic and acetic acids described above). Hence, not just the ***E-syn*** and ***Z-skew***$^{\pm}$ conformers could be prompted identified and characterized vibrationally [66], but these experiments opened the possibility for the study of their specific reactivities. Since the initially produced ***Z-skew***$^{\pm}$ conformer is stable under the experimental conditions used, a subsequent IR-irradiation at the wavenumber of its νOH stretching 1st overtone (6950 cm^{-1}) could be undertaken. In result of such irradiation, this conformer was converted into the highest-energy ***E-skew***$^{\pm}$ conformer, thus generating the last of the 4 conformers of propionic acid (this conformer also decays in the dark, by QMT, to the most stable conformer) [66].

The whole series of experiments performed on propionic acid is summarized in Figure 8 and illustrates well the power of the coordinated use of IR-induced chemistry and tunneling to manipulate chemical structures. The next example deals with an even more complex chemical system and shows how IR-excitation can be coupled not just with QMT but also with UV-excitation in a strategic way to achieve selective structural manipulations. The target compound in those studies was the nucleic acid base cytosine, and the investigations were performed within the scope of a broader program of research developed in collaboration with the group of Nowak and

Lapinski, from the Institute of Physics of the Polish Academy of Sciences, Warsaw.

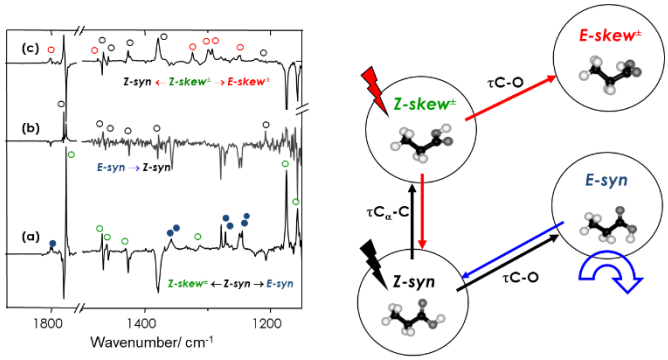


Figure 8. Schematic representation of the IR-induced and QMT experiments on propionic acid (*right*) and IR spectra showing the results (*left*): (a) spectral changes upon excitation of the 2νOH mode of ***Z-syn*** conformer; (b) dark decay of ***E-syn***; (c) spectral changes upon excitation of the 2νOH mode of the ***Z-skew±*** conformer. Difference spectra (a) and (c) were obtained by subtracting the spectra recorded before pumping from those recorded under pumping. Difference spectrum (b) was obtained by subtracting the spectra recorded under pumping from that recorded after a few minutes in the dark. Adapted from ref. 66. Copyright 2005 American Chemical Society.

Cytosine has five main isomeric species: the two lowest energy amino-hydroxy conformers (**AH1**, **AH2**, with **AH2** being ~3 kJ mol^{-1} higher in energy than **AH1**), the amino-oxo form (**AO**) that has an intermediate energy (ca. 5 kJ mol^{-1} above the most stable **AH1** form), and two higher energy imino-oxo isomers (**IO1**, **IO2**) with energies 7 and 12 kJ mol^{-1} above **AH1**. These species are represented in Figure 9, which also summarizes the sequence of experiments we successfully undertook to change the relative amounts of the five forms in a cryogenic matrix [45-47].

Upon deposition of cytosine in an argon matrix, the signatures of all the five isomers of cytosine depicted in Figure 9 were detected [45-47]. UV irradiation at 300 nm resulted in conversion of the **AO** form into the remaining species. In this way, the population of the minor imino-oxo isomers could be strongly enhanced. Subsequent irradiation at 311 nm led to interconversion between the **IO1** and **IO2** isomers. This is a typical reaction progressing toward a photostationary state and, when performed immediately after the irradiation at 300 nm that converts **AO** into both **IO1** and **IO2**, results in effective conversion of **IO1** into the higher energy **IO2** isomer. This UV irradiation does not change the populations neither of **AO** nor of the **AH1** and **AH2** isomers. On the other hand, when the matrix is let in the dark, the **AH2** form spontaneously decays by QMT to the most stable **AH1** form, in a reaction obeying to a dispersive-type kinetics [47] with an average time constant of ca. 36.5 h.

Selective interconversions between the two amino-hydroxy conformers could be achieved by IR excitation. Irradiation at 7013 cm^{-1} (νOH 1st overtone of **AH1**) led to conversion of this form into **AH2**, whereas irradiation at 7034 cm^{-1} (νOH 1st overtone of **AH2**) induced the opposite transformation [45].

It is worth mentioning that these studies were the first ever reported where IR-induced conformational isomerizations were successfully achieved for a large heterocyclic molecule under matrix isolation conditions. In polyatomic molecules containing more than 10 atoms, the higher density of vibrational states could *a priori* be expected to strongly affect the pathways of vibrational energy redistribution, and hence the efficiency of the IR-induced conformational isomerizations. Nevertheless, the results proved that for cytosine the process occurs with an efficiency that is similar to those observed for small molecules like formic and acetic acid, and this was a clear experimental evidence of the existence of preferred channels for vibrational energy redistribution.

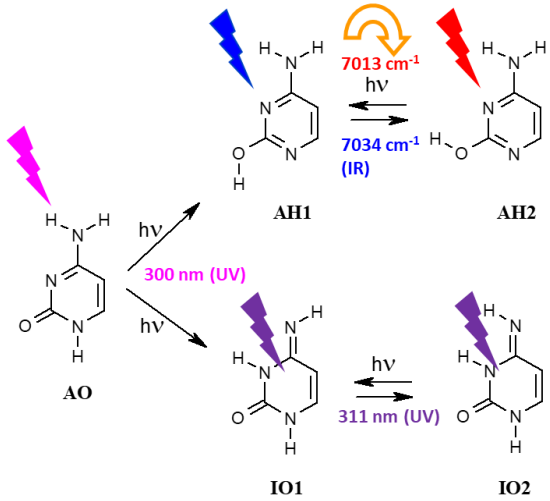


Figure 9. IR- and UV- induced and QMT reactions of matrix isolated cytosine. Adapted from ref. 46. Copyright 2011 Royal Society of Chemistry.

Another relevant development in the field was the use of selective IR excitations to generate rare high-energy dimers of carboxylic acids, showing that the method could also be applied for weakly bonded species. Formic and acetic acids are the paradigmatic examples of this type of studies. For both molecules a large number of unusual dimers was generated in cryogenic matrices upon vibrational excitation of more common dimeric species, and subsequently characterized structurally and spectroscopically [70,71]. The most interesting dimers of these two carboxylic acids that have been produced this way have at least one of their molecular units in the intrinsically less stable carboxylic *E* conformation. Since both ***E*** formic and acetic acid monomers are unstable in a cryogenic matrix, the *E* units of the dimer have to be generated *in situ*. Two different strategies have been applied: in the first, the ***E*** monomer of the acid is first produced by vibrational excitation of the ***Z*** form, and then the matrix is annealed to a higher temperature, allowing for molecular diffusion and formation of the dimers containing the *E* units (very interestingly, the ***E*** conformers were found to diffuse in the warmed matrices more efficiently than the ***Z*** forms, which facilitated the generation of *E* containing dimers [70,71]); in the second approach, the *Z-Z* dimers are first prepared from the ***Z*** monomer by warming the matrix and then the dimers are subjected to IR irradiation to convert them into dimers containing an *E* structural unit [70,71]. Figure 10 illustrates this last case, for acetic acid. In this example, note the

 This journal is © The Royal Society of Chemistry 20xx

selective character of the IR-induced process. Upon irradiation at the specific wavenumber of the νOH 1st overtone of the free OH group of the *Z-Z* dimer **D2 *Z-Z***, this species was converted to the **D2 *Z-E*** dimer, without any change taking place either for the ***Z*** monomer or for the *Z-Z* centrosymmetric dimer **D1 *Z-Z*** present in the matrix.

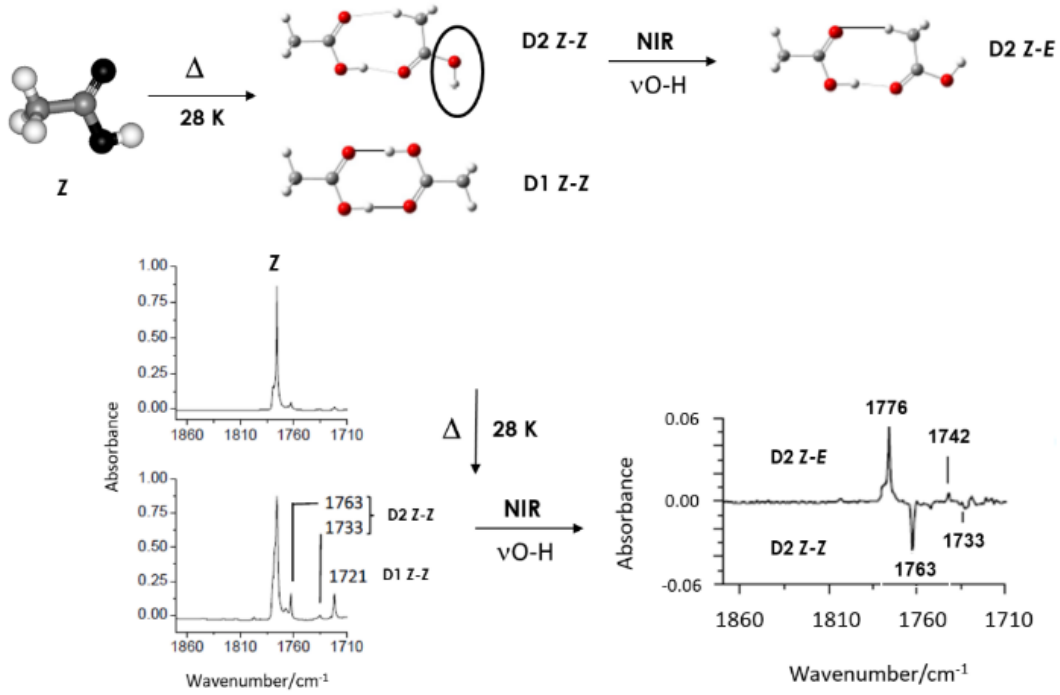


Figure 10. IR-induced selective generation of a *Z-E* dimer of acetic acid in a cryogenic matrix. The matrix was first annealed to 28 K to generate *Z-Z* dimers **D1 *Z-Z*** and **D2 *Z-Z*** and then irradiated at the νO-H first overtone of the free OH bond of **D2 *Z-Z***, generating **D2 *Z-E***. Adapted from ref. 71. Copyright 2015 American Institute of Physics.

Vibrational excitation *via* higher-order overtones: opening the gate to higher energy processes

One limitation to the generalization of vibrational excitation as a tool for inducing chemical reactivity is the relatively small range of energies accessible. If excitation is undertaken using a fundamental vibration, in the most favorable case of pumping of the νOH stretching mode, the energy introduced in the molecule is in the range of only 30–45 kJ mol^{-1} (3000-3600 cm^{-1}). First overtone excitation expands the range of energy to 75-87 kJ mol^{-1} (6300–7300 cm^{-1}), and this is enough energy to allow inducing quite efficiently many types of conformational isomerization processes. We asked ourselves about the possibility of using higher-order overtones to introduce even more energy in the molecules. If possible, excitation using the 2nd overtone of a νOH stretching mode would allow to expand the range of processes energetically accessible to those having barriers as large as ca. 130 kJ mol^{-1}. Though conceptually the idea is simple, there were some important questions to verify: *(i)* in order to choose the wavenumber to use for the excitation, the position of the 2nd overtone has to be determined, so that the corresponding band has to be experimentally observed; is this possible using the conventional detectors for near-IR?; *(ii)* for the processes to be efficient, the IR absorption cross section of the mode to excite has to be as large as possible; is that of the νOH 2nd overtone large enough?; *(iii)* since the width of the 2nd overtone bands can be expected to be larger than those of the fundamental bands or 1st overtones, can selectivity still be kept in a way that this can be useful in practical terms?; *(iv)* considering the higher energy introduced in the molecule, can the process still be selective also regarding the matrix site, or will it affect the nature of the sites?

We noticed that for reliable observation of 2nd overtone bands of matrix isolated species the detection system of the FTIR spectrometer used for studies involving excitation of fundamentals or 1st overtones had to be improved. A thermoelectrically cooled indium gallium arsenide (InGaAs) detector was then installed in our equipment. With this detector, the bands due to νOH stretching 2nd overtones are in general detectable. We also found that by appropriate choice of the excitation conditions (in particular the laser power), the absorption cross section of these vibrations is enough to guarantee efficiency of the IR-induced processes. For excitation, a continuous wave diode tunable near-IR laser system Toptica DLC TA PRO (spectral range: 10500–10100 cm^{-1}; fwhm < 1 MHz, up to 3 W) was purchased and, in a typical experiment, irradiation shall be carried on during 20 min with at least 120 mW of power.

Three structurally related molecules, hydroxyacetone, glycolic acid and glycolamide, were chosen as targets of the first experiments [72]. In all these cases, we were able to

successfully induce conformational isomerizations upon excitation of the νOH 2nd overtone. Figure 11 summarizes the results obtained for glycolamide, where the conversion of the **Tt** conformer into the **Cc** form is demonstrated. Interestingly, the process was shown to be site selective, allowing us to conclude that despite the higher energies involved compared to excitation of fundamentals and 1st overtone modes no measurable disturbance of the matrix sites takes place also upon excitation of the νOH 2nd overtone.

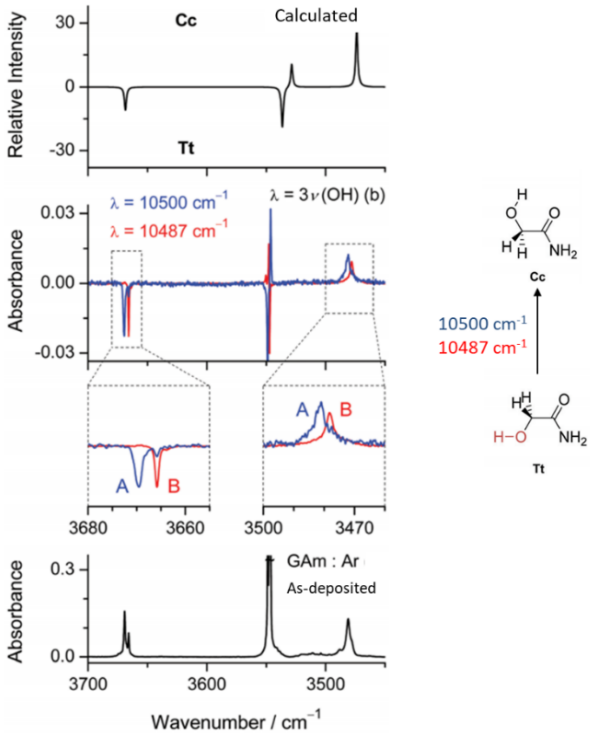


Figure 11. IR-induced conformational isomerization in glycolamine (GAm) in an argon matrix, as result of excitation of the νOH 2nd overtone (3ν(OH)). Note the site selectivity of the process (A and B designate the two sites). Adapted from ref. 72. Copyright 2019 Royal Society of Chemistry.

We also noticed that, as anticipated, the widths of the νOH 2nd overtone bands are in general larger than those of the bands ascribed to fundamental and 1st overtone modes (FWHM ~6 cm⁻¹ *vs* ~3 cm⁻¹ for acid OH group of most stable conformer of glycolic acid [72]). Nevertheless, they still allow for selective excitation to be performed in many cases, since the spacing between the absorption wavenumbers of the different conformers also tend to increase for the higher order overtones. Higher-order overtone (v = 6) excitation Raman studies on matrix isolated formic acid have been reported by Olbert-Majkut, Ahokas, Lundell and Pettersson, in studies where the ***E*** conformer was produced upon vibrational excitation of the ***Z*** conformer using visible light (532.0 nm, or 18797 cm⁻¹, provided by a continuous laser highly-focused at the sample and a power level up to 260 mW). The laser light was used simultaneously for pumping and to collect the Raman spectra [73,74]. Interestingly, the authors suggested that much higher overtone states can also be used, opening the gate for UV-region vibrational overtone induced reactions [73]. We had not yet attempted to use excitations at overtones above the second in a systematic way in our laboratory. Indeed, we performed only a very preliminary series of experiments using visible light excitation of matrix isolated formic acid, with a ns pulsed light pumping source (at 532 nm) and IR spectroscopy probing to detect the formation of the ***E*** conformer, but these experiments resulted unsuccessful. One of the reasons for that was, much probably, the irradiation power at the sample provided by our irradiation system, which is much less than the 260 mW used in the Raman experiments of Olbert-Majkut and coworkers [73,74]. The feasibility and appropriateness of excitations to higher than the second overtone as a general strategy is not yet proved, at least when IR spectroscopy is used as probing technique, and this is a field that shall be considered still open to investigation.

The concept of vibrational antenna: remote control of molecular structures

The first reported IR-induced structural transformations were limited to changes in the close proximity of the excited fragment of the molecule. Most of times, excitation of the νOH stretching mode was used to modify the orientation of the hydroxyl hydrogen atom itself, as in the case of the *Z* → *E* conformational conversion of carboxylic acids. Less frequently, internal rotation around a C–C bond vicinal to the excited hydroxyl group was observed, as in the cases of propionic acid and glycolamine described above [66,72], but also in other compounds like glycolic acid and hydroxyacetone, for example [25,72]. From the comparison of the quantum yields for the *Z* → *E* conformational conversion in formic and acetic acids, it could also be indirectly concluded that excitation of the νOH stretching mode also induced internal rotation of the methyl group around the C–C bond in the latter compound [49], as described in the introduction section.

In 2015, we reported the first example of an IR-induced conformational isomerization of a fragment in a molecule that was remotely located from the excited group [75]. The target compound of these studies was 6-methoxy indole, which has two conformers of similar energy. By excitation of the νNH stretching 1st overtone of the conformers, we were able to selectively interconvert them (Figure 12) [75]. The processes involve a structural transformation of a methoxy group located four bonds apart from the excited vibrational antenna and were found to be very efficient. Since this pioneer investigation, the concept of remote vibrational antenna has been explored in our group in several other systems, like the thiol forms of thioacetamide, kojic acid or *E*-glutaconic acid [76-78], for example. We have also shown that different antennas can be used in an interchangeable way to induce conformational changes in the same molecular fragment, as demonstrated in our studies on conformational changes of an aldehyde group connected to a 2*H*-azirine ring *via* vibrational excitation of hydroxy or amino antennas [79].

This journal is © The Royal Society of Chemistry 20xx

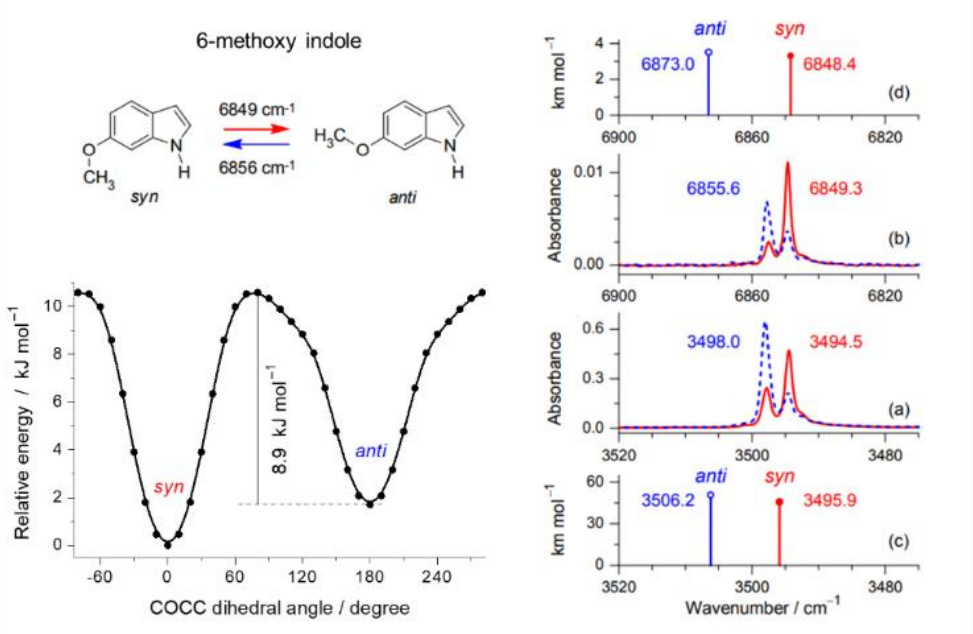


Figure 12. IR-induced conformational isomerization of the methoxy group in 6-methoxy indole using a remotely located NH vibrational antenna. Adapted from ref. 75. Copyright 2015 American Chemical Society.

IR-induced bond-breaking/bond-forming reactions

More recently, we were able to use vibrational excitation to cleave and form covalent bonds. The first example was reported in 2020 and considered the bidirectional thiol↔hydroxy tautomerization in thiotropolone [80].

Thiotropolone has two tautomers, the thiol and the hydroxy forms, each one having two conformers. As shown in Figure 13, the *syn*-hydroxy (***s*-OH-TT**) form is the most stable species, followed by the *syn*-thiol isomer (***s*-SH-TT**; 7.5 kJ mol^{-1} higher in energy than the most stable form), the *anti*-thiol form (***a*-SH-TT**; 17.1 kJ mol^{-1}), and the *anti*-hydroxy isomer (***a*-OH-TT**; 51.6 kJ mol^{-1}). In a freshly deposited argon matrix of the compound, only the ***s*-OH-TT** form is present. IR irradiation at the wavenumber of the νCH stretching 1st overtone (5940 cm^{-1}) or the combination mode at 5980 cm^{-1} of this isomer led to its conversion into the ***a*-SH-TT** form [80] (Figure 14). The reaction involves the cleavage of the O–H bond and the formation of an S–H bond. Very interestingly, the observed product is not the ***s*-SH-TT** form, which could be expected to be the direct product of the reaction, but ***a*-SH-TT**. The data shown in Figure 15 allows to understand the reasons for this observation.

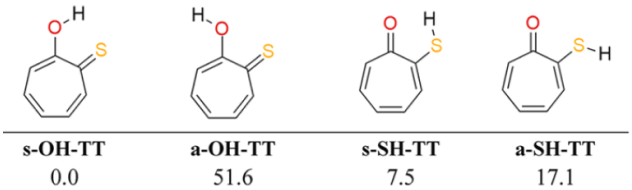


Figure 13. Tautomers of thiotropolone and respective conformers and CBS-QB3 calculated relative energies (in kJ mol^{-1}). Adapted from ref. 80. Copyright 2020 American Chemical Society.

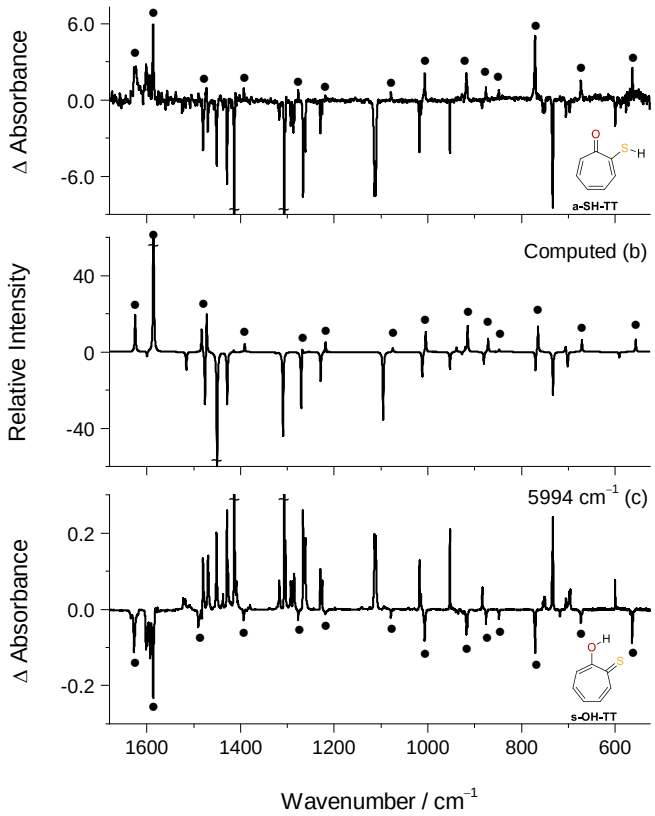


Figure 14. Difference IR spectra showing the observed IR-induced bidirectional tautomerizations of matrix isolated thiotropolone. (a) and (c), experimental difference spectra: (a) irradiation at 5940 cm^{-1}; (c) irradiation at 5994 cm^{-1}. Bands marked with circles (●) are due to ***a*-SH-TT**, which is produced by irradiation at 5940 cm^{-1} (a) and consumed by irradiation at 5994 cm^{-1} (c). (b) Simulated difference IR spectrum based on B3LYP/6-311+G(2d,p) vibrational data. Adapted from ref. 80. Copyright 2020 American Chemical Society.

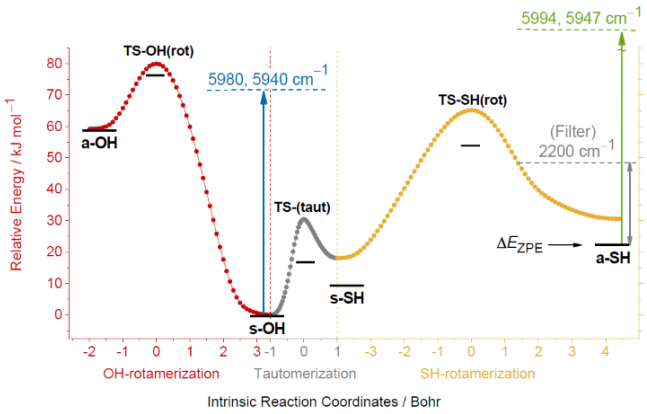


Figure 15. Potential energy profile showing the a priori possible reaction pathways for interconversion between the different tautomers (and respective conformers) of thiotropolone (B3LYP/6-311+G(2d,p) results). The horizontal bars at each stationary point (minima and transition states; TS) show the corresponding computed ZPE-corrected relative energy value. Adapted from ref. 80. Copyright 2020 American Chemical Society.

Upon excitation of ***s*-OH-TT** at 5980 or 5940 cm^{-1}, ~71 kJ mol^{-1} are introduced in the molecule. Such energy is below the transition state (TS) for OH-rotamerization (~76 kJ mol^{-1}), justifying the non-observation of the ***s*-OH-TT** → ***a*-OH-TT** process, but well above the TS for tautomerization to ***s*-SH-TT** (~17 kJ mol^{-1}) and also clearly above the TS for production of the observed ***a*-SH-TT** product (~53 kJ mol^{-1}). The important fact here is that, contrarily to ***a*-SH-TT**, which is stable once it is produced, the ***s*-SH-TT** form cannot persist, tautomerizing promptly back to ***s*-OH-TT** by spontaneous QMT because of a low (~9 kJ mol^{-1}) and thin (~0.63 Å) barrier separating these two species. With such barrier, the occurrence of extremely fast QMT is expected, making ***s*-SH-TT** a fleeting species even at cryogenic conditions (estimated $\tau_{1/2}$ ~1 × 10^{-11} s applying the Wentzel–Kramers–Brillouin model [80]). These data unequivocally justify the experimental capture and identification of the thiol ***a*-SH-TT** form and not of ***s*-SH-TT** form upon vibrational excitation of ***s*-OH-TT**.

The observed tautomerization of ***a*-SH-TT** back to ***s*-OH-TT** was also successfully induced upon irradiation at the wavenumber of the νCH stretching 1st overtone (5947 cm^{-1}) or the combination mode at 5990 cm^{-1} of this isomer (see Figure 14). In this case, the energy deposited in the molecule (~71 kJ mol^{-1}) is high enough to activate the SH-rotamerization to ***s*-SH-TT** (~33 kJ mol^{-1}), which rapidly tautomerizes by tunneling to ***s*-OH-TT**.

Globally, these results demonstrate that the hydroxyl → thiol and thiol → hydroxyl tautomerizations in thiotropolone, which imply cleavage of an OH or SH bond and formation of and SH or OH bond, respectively, were both promoted by vibrational excitation of the corresponding reactant tautomeric species, generalizing the use of IR-induced chemistry also to covalent bond-breaking/bond-forming processes. More recently, we have shown that IR-induced bond-breaking/bond-forming reactions can also be successfully promoted for neat solid samples at low temperature [81].

Another advance in the field of IR-induced chemistry was our recent demonstration that bond-breaking/bond-forming reactions can likewise be induced by vibrational excitation of an antenna remotely located in relation to the molecular reaction site [82]. This generalization of the use of remote vibrational antennas to promote chemical reactions involving cleavage and formation of covalent bonds opened the gate for a wider application of IR-induced chemistry, in particular in organic chemistry.

The selected reactant molecule was a fluoro-substituted benzazirine bearing an OH vibrational antenna (2,6-difluoro-4-hydroxy-2*H*-benzazirine; Figure 16). This species was produced *in situ* in a low temperature (15 K) krypton matrix by UV (455 nm) irradiation of the corresponding nitrene, which was also generated *in situ* by photolysis (255 nm) of the azide precursor (Figure 16).

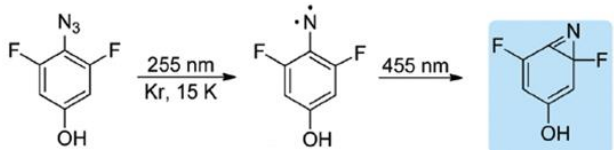


Figure 16. *In situ* generation of the 2,6-difluoro-4-hydroxy-2*H*-benzazirine from the corresponding azide precursor isolated in a krypton matrix (15 K). Two successive irradiations were performed, at different wavelengths, the first giving rise to the nitrene species and the second converting this latter into the desired benzazirine. Adapted from ref. 82. Copyright 2021 Royal Society of Chemistry.

As shown in Figure 17, IR irradiation of the benzazirine through the remotely located OH vibrational antenna (via its νOH 1st overtone at 7054 cm^{-1}) led to its transformation into the cyclic ketenimine 3,7-difluoro-5-hydroxy-1-aza-1,2,4,6-cycloheptatetraene, with breaking of a C–C bond and extensive rearrangement of the electronic π-bonding system. It is worth noticing that both the benzazirine and the photoproduced ketenimine were found to be present in the matrix in a single conformer, the ***syn*** and ***anti*** forms, respectively, while two conformers of each molecule exist (no IR bands ascribable to the alternative conformers of these molecules were observed experimentally [82]). The explanation for this can be rationalized based on Figure 18 and involves again reactions taking place through the QMT mechanism.

The OH-rotamerization barrier converting the non-observed ***anti*** conformer of the benzazirine to the observed most stable ***syn*** conformer is only 7.5 kJ mol^{-1}, whereas the barrier of conversion of the non-observed less stable ***syn*** conformer of the ketenimine to the observed most stable ***anti*** form is 14.6 kJ mol^{-1} [82]. These low energy barriers allow for fast OH-rotamerization QMT to take place, precluding observation of the higher-energy forms of the two molecules. In consonance with this interpretation, tunneling calculations using the Wentzel–Kramers–Brillouin model [82] estimated very short half-lives for both the ***anti***-benzazirine [$t_{1/2}$ ~10^{-7} s] and ***syn***-ketenimine [$t_{1/2}$ ~10^{-4} s]. In this regard, it is then likely that the IR vibrational excitation of the ***syn***-benzazirine induces ring-

 This journal is © The Royal Society of Chemistry 20xx

expansion to the ***syn***-ketenimine, which then undergoes fast QMT OH-rotamerization to the observed ***anti***-ketenimine form.

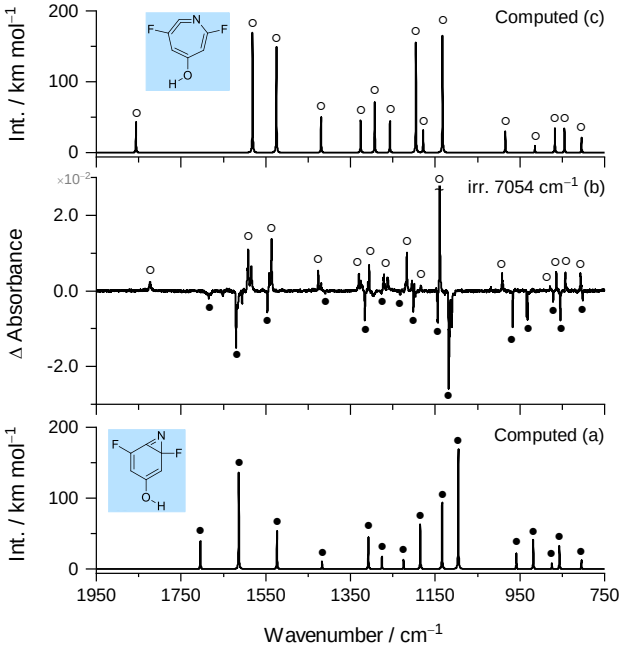


Figure 17. Experimental IR difference spectrum (b) showing the result of the IR-induced conversion of the studied benzazirine into the corresponding cyclic ketenimine, *via* 1st stretching overtone of the remotely located OH vibrational antenna, and calculated spectra of the benzazirine (a) and ketenimine (c). Adapted from ref. 82. Copyright 2021 Royal Society of Chemistry.

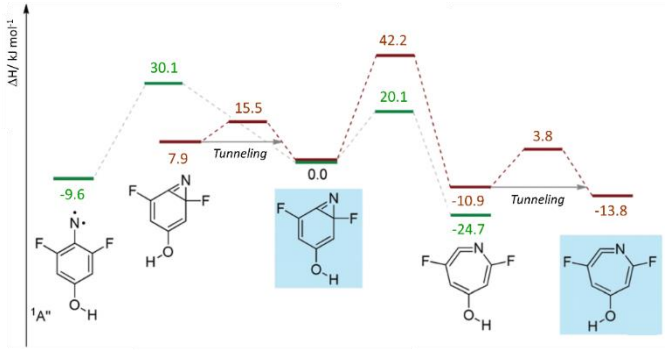


Figure 18. Reaction pathways, computed at CCSD(T)/cc-pVTZ//B3LYP/6-311+G(2d,p)+ZPVE (red) and MRMP/cc-pVTZ//CASSCF(8,8)/ccpVTZ +ZPVE (green) levels of theory for interconversion between the different species relevant for the understanding of the observed IR-induced conversion of the studied benzazirine into the corresponding cyclic ketenimine, *via* 1st stretching overtone of the remotely located OH vibrational antenna. 1A'' = open-shell singlet state. Adapted from ref. 82. Copyright 2021 Royal Society of Chemistry.

In summary, in our study [82], we demonstrated that the selective IR vibrational excitation of a remote antenna allows inducing a bond-breaking/bond-forming reaction in an organic molecule, in an efficient way. This accomplishment paves the way for developing a general approach to guide a variety of molecular structure manipulations using IR-light and creates unprecedented opportunities for highly-selective transformations, in ways not attainable by thermal or electronic excitation processes.

Switching on H-tunneling through IR-induced conformational control

In one of our most recent investigations [83], we demonstrated the feasibility of using IR-induced chemistry as a switch to control H-atom tunneling. This was outlined with a triplet 2-hydroxyphenylnitrene generated in an N_2 matrix at 10 K by UV-irradiation of an azide precursor. The ***anti*** conformer of the nitrene, where the OH moiety points to the opposite side of the nitrogen atom, could be selectively converted into the ***syn*** conformer upon vibrational excitation at the wavenumber of its νOH stretching 1st overtone (6976 cm^{-1}). By this way, the hydroxyl hydrogen atom moves closer to the vicinal nitrene center, triggering spontaneous H-tunneling to a singlet 6-imino-2,4-cyclohexadienone (Figure 19). The reaction was monitored by IR spectroscopy using a long-pass filter blocking IR light above 1580 cm^{-1} to exclude the absorption of photons above the OH-rotamerization barrier of the nitrene (~1700 cm^{-1} as calculated at the B3LYP/6-311+G(2d,p) level [83]) (Figure 20). Computations reveal that such fast H-tunneling occurs through crossing the triplet-to-singlet potential energy surfaces [83], establishing in this way a rare model for a nonadiabatic H-atom QMT. Note that the alternative conceivable mechanism for the reaction of the ***syn*** triplet nitrene that considers the occurrence of H-atom QMT on the triplet surface to the triplet 6-imino-2,4-cyclohexadienone, followed by intersystem crossing, could be safely excluded [83]. Indeed, the height (~98.2 kJ mol^{-1}) of the barrier for the reaction in the triplet surface is incompatible with the occurrence of a very fast QMT reaction and with the elusive nature of the ***syn*** triplet nitrene (according to Wentzel–Kramers–Brillouin calculations, its half-life time would be 1.14 × 10^3 s, if tunneling occurred in the triplet surface [83]).

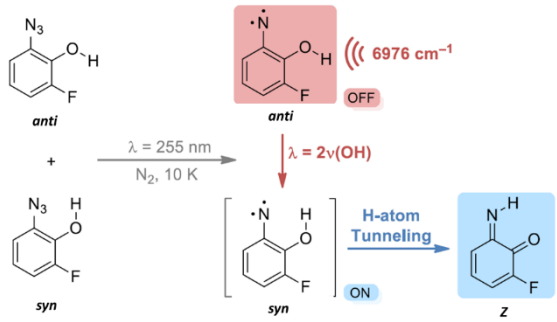


Figure 19. IR-switch for the H-atom tunneling reaction of triplet 2-hydroxyphenylnitrene generated in an N_2 matrix from the azide precursor. Adapted from ref. 83. Copyright 2021 American Chemical Society.

This study provides an exciting novel strategy to attain control over tunneling, opening new avenues for directing chemical transformations. These results are also important as a contribution to the understanding of enzyme-catalyzed reactions, since it has been suggested that enzymatic C–H

Please do not adjust margins

transfer reactions rely on the dynamic sampling of enzyme-substrate conformations to tune the donor–acceptor distance conductive to QMT [84,85].

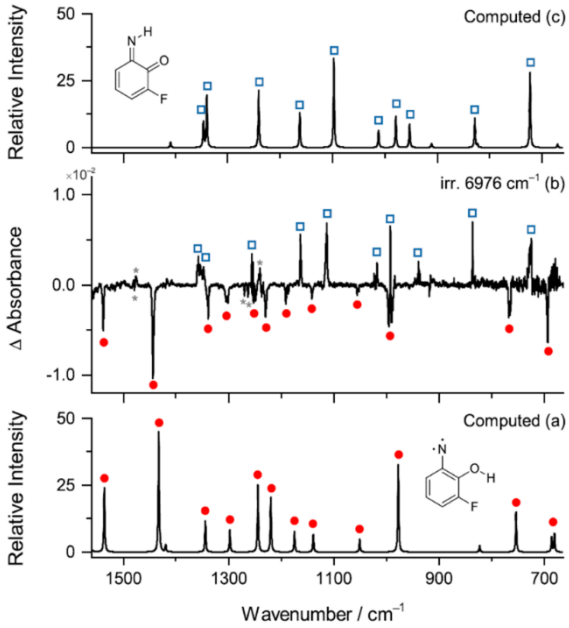


Figure 20. (a) B3LYP/6-311+G(2d,p) computed IR spectrum of triplet *anti*-3-fluoro-2-hydroxyphenylnitrene. (b) Experimental difference IR spectrum showing changes resulting from irradiation at 6976 cm^{-1}. (*) indicate minor changes in the population of conformers of the azide precursor of the nitrene. (c) B3LYP/6-311+G(2d,p) computed IR spectrum of (*Z*)-2-fluoro-6-imino-2,4-cyclohexadienone. Adapted from ref. 83. Copyright 2021 American Chemical Society.

Heavy-atom QMT

As emphasized in the Introduction section of this article, examples of QMT-driven reactions involving the motion of light hydrogen atoms are relatively abundant and this phenomenon has been recognized to play an important role in organic chemistry, biochemistry, and catalysis [86-90]. Because the tunneling probabilities decrease exponentially with the square root of the moving mass, atoms heavier than hydrogen were for long assumed to behave essentially classically [90]. However, recent evidence indicates that heavy-atom QMT can have significant implications for many chemical reactions [91,92]. About a dozen of examples of direct spectroscopic observation of carbon-atom QMT occurring under matrix isolation conditions have been reported [92-96]. In recent investigations, we have also discovered a new and distinctive case of a heavy-atom QMT reaction involving the displacement of both nitrogen and oxygen atoms [97].

The 2-formyl-3-fuorophenylazide precursor, which was designed to achieve stabilization of the *syn*-aldehyde conformation, allows generation of the corresponding triplet *syn*-2-formylarylnitrene upon UV-irradiation under cryogenic conditions. Once produced, this nitrene species was observed to spontaneously cyclize to the corresponding singlet 2,1-benzisoxazole (Figure 21). The experimental IR spectrum of the consumed and produced species is well reproduced by the B3LYP/6-311+G(2d,p) computed IR spectra, providing unequivocal identification for the occurrence of such cyclization reaction (Figure 22). The reaction kinetics was measured in the dark in an argon matrix at 10, 15 and 20 K, and rate constants of ~1.4 × 10^{-3} s^{-1} were obtained. The observation of a fast and temperature-independent cyclization rate at those low temperatures provided convincing evidence for the occurrence of a heavy-atom QMT cyclization [97].

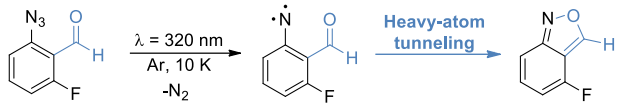


Figure 21. Summary of the heavy-atom QMT cyclization of a triplet *syn*-2-formylarylnitrene to a singlet 2,1-benzisoxazole, which involves the displacement of nitrogen and oxygen atoms. Adapted from ref. 97 with permission from John Wiley and Sons. Copyright 2020 WILEY-VCH Verlag GmbH & Co. KGaA, Weinheim.

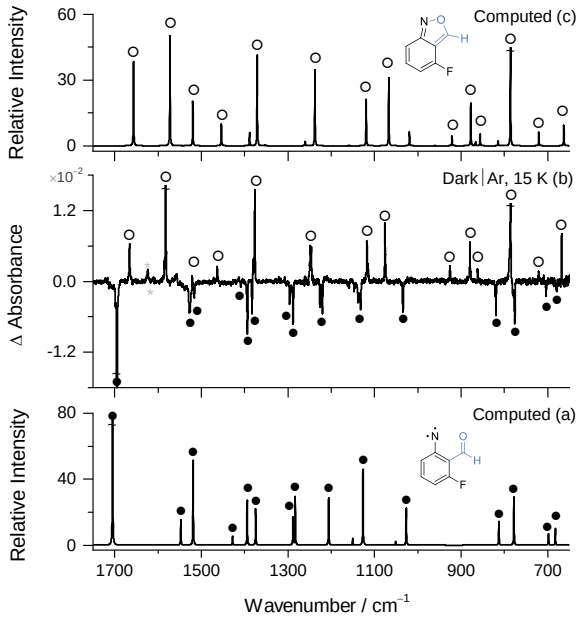


Figure 22. B3LYP/6-311+G(2d,p) computed IR spectrum of (a) triplet *syn*-2-formyl-3-fluorophenyl-nitrene and (c) singlet 3-fluoro-2,1-benzisoxazole. Experimental difference IR spectrum showing changes after keeping the sample at 15 K (Ar matrix) in the dark for 40 min, subsequent to the generation of triplet nitrene by UV-irradiation of the corresponding azide precursor. Adapted from ref. 97 with permission from John Wiley and Sons. Copyright 2020 WILEY-VCH Verlag GmbH & Co. KGaA, Weinheim.

A reaction mechanism involving heavy-atom QMT on the triplet surface was excluded, because the triplet state of the product is energetically higher than the triplet state of the reactant. A minimum energy crossing point (MECP) between the triplet nitrene and singlet benzisoxazole surfaces was found at ~50 kJ mol^{-1}. Such large reaction energy requirement is clearly prohibitive to be achieved by a classical process at the cryogenic temperatures of the experiment. On the other hand, a spin-forbidden heavy-atom QMT rate calculated by nonadiabatic transition state theory (NA-TST) using the weak coupling (WC) model, at the MRMP(10,10)//CASSCF(10,10) or M06-2X levels of theory, provides a qualitative agreement with the experimental values, supporting the exclusive existence of a

This journal is © The Royal Society of Chemistry 20xx

Please do not adjust margins

mechanism of heavy atom tunneling through crossing triplet and singlet potential energy surfaces [97]. To the best of our knowledge, the WC formulation of nonadiabatic-TST was for the first time successfully applied in this study to calculate vibrational ground state QMT reactions rates.

We also recently unveiled a new reactivity paradigm in this area by demonstrating that a well-defined chemical starting material spontaneously decay at cryogenic temperatures into two different products *via* two competitive heavy-atom QMT processes [98]. After generation of 4-amino-2*H*-benzazirine in an argon matrix (3–18 K), this species was observed to concomitantly undergo spontaneous ring-opening to a triplet nitrene and ring-expansion to a cyclic ketenimine (Figure 23). The process was monitored by IR spectroscopy, which allows the identification of these two products by comparison with their IR spectra signature (obtained during UV-irradiation experiments starting from an azide precursor), and the identification of the consumed benzazirine with the support of its B3LYP/6 311+G(2d,p) computed IR spectrum (Figure 24). The reaction kinetic was measured at 3, 10 and 18 K, and rate constants of ~5.5 × 10^{-5}, ~6.0 × 10^{-5} and ~7.0 × 10^{-5} s^{-1}, respectively, were obtained. The observed triplet nitrene : cyclic ketenimine product ratio was ~15:85 (3 K), ~18:82 (10 K) and ~17:83 (18 K). The evidence that the reaction rate is nearly constant upon increasing of the temperature by a factor of five and that the product rate practically did not change confirmed that the observed benzazirine transformations were due to two independent and competitive heavy-atom tunneling reactions [98].

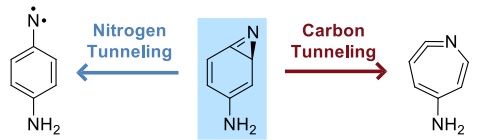


Figure 23. Summary of the competitive heavy-atom QMT ring-open versus ring-expansion of 4-amino-2*H*-benzazirine to triplet nitrene and cyclic ketenimine, respectively. Adapted with permission from ref. 98. Copyright 2019 American Chemical Society.

The ring-opening mechanism of 4-amino-2*H*-benzazirine should involve the formation of the corresponding open-shell singlet (OSS) nitrene, followed by fast ISC to triplet nitrene ground state. Due to the need of using multi-configurational methods to correctly described OSS nitrenes, such transformation was computed at NEVPT2(8,8)//CASSCF(8,8) level and an energy barrier of ~10.5 kJ mol^{-1} was estimated. The ring-expansion mechanism of 4-amino-2*H*-benzazirine to the corresponding cyclic ketenimine was found to be most reliably computed at the CCSD(T)//B3LYP level, and an energy barrier of ~30.5 kJ mol^{-1} was estimated (Figure 25). According to the classic TST, even such low energy barriers are prohibitive at the cryogenic temperatures of the experiment. Moreover, the formation of cyclic ketenimine as major product, having a higher energy barrier than the minor nitrene product, contradicts the rules inferred from classic TST. Therefore, it becomes clear that a thermal over-the-barrier process cannot explain the observed transformation but only the occurrence of heavy-atom QMT dominated by tunneling control. Indeed, computed tunneling probabilities through those two barriers (applying the Wentzel-Kramers-Brillouin formalism), predict the existence of two competitive reactions of the benzazirine, in line with the experimental observations. Computations also show that for the tunneling of the benzazirine to the nitrene the nitrogen atom in the three-membered ring is clearly the heavy-atom with the largest displacement, whereas for the tunneling of the benzazirine to the ketenimine the two carbon atoms in the three-membered ring have by far the largest displacement [98]. Therefore, they support a case for the existence of competitive nitrogen *vs.* carbon QMT reactions occurring simultaneously with 4-amino-2*H*-benzazirine as the reactant species.

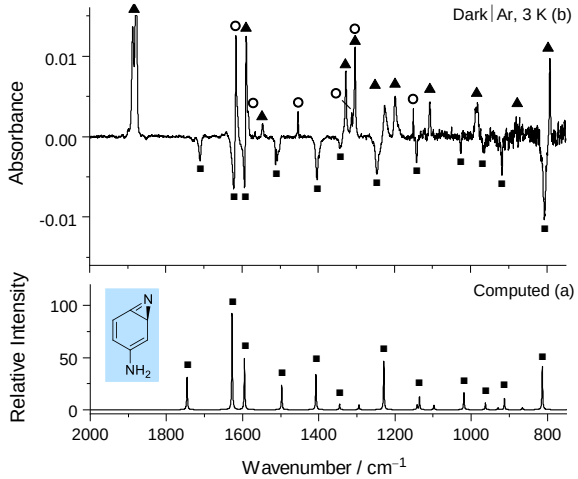


Figure 24. (a) B3LYP/6-311+G(2d,p) computed IR spectrum of 4-amino-2*H*-benzazirine. (b) Experimental difference IR spectrum showing changes after keeping the sample at 3 K (argon matrix) in the dark for 24 h. The downward bands are due to the consumption of 4-amino-2*H*-benzazirine (squares) and the upward bands due to the formation of the corresponding triplet nitrene (circles) and cyclic ketenimine (triangles). Adapted with permission from ref. 98. Copyright 2019 American Chemical Society.

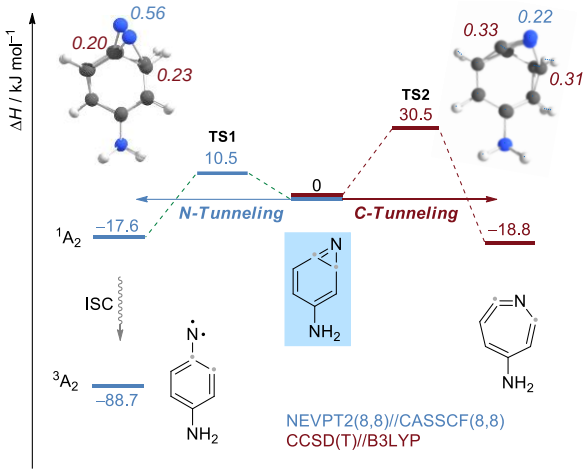


Figure 25. (a) Computed reactions pathways for the transformation of 4-amino-2*H*-benzazirine at NEVPT(8,8)/6-311+G(2d,p)//CASSCF(8,8)6-311+G(2d,p)+ZPVE (blue), and CCSD(T)/cc-pVTZ//B3LYP/6-311+ G(2d,p) +ZPVE (red), $^1A_2$ = open-shell singlet state, $^3A_2$ = triplet ground state. Top left and right images show the structural overlap of the turning point geometries and the most significant tunneling distances of the individual atoms (arc lengths in Å in *italic*) involved in N and C-tunneling, respectively. Adapted with permission from ref. 98. Copyright 2019 American Chemical Society.

Please do not adjust margins

Conclusion and Outlook

Along the previous sections, we have surveyed the major progresses in the field of IR-induced and tunneling-driven chemistry for matrix isolated species. As mentioned in the Introduction section, we focused essentially on our own contributions to develop vibrationally induced chemistry as a powerful tool to manipulate molecular structures in a highly selective way, and to use and control QMT as a tool to explore the reactivity of organic molecules in an unprecedented way. Figure 26 provides a timeline graph that summarizes these major achievements in a historical perspective.

We have showed that using tunable narrowband IR-light and matrix isolation conditions, it is possible to manipulate the structure and reactivity of chosen molecular species in a very selective way. This methodology has been applied successfully to trigger conformational isomerizations in a different range of organic compounds, including weakly-bonded (dimeric) species. Noteworthy, the feasibility to produce high-energy conformers of different species by vibrational excitation, which otherwise are not accessible to experimentation, opened the gate to new fascinating investigations such as conformational selective chemistry or the synthesis of unusual high-energy crystals composed by rare conformers.

From the first cases studied, where the IR-induced conformational isomerizations comprised changes in the moiety where the vibrational excitation was applied or in an adjacent bond, we and others expanded the scope of the technique to consider also reversible interconversions between conformers by vibrational excitation of a group (having the role of an antenna) remotely located from the fragment undergoing conformational changes. Moreover, we have demonstrated that different antennas can be used in an interchangeable way to trigger conformational isomerizations of the same remote molecular fragment.

Our recent demonstration that vibrational excitation can be used to induce bond-breaking/bond-forming reactions for matrix-isolated organic molecules established a new domain in vibrationally-driven chemistry. Furthermore, envisioning a generalized strategy to guide a variety of chemical reactions using IR light, we demonstrated as proof-of-principle the triggering of an electrocyclic reaction by vibrational excitation of an antenna remotely located in relation to the reaction center. We expect that future studies using target molecules with more than one vibrational antenna and more than one possible reaction coordinates will give fundamental answers regarding the relation between the nature of the excited mode and the activated reactions. By introducing vibrational energy in a molecule in an amount above the threshold required to induce different transformations, the possibility to activate a higher-energy pathway, so that it can effectively compete with a lower-energy one, is a problem currently under study in our laboratories. Such investigations can be expected to strongly expand the power of IR-induced processes for more practically oriented uses and provide important hints regarding intramolecular vibrational energy redistribution in different types of molecular systems.

Up until quite recently, all IR-induced processes carried out for matrix isolated species resorted on the vibrational excitation of fundamental vibrations or first overtones (or combination modes) of favorable stretching modes, such as that of an OH group. A significant progress was achieved when we demonstrated that selective vibrational excitation of second overtone modes, 3ν(OH), also successfully triggers conformational isomerizations in the target molecules. Such approach allows to introduce much more energy in a molecule [~120 kJ mol^{-1} for 3ν(OH) *vs.* ~80 kJ mol^{-1} for 2ν(OH)] and, therefore, offer prospects to control the manipulation of chemical species stable even at temperatures close to room temperature. In conjugation with our recent breakthrough on inducing bond-breaking/bond-forming reactions by infrared vibrational excitation and the demonstration of the feasibility of such approach also to neat solid conditions, we might foresee the development of this methodology to achieve the activation of drugs *in vivo* or the switch of materials in optical and electronic devices in a highly controlled and selective way, not attainable by thermal and electronic excitation.

We have also shown here that IR-induced processes in cryogenic matrices are frequently entangled with tunneling-driven reactions. Several investigations on direct spectroscopic observation of spontaneous conformational isomerizations of high-energy conformers (produced by vibrational excitation of lower energy forms) at cryogenic temperatures have provided important data to improve our knowledge of fundamental principles of the QMT phenomenon. Interestingly, some studies have unrevealed the occurrence of vibrationally-assisted QMT processes, by showing that conformational isomerizations can take place even when the vibration excitation energy introduced in the target conformer is below that corresponding to the isomerization energy barrier. As described in details above, more recently, we have demonstrated how to switch on H-atom QMT by IR-induced conformation control. To the best of our knowledge, such approach represented the first ever achievement of the control of tunneling by means of external radiation. We can expect future advances in such new conceptual strategy to harness the control of QMT, which will be likely to inspire progress in the fields of enzymatic catalysis and quantum switches, and to provide new avenues for directing chemical transformations.

Contributing to a paradigm shift, we and others have been reported direct spectroscopic observation of heavy-atom QMT reactions in cryogenic matrices, in this way demonstrating that this phenomenon can have much more significant implications in chemical reactivity than previously thought. Although most examples comprise carbon-atom QMT, we have also discovered a distinctive case of a heavy-atom QMT reaction involving the displacement of both nitrogen and oxygen atoms. One can expect that future studies will extend the limits of observed QMT to even heavier elements, such as fluorine. Besides, we have also unraveled a new, fascinating reactivity pattern, by demonstrating a unique case of two competitive heavy-atom QMT reactions (nitrogen *vs.* carbon) occurring simultaneously from a well-defined chemical starting material, leading to two

 This journal is © The Royal Society of Chemistry 20xx

2021 -Nunes, Pereira, Viegas, Pinho e Melo & Fausto described the first example of an IR-induced bond-breaking-bond-forming reaction through use of a remotely located vibrational antenna.
-Together with Shreiner, we reported the case of conformational control of tunneling in triplet 2-hydroxyphenylnitrene.

2020 -Our group reported the bidirectional IR-induced bond-breaking-bond-forming tautomerization of thiotropolone.
-We presented the case of heavy atom tunneling through crossing triplet and singlet potential energy surfaces: cyclization of a triplet 2-formylarylnitrene to a singlet 2,1-benzisoxazole.

2019 -Use of higher order overtones to induce conformational isomerizations with IR detection, by Nunes, Reva Fausto.
-With the group of Schreiner, we reported the first case of competitive heavy-atom tunneling (N *vs.* C).

2014-2015 -IR-induced production of rare dimers of formic and acetic acids by Räsänen's and our groups.
-Our group introduces the concept of "remote vibrational antenna".

2010-2011 -In collaboration with the Nowak's group we reported the first studies on the conformational isomerization of cytosine.
-Schreiner introduced the concept of tunneling control of chemical reactivity.

2008-2009 -Olbert-Majkut, Ahokas, Lundell & Pettersson reported use of higher-order overtones in the visible range to induce conformational isomerizations in formic acid and its dimers, with simultaneous Raman probing.

2005 -Maçôas, Khriachtchev, Pettersson, Fausto & Räsänen reported the IR and tunneling rotamerizations in propionic acid.

2003 -Tunneling assisted IR-induced conformational isomerization in formic acid was described by our group in collaboration with Räsänen's group.

2002 -IR-induced conformational isomerization studies on dicarboxylic acids reported by our group in collaboration with Räsänen's group.

2000-2001 -Dissipative tunneling in formic acid was reported by Pettersson, Maçôas, Khriachtchev, Lundell, Räsänen & Fausto.
-Conformational dependent photochemistry of formic acid was reported by Khriachtchev, Maçôas, Pettersson & Räsänen.

1997 -Pettersson, Lundell, Khriachtchev & Räsänen introduced narrowband tunable IR light to selectively promote the conformational isomerization of formic acid.

1993 -Kulbida & Fausto used monochromated IR light of a globar source to induce conformational isomerization in matrix isolated dichloroacetic acid.

1963 -Hall & Pimentel reported the first IR-induced conformational isomerization for matrix isolated nitrous acid.

Figure 26. Timeline showing some of the most relevant keystones in the field of IR-induced and related tunneling-driven chemistry for matrix isolated organic molecules.

different products. This paradigmatic example offers an excellent opportunity to investigate how electronic effects imposed internally by different substituents or externally by different media can tune the selectivity of a QMT reaction. Electronic effects will most likely affect QMT differently than an over-the-barrier process, rationalized by classical TST, and, therefore, new fundamental understanding will likely emerge from such studies. Due to the recent progress witness on the field of QMT reactions, we foresee their entrance in synthetic organic chemistry and synthetic planning disciplines for the very near future. In this way, new reactivity paradigms and synthetic strategies will likely emerge under more conventional laboratory conditions, opening new avenues for the design of new molecules.

This is the story of a still ongoing endeavor, and by this reason necessarily an incomplete (but opportune) story. We can only expect that this survey can stimulate others to contribute to the development of the field and inspire young scientists to follow our steps in this captivating adventure. But, as pointed out in the beginning of this article, this story is also incomplete in the sense that many others have also been given very important contributions to the development of the research areas here addressed. To all of them we have to pay our respect and acknowledge for their invaluable efforts.

Author Contributions

All authors contributed equally to the article.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

This work was supported by Projects POCI-01-0145-FEDER-028973 and PTDC/QUI-QFI/1880/2020, funded by National Funds *via* the Portuguese Foundation for Science and Technology (FCT), the first being also funded by FEDER, *via* Portugal 2020 – POCI. The Coimbra Chemistry Centre – Institute of Molecular sciences (CQC-IMS) is supported by FCT through projects UIDB/QUI/0313/2020 and UIDP/QUI/0313/2020 and LA/P/0056/2020 (national funds). C.M.N. acknowledges FCT for an Auxiliary Researcher grant. All our co-workers that have participated in the studies mentioned in this article are acknowledged. The acknowledgements are also extended to all members of the groups with whom we have collaborated and that have also participated in this endeavor.

References

1. R. T. Hall and G. C. Pimentel, Isomerization of Nitrous Acid: An Infrared Photochemical Reaction, *J. Chem. Phys.*, **38** (1963) 1989.
2. M. Pettersson, J. Lundell, L. Khriachtchev and M. Räsänen, IR Spectrum of the Other Rotamer of Formic Acid, *cis*-HCOOH, *J. Am. Chem. Soc.*, **119** (1997) 11715.
3. M. Pettersson, E. M. S. Maçôas, L. Khriachtchev, J. Lundell, M. Räsänen and R. Fausto, *Cis→trans* Conversion of Formic Acid by Dissipative Tunneling in Solid Rare Gases: Influence of Environment on the Tunneling Rate, *J. Chem. Phys.*, **117** (2002) 9095.
4. L. Khriachtchev, E. M. S. Maçôas, M. Pettersson and M. Räsänen, Conformational Memory in Photodissociation of Formic Acid, *J. Am. Chem. Soc.*, **124** (2002) 10994.
5. E. M. S. Maçôas, J. Lundell, M. Pettersson, L. Khriachtchev, R. Fausto and M. Räsänen, Vibrational Spectroscopy of *cis*- and *trans*-Formic Acid in Solid Argon, *J. Mol. Spectrosc.*, **219** (2003) 70.
6. M. Pettersson, E. M. S. Maçôas, L. Kriachtchev, R. Fausto and M. Räsänen, Conformational Isomerization of Formic Acid by Vibrational Excitation at Energies below the Torsional Barrier, *J. Am. Chem. Soc.*, **125** (2003) 4058.
7. S. Lopes, A. V. Domanskaya, R. Fausto, M. Räsänen and L. Khriachtchev, Formic and Acetic acids in a Nitrogen Matrix: Enhanced Stability, *J. Chem. Phys.*, **133** (2010) 144507
8. S. V. Ryazantsev and V. I. Feldman, Radiation-induced Transformations of Matrix-isolated Formic Acid: Evidence for the HCOOH → HOCO + H Channel, *Phys. Chem. Chem. Phys.*, **17** (2015) 30648.
9. S. Lopes, R. Fausto and L. Khriachtchev, Formic Acid in Deuterium and Hydrogen Matrices, Mol. Phys., 117 (2019) 1587.
10. A. Aerts, P. Carbonnière, F. Richter and A. Brown. Vibrational States of Deuterated *trans*- and *cis*-Formic Acid: DCOOH, HCOOD, and DCOOD, *J. Chem. Phys.*, **152** (2020) 024305.
11. E. M. S. Maçôas, L. Khriachtchev, R. Fausto and M. Räsänen, Photochemistry and Vibrational Spectroscopy of the *trans* and *cis* Conformers of Acetic Acid in Solid Argon, *J. Phys. Chem. A*, **108** (2004) 3380.
12. E. M. S. Maçôas, R. Fausto, M. Pettersson, L. Khriachtchev and M. Räsänen, Infrared Induced Rotamerization of Oxalic Acid Monomer in an Argon Matrix, *J. Phys. Chem. A*, **104** (2000) 6956.
13. E. M. S. Maçôas, R. Fausto, J. Lundell, M. Pettersson, L. Khriachtchev and M. Räsänen, Conformational Analysis and Near-Infrared-Induced Rotamerization of Malonic Acid in an Argon Matrix, *J. Phys. Chem. A*, **104** (2000) 11725.
14. E. M. S. Maçôas, R. Fausto, J. Lundell, M. Pettersson, L. Khriachtchev and M. Räsänen, A Matrix Isolation Spectroscopic and Quantum Chemical Study of Fumaric and Maleic Acid, *J. Phys. Chem. A*, **105** (2001) 3922.
15. R. Fausto and E. M. S. Maçôas, Photochemical Reactivity of Matrix-Isolated Monomeric Carboxylic Acids, *J. Mol. Struct.*, **563/564** (2001) 29.
16. R. F. G. Apóstolo, R. R. F. Bento, G. Tarczay and R. Fausto, The First Experimental Observation of the Higher-Energy *trans* Conformer of Trifuoroacetic Acid, *J. Mol. Struct.*, **1125** (2016) 288.
17. R. F. G. Apóstolo, R. R. F. Bento and R. Fausto, Narrowband IR-Induced In Situ Generation of the High-Energy *trans* Conformer of Trichloroacetic Acid Isolated in Solid Nitrogen and its Spontaneous Decay by Tunneling to the Low-Energy *cis* Conformer, *Croat. Chem. Acta*, **88** (2015) 377.
18. R. F. G. Apóstolo, G. Bazsó, G. O. Ildiz, G. Tarczay and R. Fausto, Near-Infrared *In Situ* Generation of the Higher-Energy *trans* Conformer of Tribromoacetic Acid: Observation of a Large-Scale Matrix-Site Changing Mediated by Conformational Conversion, *J. Chem. Phys.*, **148** (2018) 044303.
19. G. Bazsó, S. Góbi and G. Tarczay, Near-Infrared Radiation Induced Conformational Change and Hydrogen Atom Tunneling of 2-Chloropropionic Acid in Low-Temperature Ar Matrix, *J. Phys. Chem. A*, **116** (2012) 4823.
20. S. Lopes, T. Nikitin and R. Fausto, Propiolic Acid in Solid Nitrogen: NIR- and UV-Induced *cis* → *trans* Isomerization and Matrix-Site-Dependent *trans* → *cis* Tunneling, *J. Phys. Chem. A*, **123** (2019) 1581.
21. N. Kuş and R. Fausto, Near-infrared and Ultraviolet Induced Isomerization of Crotonic Acid in N_2 and Xe Cryomatrices: First Observation of Two High-energy *trans* C–O Conformers and Mechanistic Insights, *J. Chem. Phys.*, **141** (2014) 234310.
22. I. D. Reva, S. Stepanian, L. Adamowicz and R. Fausto, Combined FTIR Matrix Isolation and Ab Initio Studies of Pyruvic Acid: Proof for Existence of the Second Conformer, *J. Phys. Chem. A*, **105** (2001) 4773.
23. S. G. Stepanian, I. D. Reva, E. D. Radchenko, M. T. S. Rosado, M. L. T. S. Duarte, R. Fausto, and L. Adamowicz, Matrix-Isolation Infrared and Theoretical Studies of the Glycine Conformers, *J. Phys. Chem. A*, **102** (1998) 1041.
24. I. D. Reva, S. Jarmelo, L. Lapinski and R. Fausto, IR-Induced Photoisomerization of Glycolic Acid in Low Temperature Matrices, *J. Phys. Chem. A*, **108** (2004) 6982.
25. A. Halasa, L. Lapinski, I. Reva, H. Rostkowska, R. Fausto and M. J. Nowak, NIR-Laser-Induced Generation of Three Rare Conformers of Glycolic Acid, *J. Phys. Chem. A*, **118** (2014) 5626.
26. D. Gerbig and P. R. Schreiner, Hydrogen-Tunneling in Biologically Relevant Small Molecules: The Rotamerizations of α-Ketocarboxylic Acids, *J. Phys. Chem. B*, **119** (2015) 693.
27. N. Kuş and R. Fausto, Effects of the Matrix and Intramolecular Interactions on the Stability of the Higher-energy Conformers of 2-Fluorobenzoic Acid, *J. Chem. Phys.*, **146** (2017) 124305.
28. L. Lapinski, I. Reva, H. Rostkowska, R. Fausto and M. J. Nowak, Conformational Transformation in Squaric Acid Induced by Near-IR Laser Light, *J. Phys. Chem. A*, **117** (2013) 5251.

This journal is © The Royal Society of Chemistry 20xx

29. A. Halasa, L. Lapinski, I. Reva, H. Rostkowska, R. Fausto and M. J. Nowak, Three Conformers of 2-Furoic Acid: Structure Changes Induced with Near IR Laser Light, *J. Phys. Chem. A*, 119 (2015) 1037.
30. L. L. G. Justino, I. Reva and R. Fausto, Thermally- and Vibrationally-Induced Conformational Isomerizations, Infrared Spectra and Photochemistry of Gallic Acid in Low-Temperature Matrices, *J. Chem. Phys.*, **145** (2016) 014304.
31. S. Amiri, H. P. Reisenauer and P. R. Schreiner, Electronic Effects on Atom Tunneling: Conformational Isomerization of Monomeric Para-Substituted Benzoic Acid Derivatives, *J. Am. Chem. Soc.*, **132** (2010) 15902.
32. S. Nishino and M. Nakata, Intramolecular Hydrogen Atom Tunneling in 2-Chlorobenzoic Acid Studied by Low-temperature Matrix-isolation Infrared Spectroscopy, *J. Phys. Chem. A*, **111** (2007) 7041.
33. A. Halasa, I. Reva, L. Lapinski, M. J. Nowak and R. Fausto, Conformational Transformations in Thiazole-2-Carboxylic Acid Induced by Selective Near-IR and UV Narrowband Laser Light, *J. Phys. Chem. A*, **120** (2016) 2078.
34. P. R. Schreiner, J. P. Wagner, H. P. Reisenauer, D. Gerbig, D. Ley, J. Sarka, A. G. Császár, A. Vaughn and W. D. Allen, Domino Tunneling, *J. Am. Chem. Soc.*, **137** (2015) 7828.
35. N. Kuş, A. Sharma, I. Peña, M. C. Bermúdez, C. Cabezas, J. L. Alonso and R. Fausto, Conformers of β-Aminoisobutyric Acid Probed by Jet-Cooled Microwave and Matrix Isolation Infrared Spectroscopic Techniques, *J. Chem. Phys.*, **138** (2013) 144305.
36. C. M. Nunes, L. Lapinski, R. Fausto and I. Reva, Near-IR Laser Generation of a High-energy Conformer of L-Alanine and the Mechanism of Its Decay in a Low Temperature Nitrogen Matrix, *J. Chem. Phys.*, **138** (2013) 125101.
37. G. Bazsó, G. Magyarfalvi and G. Tarczay, Tunneling Lifetime of the ttc/VIp Conformer of Glycine in Low-Temperature Matrices, *J. Phys. Chem. A*, **116** (2012) 10539.
38. G. Bazsó, E. E. Najbauer, G. Magyarfalvi and G. Tarczay, Near-Infrared Laser Induced Conformational Change of Alanine in Low-Temperature Matrixes and the Tunneling Lifetime of Its Conformer VI, *J. Phys. Chem. A*, **117** (2013) 1952.
39. G. Bazsó, G. Magyarfalvi and G. Tarczay, Near-infrared Laser Induced Conformational Change and UV Laser Photolysis of Glycine in Low-temperature Matrices: Observation of a Short-lived Conformer, *J. Mol. Struct.*, **1025** (2012) 33.
40. E. E. Najbauer, G. Bazsó, R. Apóstolo, R. Fausto, M. Biczysko, V. Barone and G. Tarczay, Identification of Serine Conformers by Matrix-Isolation IR Spectroscopy Aided by Near-Infrared Lased Induced Conformational Change and 2D Correlation Analysis, *J. Phys. Chem. B*, **119** (2015) 10496.
41. E. E. Najbauer, G. Bazsó, S. Góbi, G. Magyarfalvi and G. Tarczay, Exploring the Conformational Space of Cysteine by Matrix Isolation Spectroscopy Combined with Near-infrared Laser Induced Conformational Change, *J. Phys. Chem. B*, **118** (2014) 2093.
42. A. J. Lopes Jesus, C. M. Nunes, I. Reva, S. M. V. Pinto and R. Fausto, The Effects of Entangled IR-Radiation and Tunneling on the Conformational Interconversion of 2-Cyanophenol, *J. Phys. Chem. A*, **123** (2019) 4396.
43. A. J. Lopes Jesus, I. Reva, C. M. Nunes, J. P. L. Roque, S. M. V. Pinto and R. Fausto, Kinetically Unstable 2-Isocyanophenol Isolated in Cryogenic Matrices: Vibrational Excitation, Conformational Changes and Spontaneous Tunneling, *Chem. Phys. Lett.*, **747** (2020) 137069.
44. L. Lapinski, I. Reva, H. Rostkowska, R. Fausto and M. J. Nowak, Near-IR-Induced, UV-Induced and Spontaneous Isomerizations in 4-Methylcytosine and 5-Fluorocytosine, *J. Phys. Chem. B*, **118** (2014) 2831.
45. L. Lapinski, M. J. Nowak, I. Reva, H. Rostkowska and R. Fausto, NIR-Laser-Induced Selective Rotamerization of Hydroxy Conformers of Cytosine, *Phys. Chem. Chem. Phys.*, **12** (2010) 9615.
46. L. Lapinski, I. Reva, M. J. Nowak and R. Fausto, Five Isomers of Monomeric Cytosine and Their Interconversions Induced by Tunable UV Laser Light, *Phys. Chem. Chem. Phys.*, **13** (2011) 9676.
47. I. D. Reva, M. J. Nowak, L. Lapinski and R. Fausto, Spontaneous Tunneling and NIR/IR Induced Interconversion between the Amino-Hydroxy Conformers of Cytosine, *J. Chem. Phys.*, **136** (2012) 064511.
48. R. Fausto, L. Khriachtchev and P. Hamm, Conformational Changes in Cryogenic Matrices, in Physics and Chemistry at Low Temperatures, (Ed. L. Khriachtchev), Jenny Stanford Publishing, Boca Raton, FL (USA), 2011, Chapter 3. pp. 51-84.
49. E. M. S. Maçôas, L. Khriachtchev, M. Pettersson, R. Fausto and M. Räsänen, Rotational Isomerism of Acetic acid Isolated in Rare-gas Matrices: Effect of Medium and Isotopic Substitution on IR-Induced Isomerization Quantum Yield and *cis* → *trans* Tunneling Rate, *J. Chem. Phys.*, **121** (2004) 1331.
50. P. R. Schreiner, Tunneling Control of Chemical Reactions: The Third Reactivity Paradigm, *J. Am. Chem. Soc.*, **139** (2017) 15276.
51. P. R. Schreiner, H. P. Reisenauer, D. Ley, D. Gerbig, C.-H. Wu and W. D. Allen, Methylhydroxycarbene: Tunneling Control of a Chemical Reaction, *Science*, **332** (2011) 1300.
52. P. Zuev and R. S. Sheridan, Tunneling in the C-H Insertion of a Singlet Carbene: *tert*-butylchlorocarbene, *J. Am. Chem. Soc.*, **116** (1994) 4123.
53. L. Windhorn, J. S. Yeston, T. Witte, W. Fuß, M. Motzkus, D. Proch, and K.-L. Kompa, Getting Ahead of IVR: A Demonstration of Mid-infrared Induced Molecular Dissociation on a Sub-Statistical Time Scale, *J. Chem. Phys.*, **119** (2003) 641.
54. S. Jarmelo and R. Fausto, Entropy Effects in Conformational Distribution and Conformationally Dependent UV-Induced Photolysis of Serine Monomer Isolated in Solid Argon, *J. Mol. Struct.*, **786** (2006) 175.
55. A. Borba, A. Gómez-Zavaglia and R. Fausto, Conformational Cooling and Conformationally Selective Aggregation in

Dimethyl Sulfite Isolated in Solid Rare Gases, *J. Mol. Struct.*, **794** (2006) 196.

56. A. M. Ismael, M. L. S. Cristiano, R. Fausto and A. Gómez-Zavaglia, Tautomer Selective Photochemistry in 1-(Tetrazol-5-yl)ethanol, *J. Phys. Chem. A*, **114** (2010) 13076.
57. M. Pagacz-Kostrewa, I. Reva, R. Bronisz, B. M. Giuliano, R. Fausto and M. Wierzejewska, Conformational Behavior and Tautomer Selective Photochemistry in Low Temperature Matrices: The Case of 5-(1H-tetrazol-1-yl)-1,2,4-triazole, *J. Phys. Chem. A*, **115** (2011) 5693.
58. R. Fausto and A. Gómez-Zavaglia, Light Induced Reactions in Cryogenic Matrices, in Specialistic Reports in Photochemistry, (Ed. Angelo Albini), Royal Society of Chemistry, London (UK), Vol. 37 (2009), Chapter 3. pp. 72-99.
59. R. Fausto and A. Gómez-Zavaglia, Light Induced Reactions in Cryogenic Matrices, in Specialistic Reports in Photochemistry, (Ed. Angelo Albini), Royal Society of Chemistry, London (UK), Vol. 38 (2010), Chapter 2. pp. 37-66.
60. R. Fausto and A. Gómez-Zavaglia, Light Induced Reactions in Cryogenic Matrices, in Specialistic Reports in Photochemistry, (Ed. Angelo Albini), Royal Society of Chemistry, London (UK), Vol. 39 (2011), Chapter 1. pp. 1-27.
61. R. Fausto and A. Gómez-Zavaglia, Light Induced Reactions in Cryogenic Matrices. Highlights 2011-2012, in Specialistic Reports in Photochemistry, (Ed. A. Albini and E. Fasani), Royal Society of Chemistry, London (UK), Vol. 41 (2013), Chapter 2. pp. 12-58.
62. R. Fausto, A. Borba and A. Gómez-Zavaglia, Light Induced Reactions in Cryogenic Matrices. Highlights 2013-2014, in Specialistic Reports in Photochemistry, (Ed. A. Albini and E. Fasani), Royal Society of Chemistry, London (UK), Vol. 43 (2015), Chapter 2. pp. 20-82.
63. R. Fausto, T. Nikitin and A. Gómez-Zavaglia, Light Induced Reactions in Cryogenic Matrices. Highlights 2015-2016, in Specialistic Reports in Photochemistry, (Ed. A. Albini, E. Fasani and S. Protti), Royal Society of Chemistry, London (UK), Vol. 45 (2017), Chapter 1. pp. 22-67.
64. R. Fausto, T. Nikitin and E. M. Brás, Light Induced Reactions in Cryogenic Matrices. Highlights 2017-2018, in Specialistic Reports in Photochemistry, (Ed. A. Albini, E. Fasani and S. Protti), Royal Society of Chemistry, London (UK), Vol. 47 (2019), Chapter 1. pp. 22-67.
65. R. Fausto, T. Nikitin and E. M. Brás, Light Induced Reactions in Cryogenic Matrices. Highlights 2019-2020, in Specialistic Reports in Photochemistry, (Ed. S. Crespi and S. Protti), Royal Society of Chemistry, London (UK), Vol. 49 (2022) Chapter 3. pp. 53-108.
66. E. M. S. Maçôas, L. Khriachtchev, M. Pettersson, R. Fausto and M. Räsänen, Internal Rotation in Propionic Acid: Infrared Induced Isomerization in Solid Argon, *J. Phys. Chem. A*, **109** (2005) 3617.
67. I. D. Reva, S. G. Stepanian, L. Adamowicz and R. Fausto, Missing Conformers: Comparative Study of Conformational Cooling in Cyanoacetic Acid and Methyl Cyanoacetate Isolated in Low Temperature Inert Gas Matrixes, *Chem. Phys. Lett.*, **374** (2003) 631.
68. A. Borba, A. Gómez-Zavaglia and R. Fausto, Conformational Cooling and Conformationally Selective Aggregation in Dimethyl Sulfite Isolated in Solid Rare Gases, *J. Mol. Struct.*, **794** (2006) 196.
69. I. D. Reva, A. J. Lopes Jesus, M. T. S. Rosado, R. Fausto, M. E. Eusébio and J. S. Redinha, Stepwise Conformational Cooling Towards a Single Isomeric State in the Four Internal Rotors System 1,2-Butanediol, *Phys. Chem. Chem. Phys.*, **8** (2006) 5339.
70. S. Lopes, R. Fausto and L. Khriachtchev, Formic Acid Dimers in a Nitrogen Matrix, *J. Chem. Phys.*, **148** (2018) 034301.
71. S. Lopes, A. Domanskaya, M. Räsänen, L. Khriachtchev and R. Fausto, Acetic Acid Dimers in a Nitrogen Matrix: Observation of Structures Containing the Higher-Energy Conformer, *J. Chem. Phys.*, **143** (2015) 104307.
72. C. M. Nunes, I. Reva and R. Fausto, Conformational Isomerization Triggered by Vibrational Excitation of a Second Stretching Overtones, *Phys. Chem. Chem. Phys.*, **21** (2019) 24993.
73. A. Olbert-Majkut, J. Ahokas, J. Lundell and M. Pettersson, Investigating Isomerization Reactions in Solid State by Using Simultaneous High Overtone Pumping and Raman Detection, *J. Chem. Phys.*, **129** (2008) 041101.
74. A. Olbert-Majkut, J. Ahokas, J. Lundel and M. Pettersson, Raman Spectroscopy of Formic Acid and its Dimers Isolated in Low Temperature Argon Matrices, *Chem. Phys. Lett.*, **468** (2009) 176.
75. A. J. Lopes Jesus, I. Reva, C. Araujo-Andrade and R. Fausto, Conformational Switching by Vibrational Excitation of a Remote NH Bond, *J. Am. Chem. Soc.*, **137** (2015) 14240.
76. A. Halasa, I. Reva, L. Lapinski, H. Rostkowska, R. Fausto and M.J. Nowak, Conformers of Kojic Acid and Their Near-IR-Induced Conversions: Long-Range Intramolecular Vibrational Energy Transfer, *J. Phys. Chem. A*, **120** (2016) 2647.
77. B. Kovács, N. Kuş, G. Tarczay and R. Fausto, Investigation of Long-Range Intramolecular Vibrational Energy Redistribution by NIR Irradiation Induced Conformational Transformation of E-Glutaconic Acid, *J. Phys. Chem. A*, **121** (2017) 3392.
78. S. Góbi, I. Reva, I. Csonka, C. M. Nunes, G. Tarczay and R. Fausto, Conformational Control over Thiol Forms of Thioacetamide by Selective Excitation of NH Imino Vibrational Antennas, *Phys. Chem. Chem. Phys.*, **21** (2019) 24935.
79. A. J. Lopes Jesus, C. M. Nunes, R. Fausto and I. Reva, Conformational Control over an Aldehyde Fragment by Selective Vibrational Excitation of Interchangeable Remote Antennas, *Chem. Comm.*, **54** (2018) 4778.
80. C. M. Nunes, N. A. M. Pereira, I. Reva, P. S. M. Amado, M. L. S. Cristiano and R. Fausto, Bond-Breaking/Bond-Forming Reactions by Vibrational Excitation: Infrared-Induced Bidirectional Tautomerization of Matrix-Isolated Thiotropolone, *J. Phys. Chem. Lett.*, **11** (2020) 8034.

This journal is © The Royal Society of Chemistry 20xx

81. C. M. Nunes, N. A. M. Pereira, I. Reva and R. Fausto, Evidence of IR-Induced Chemistry in Neat Solid: Tautomerization of Thiotropolone by Thermal, Electronic and Vibrational Excitations, *J. Phys. Chem. A*, **125** (2021) 6394.
82. C. M. Nunes, N. A. M. Pereira, L. P. Viegas, T. M. V. D. Pinho e Melo and R. Fausto, Inducing Molecular Reactions by Selective Vibrational Excitation of a Remote Antenna with Near-Infrared Light, *Chem. Comm.*, **57** (2021) 9570.
83. J. P. L. Roque, C. M. Nunes, L. P. Viegas, N. A. M. Pereira, T. M. D. V. Pinho e Melo, P. R. Schreiner and R. Fausto, Switching on H-tunneling Through Conformation Control, *J. Am. Chem. Soc.*, **143** (2021) 8266.
84. J. P. Klinman and A. Kohen, Hydrogen Tunneling Links Protein Dynamics to Enzyme Catalysis, *Annu. Rev. Biochem.*, **82** (2013) 471.
85. J. P. Klinman, An Integrated Model for Enzyme Catalysis Emerges from Studies of Hydrogen Tunneling, *Chem. Phys. Lett.*, **471** (2009) 179.
86. D. Ley, D. Gerbig, P. R. Schreiner, Tunnelling control of chemical reactions – the organic chemist's perspective, *Org. Biomol. Chem.*, **10** (2012) 3781.
87. J. Meisner, J. Kästner, Atom Tunneling in Chemistry, *Angew. Chem. Int. Ed.*, **55** (2016) 5400.
88. E. M. Greer, K. Kwon, A. Greer, C. Doubleday, Thermally activated tunneling in organic reactions, *Tetrahedron*, **72** (2016) 7357.
89. P. R. Schreiner, Quantum Mechanical Tunneling Is Essential to Understanding Chemical Reactivity, *Trends in Chemistry*, **2** (2020) 980.
90. R. P. Bell, The Tunnel Effect in Chemistry, Springer, Boston, 1980.
91. C. Castro, W. L. Karney, Heavy-Atom Tunneling in Organic Reactions, *Angew. Chem. Int. Ed.*, **59** (2020) 8355.
92. C. M. Nunes, I. Reva, R. Fausto, Direct Observation of Tunnelling Reactions by Matrix Isolation Spectroscopy. In Tunnelling in Molecules: Nuclear Quantum Effects from Bio to Physical Chemistry; J. Kästner, S. Kozuch, Eds. The Royal Society of Chemistry: 2021; pp 1– 60.
93. T. Schleif, J. Mieres-Perez, S. Henkel, E. Mendez-Vega, H. Inui, R. J. McMahon, and W. Sander, Conformer-Specific Heavy-Atom Tunneling in the Rearrangement of Benzazirines to Ketenimines, *J. Org. Chem.*, **84** (2019) 16013.
94. T. Schleif, J. Tatchen, J. F. Rowen, F. Beyer, E. Sanchez-Garcia, W. Sander, Heavy-Atom Tunneling in Semibullvalenes: How Driving Force, Substituents, and Environment Influence the Tunneling Rates, *Chem. Eur. J.*, **26** (2020) 10452.
95. T. Schleif, M. P. Merini, W. Sander, The Mystery of the Benzene-Oxide/Oxepin Equilibrium—Heavy-Atom Tunneling Reversed by Solvent Interactions, *Angew. Chem. Int. Ed.*, **59** (2020) 20318.
96. S. Henkel, M. P. Merini, E. Mendez-Vega and W. Sander, Lewis acid catalyzed heavy atom tunneling – the case of 1H-bicyclo[3.1.0]-hexa-3,5-dien-2-one, *Chem. Sci.*, **12** (2021) 11013.
97. C. M. Nunes, L. P. Viegas, S. A. Wood, J. P. L. Roque, R. J. McMahon, R. Fausto, Heavy-Atom Tunneling Through Crossing Potential Energy Surfaces: Cyclization of a Triplet 2-Formylarylnitrene to a Singlet 2,1-Benzisoxazole, *Angew. Chem. Int. Ed.*, **59** (2020) 17622.
98. C. M. Nunes, A. K. Eckhardt, I. Reva, R. Fausto, and P. R. Schreiner, Competitive Nitrogen versus Carbon Tunneling, *J. Am. Chem. Soc.*, **141** (2019) 14340.