

VIP Tunneling Reactions Very Important Paper

Heavy-Atom Tunneling Through Crossing Potential Energy Surfaces:
Cyclization of a Triplet 2-Formylarylnitrene to a Singlet
2,1-BenzisoxazoleCláudio M. Nunes,* Luís P. Viegas,* Samuel A. Wood, José P. L. Roque, Robert J. McMahon,
and Rui Fausto

Abstract: Not long ago, the occurrence of quantum mechanical tunneling (QMT) chemistry involving atoms heavier than hydrogen was considered unreasonable. Contributing to the shift of this paradigm, we present here the discovery of a new and distinct heavy-atom QMT reaction. Triplet syn-2-formyl-3-fluorophenylnitrene, generated in argon matrices by UV-irradiation of an azide precursor, was found to spontaneously cyclize to singlet 4-fluoro-2,1-benzisoxazole. Monitoring the transformation by IR spectroscopy, temperature-independent rate constants ($k \approx 1.4 \times 10^{-3} \text{ s}^{-1}$; half-life of $\approx 8 \text{ min}$) were measured from 10 to 20 K. Computational estimated rate constants are in fair agreement with experimental values, providing evidence for a mechanism involving heavy-atom QMT through crossing triplet to singlet potential energy surfaces. Moreover, the heavy-atom QMT takes place with considerable displacement of the oxygen atom, which establishes a new limit for the heavier atom involved in a QMT reaction in cryogenic matrices.

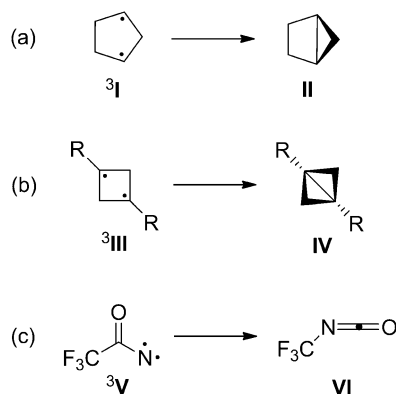
Introduction

The relevance of quantum mechanical tunneling (QMT) to chemistry has been recognized since the 1930's, when Bell published his seminal theoretical work demonstrating the need to consider tunneling in reactions involving the motion of a hydrogen atom or proton.^[1] In particular, H-atom QMT is known to play an important role in many reactions in organic chemistry,^[2–4] biochemistry,^[5,6] catalysis,^[7,8] and interstellar chemistry.^[9,10] The existence of QMT contribution to a chemical reaction is typically detected indirectly by the observation of nonlinear Arrhenius plots or abnormal kinetic isotope effects.^[2,3] Experimental evidence of QMT has also been obtained using cryogenic temperatures (e.g., 3–10 K).^[11] Under these conditions, thermally activated rates become negligible for systems having barriers as low as 1 kcal mol⁻¹,

so that chemical transformations can only take place by vibrational ground-state QMT. Investigations involving direct observation of QMT in cryogenic conditions have contributed significantly to a better understanding of the tunneling phenomenon and its role in chemistry.^[11] It is now established that not only can QMT have a profound influence on reaction rates, but it can also control the selectivity of chemical reactions.^[8,12,13]

Because tunneling probability decreases exponentially with the square root of the moving mass, tunneling of atoms heavier than hydrogen (such as carbon, 12 times heavier) is predicted to be very unlikely.^[14–16] So far only about a dozen examples of direct experimental observations of heavy-atom QMT reactions in cryogenic conditions have been reported.^[17–30] Even fewer cases with clear experimental evidence of heavy-atom QMT contribution are known for reactions in solution.^[2] The increasing number of recent reports on experimental and theoretical heavy-atom QMT reactions, however, seems to suggest that this phenomenon occurs more frequently than had been assumed and can have significant implications for many chemical reactions.^[31–36]

One of the first examples of heavy-atom QMT was described by Buchwalter and Closs in 1975, regarding the ring-closure of triplet 1,3-cyclopentadiyl ³I to bicyclopentane **II** in cryogenic glasses at 1.3 to 20 K (Scheme 1 a).^[17] Additional evidence of heavy-atom QMT on the ring-closure of triplet 1,3-diradicals was described later by Dougherty and co-workers for the transformation of triplet 1,3-cyclobutane-diyls ³III to bicyclobutanes **IV** in cryogenic matrices at 4 to



Scheme 1. Cases of heavy-atom QMT reactions from a triplet ground-state reactant to a singlet product directly observed at cryogenic temperatures.^[17,18,26]

[*] C. M. Nunes, L. P. Viegas, J. P. L. Roque, R. Fausto
University of Coimbra, CQC, Department of Chemistry
3004-535 Coimbra (Portugal)
E-mail: cmnunes@qui.uc.pt
lpviegas@ci.uc.pt

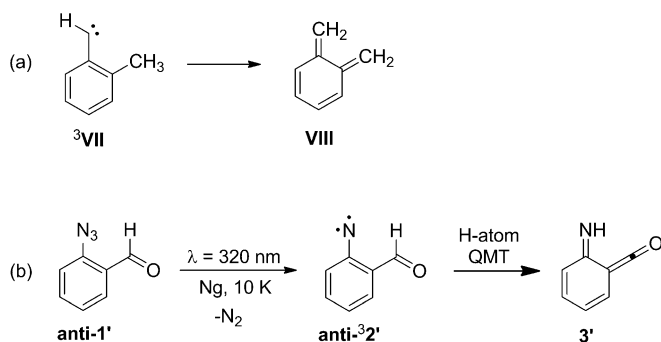
S. A. Wood, R. J. McMahon
Department of Chemistry, University of Wisconsin-Madison,
Madison, WI 53706-1322 (USA)

Supporting information and the ORCID identification number(s) for the author(s) of this article can be found under:
<https://doi.org/10.1002/anie.202006640>.

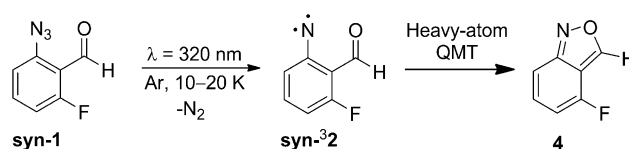
20 K (Scheme 1b).^[18] Interestingly, in both cases triplet 1,3-diradicals must undergo intersystem crossing (ISC) to form the singlet products. However, it is not clear if QMT takes place in the triplet surface, to a geometry that then undergoes ISC to the singlet surface, or if QMT occurs through crossing surfaces from triplet to singlet. To the best of our knowledge, the only established case of heavy-atom QMT through crossing potential energy surfaces was recently reported by Abe, Zeng and co-workers for the rearrangement of triplet nitrene $^3\mathbf{V}$ to isocyanate \mathbf{VI} in cryogenic matrices at 2.8 to 23 K (Scheme 1c).^[26]

Several H-atom QMT reaction involving a triplet ground-state reactant to a singlet product are known; mostly H-abstraction in triplet carbenes.^[4,37,38] One early example was reported by McMahon and Chapman, who directly observed the intramolecular [1,4]H-shift from triplet 2-methylphenylcarbene $^3\mathbf{VII}$ to singlet *o*-xylylene \mathbf{VIII} in cryogenic matrices at 4.6 K (Scheme 2a).^[39] We discovered in 2016 the first direct evidence of H-atom QMT in nitrene chemistry, namely the rearrangement of triplet *anti*-2-formylphenylnitrene $\mathbf{anti}^{-3}2'$ to singlet imino-ketene $\mathbf{3}'$ in noble-gas matrices at 10 K (Scheme 2b).^[40] It was proposed that H-atom QMT occurs on the triplet surface from $\mathbf{anti}^{-3}2'$ to $\mathbf{3}'$, followed by ISC to the singlet $\mathbf{3}'$. Indeed, calculations of tunneling probability on the corresponding triplet surface provided rates in reasonable agreement with the experimental observations. As far as we know, no clear-cut evidence has been reported for H-atom QMT occurring at cryogenic temperatures through crossing surfaces from triplet to singlet (instead of H-atom QMT in a triplet surface succeed by an ISC process).

Following our investigations with arylnitrene $\mathbf{2}'$, in the current work we demonstrate that changing the conformation of the aldehyde moiety from *anti* to *syn* opens access to a new heavy-atom QMT reaction (Scheme 3). Arylazide $\mathbf{1}$, with a fluorine substituent to act as a hydrogen-bond acceptor for the aldehyde hydrogen atom, was designed as a gateway to triplet *syn*-2-formyl-3-fluorophenylnitrene $\mathbf{syn}^{-3}2$. Upon generating $\mathbf{syn}^{-3}2$ in a cryogenic matrix, we discovered that $\mathbf{syn}^{-3}2$ spontaneously cyclizes by heavy-atom QMT to singlet 2,1-benzisoxazole $\mathbf{4}$. Non-adiabatic transition state theory (NATST) computations, based on the weak-coupling (WC) formulation, provide evidence for the occurrence of heavy-atom QMT from $\mathbf{syn}^{-3}2$ to $\mathbf{4}$ through crossing potential energy surfaces (PESs).



Scheme 2. Examples of H-atom QMT reactions from a triplet ground-state reactant to a singlet product directly observed in cryogenic matrices.^[39,40]



Scheme 3. Summary of experimental observations for heavy-atom QMT in the cyclization of triplet *syn*-2-formyl-3-fluorophenylnitrene $\mathbf{syn}^{-3}2$ to singlet 4-fluoro-2,1-benzisoxazole $\mathbf{4}$ in an argon matrix at 10 to 20 K.

Results and Discussion

Conformational Analysis

Computations at the CBS-QB3 (complete basis set—quadratic Becke-3 composite method) level of theory estimate that 2-formylphenylazide $\mathbf{1}'$ in the gas-phase at room temperature exists essentially in its most stable conformation \mathbf{aa}^{-1}' , with the aldehyde (carbonyl) assuming *anti*-orientation regarding the azide moiety (Table 1). Conformer \mathbf{as}^{-1}' , with the aldehyde in *syn*-orientation, is $\approx 2.7 \text{ kcal mol}^{-1}$ ($\Delta G_{298\text{K}}$) higher in energy than \mathbf{aa}^{-1}' and its population is estimated to be no more than $\approx 1\%$. In agreement with the computed data, the IR spectrum of matrix-isolated $\mathbf{1}'$ (obtained from sublimation of $\mathbf{1}'$ at room temperature) shows only contribution from the \mathbf{aa}^{-1}' conformer (Figure S1 in the Supporting Information).^[40] To obtain a significant population of the *syn*-aldehyde conformer in a 2-formylphenylazide derivative, the stabilization effect of several different substituents acting as a hydrogen-bond acceptor for the aldehyde hydrogen atom was considered (Table S1). 2-Formyl-3-fluorophenylazide $\mathbf{1}$ was found to be a promising system. At the CBS-QB3 level of theory, the most stable *syn*-aldehyde conformer \mathbf{as}^{-1} is only $\approx 0.4 \text{ kcal mol}^{-1}$ higher in energy than the most stable *anti*-aldehyde conformer \mathbf{aa}^{-1} , and the predicted gas-phase equilibrium population of the two *syn*-aldehyde conformers (\mathbf{as}^{-1} and \mathbf{ss}^{-1}) is $\approx 45\%$ at room temperature (Table 1).

Matrix-Isolation IR Spectroscopy

2-Formyl-3-fluorophenylazide $\mathbf{1}$ was synthesized using standard procedures as described in detail in the Supporting Information. Monomeric $\mathbf{1}$ was isolated in an argon matrix at 15 K by sublimating the sample at room temperature. The IR spectrum of matrix-isolated $\mathbf{1}$ shows the presence of *anti* (\mathbf{aa}^{-1}) and *syn* (\mathbf{as}^{-1} and \mathbf{ss}^{-1}) aldehyde conformers in a ratio comparable to the predicted 55:45 ratio (Figures S2 and S3). UV irradiation ($\lambda = 320 \text{ nm}$) of $\mathbf{1}$ led to the formation of several species (Figure S4), presumably the corresponding triplet arylnitrenes $\mathbf{anti}^{-3}2$ and $\mathbf{syn}^{-3}2$ and the products of their chemistry. Irradiation for shorter times and at slightly different wavelengths (e.g., 275 or 308 nm) did not lead to any significant simplification of the photochemistry. Interestingly, however, we found that one of the photoproducts of $\mathbf{1}$ spontaneously converts into another species after the UV-irradiation was stopped and the sample was left in the dark at 15 K. The IR signatures of these two species were obtained



Table 1: Relative Gibbs energy at 298.15 K (ΔG_{298K} in kcal mol⁻¹) computed at the B3LYP/6-311+G(2d,p) and CBS-QB3 levels of theory for conformers of 2-formylphenylazide **1'** and 2-formyl-3-fluorophenylazide **1** and their equilibrium populations at 298.15 K (Pop_{298K} in %).^[a]

Structure								
1', 1	R = H, F							
Name	aa-1'	aa-1	sa-1'	sa-1	as-1'	as-1	ss-1'	ss-1
ΔG_{298K} (B3LYP)	0.0	0.0	4.1	4.4	2.5	0.3	3.4	1.3
ΔG_{298K} (CBS-QB3)	0.0	0.0	3.6	3.5	2.7	0.4	2.9	0.6
Pop_{298K}	98	55	0	0	1	26	1	19

[a] Equilibrium populations were estimated from Boltzmann distribution based on the ΔG_{298K} values computed at the CBS-QB3 level of theory. In the names of structures, a stands for *anti* and s stands for *syn*, which corresponds to the orientation of the azide (first letter) and aldehyde (second letter) moieties, relative to one another.

and allowed identification of the spontaneous cyclization of triplet *syn*-2-formyl-3-fluorophenyl nitrene **syn-32** to singlet 4-fluoro-2,1-benzisoxazole **4** (Figure 1 and Scheme 3).

The experimental IR bands of the consumed and produced species in the reaction taking place in the dark are well reproduced by the B3LYP/6-311+G(2d,p) computed IR spectra of **syn-32** and **4**, respectively (Figure 1). The most characteristic IR bands of triplet aryl nitrene **syn-32** are observed at 1695, 1517, 1393, 1296, 1035 and ≈ 776 cm⁻¹,

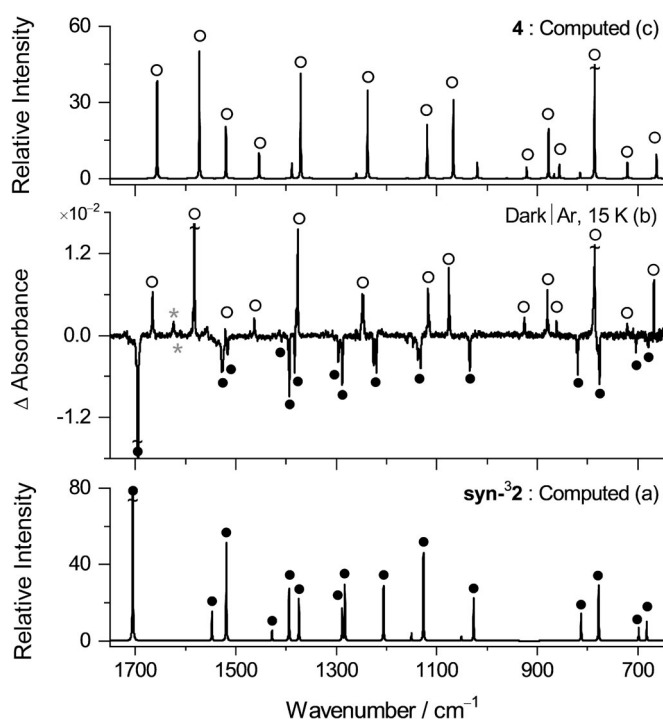


Figure 1. a) IR spectrum of triplet *syn*-2-formyl-3-fluorophenyl nitrene **syn-32** computed at the B3LYP/6-311+G(2d,p) level of theory. b) Experimental difference IR spectrum showing changes after keeping the sample at 15 K (Ar matrix) in the dark for 40 min, subsequent to irradiation of **1** at $\lambda = 320$ nm (Figure S4). The downward bands are due to consumed species assigned to **syn-32**. The upward bands are due to the product assigned to **4**. Asterisk (*) signals traces of monomeric water. c) IR spectrum of 4-fluoro-2,1-benzisoxazole **4** computed at the B3LYP/6-311+G(2d,p) level of theory.

corresponding to the vibrational modes computed at 1705 [$\nu(\text{C}=\text{O})$], 1519 [$\nu(\text{CC})_{\text{ring}} + \delta(\text{CH})_{\text{ring}}$], 1394 [$\delta(\text{OC-H})$], 1288 [$\nu(\text{C-N})$], 1027 [$\nu(\text{CC})_{\text{ring}} + \nu(\text{C-F})$] and 778 [$\gamma(\text{CH})_{\text{ring}}$] cm⁻¹, respectively. Representative IR bands of benzisoxazole **4** are observed at 1666, ≈ 1582 , ≈ 1117 , 1076, 880 and 786 cm⁻¹, corresponding to the vibrational modes computed at 1657 [$\nu(\text{CC})$], 1572 [$\nu(\text{CC})$], 1119 [$\nu(\text{CO})$], 1067 [$\nu(\text{C-F}) + \delta(\text{Is-ring})$], 878 [$\nu(\text{N-O})$] and 786 [$\gamma(\text{CH})$] cm⁻¹, respectively. Comprehensive assignments of the IR spectra of **syn-32** and **4** are given in Tables S4 and S5.

Kinetics and Tunneling

The kinetics of spontaneous cyclization of **syn-32** to **4** in an argon matrix at 15 K were followed by monitoring the intensity changes of the most intense IR bands of **syn-32** to **4** with time (Figure 2). Fitting the experimental data with first-order exponential decay and growth equations, for the consumption of **syn-32** and the production of **4**, rate constants equal to 1.3×10^{-3} s⁻¹ were obtained (half-life of 8.7 min). During the collection of IR spectra, a cutoff filter above 2200 cm⁻¹ was used to minimize the sample exposure to the IR spectrometer source light. Possible effects of IR light with frequencies below 2200 cm⁻¹ were excluded based on the observation of similar reaction kinetics at the end of 20 min with a sample held in the complete absence of light (Figure S5). Following the same procedure, kinetics measure-

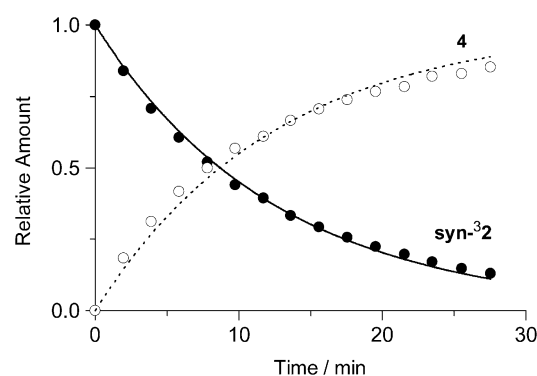


Figure 2. Kinetics of spontaneous rearrangement of triplet *syn*-2-formyl-3-fluorophenyl nitrene **syn-32** to singlet 4-fluoro-2,1-benzisoxazole **4** in an argon matrix at 15 K. Solid (●) and open (○) circles represent the time evolution of the amount of **syn-32** (consumption) and **4** (production), respectively. The solid and dotted line represent the best fits obtained using a first-order exponential decay and growth equations, respectively. The rate constants obtained were $k_{(15K)} = 1.3 \times 10^{-3}$ s⁻¹ ($\tau_{1/2} = 8.7$ min) for the consumption of **syn-32** and $k'_{(15K)} = 1.3 \times 10^{-3}$ s⁻¹ ($\tau_{1/2} = 8.7$ min) for the production of **4** (see the Experimental and Computational Methods section in the Supporting Information for more details).

ments were also performed for the spontaneous decay of **syn**-³**2** at 10 and 20 K. Rate constants of 1.4×10^{-3} and $1.5 \times 10^{-3} \text{ s}^{-1}$ were determined for the reaction at these temperatures, which correspond to a half-life of ≈ 8 min (Figure S6). Because the cyclization rate of **syn**-³**2** to **4** does not increase upon doubling the temperature, a thermal over-the-barrier process is ruled out, providing strong evidence for the occurrence of heavy-atom QMT (Scheme 3).

Computations

It is interesting to note that the reaction mechanism of heavy-atom QMT in the triplet surface, from triplet nitrene **syn**-³**2** to triplet benzisoxazole ³**4**, followed by ISC to the singlet **4**, is not feasible because triplet ³**4** is much higher in energy than triplet **syn**-³**2** ($> 40 \text{ kcal mol}^{-1}$; see Figure 3). Therefore, the cyclization of **syn**-³**2** to **4** should involve heavy-atom QMT through crossing triplet to singlet potential energy surfaces. Computations at the complete active space self-consistent field CASSCF(10,10)/cc-pVDZ level of theory were carried out to search for a minimum-energy crossing point (MECP) between the triplet **syn**-³**2** and singlet **4** surfaces (see Figure 3, which has been obtained by using just the R(N-O) distance from the intrinsic reaction coordinate (IRC) data depicted in Figure S7). An MECP was found by starting from a geometry where the two PESs cross, as a function of R(N-O). Its relative energy was estimated to be $17.8 \text{ kcal mol}^{-1}$ (ZPE included, which for the MECP was calculated using our own gamread script together with the GLOWfreq code;^[41] details are provided in the Supporting Information), and the reaction being exothermic by $18.2 \text{ kcal mol}^{-1}$. To include dynamical correlation, which is well-known to be critical for reliable kinetics calculations, single-point energies were subsequently computed at the multireference Møller-Plesset MRMP(10,10)/cc-pVDZ level of theory. Using this approach, the MECP energy connecting triplet **syn**-³**2** to

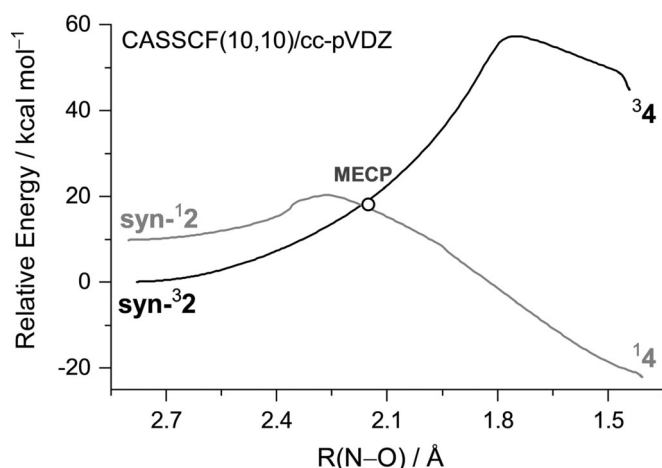


Figure 3. IRC path for the cyclization **syn**-³**2** → **4** on the singlet (grey) and triplet (black) surfaces computed at the CASSCF/cc-pVDZ level of theory as a function of the N...O distance [Å]. Energies (kcal mol^{-1}) are given relative to the energy of **syn**-³**2**. The MECP is shown in an open circle.

singlet **4** reduces to $12.1 \text{ kcal mol}^{-1}$. An identical MECP energy value was estimated at the density functional theory (DFT) M06-2X/6-311++G(d,p) level of theory.

Reaction rates for the cyclization of triplet **syn**-³**2** to singlet **4** were computed by accounting for the different spin multiplicities of the crossing PESs. Two different methods were employed based on the non-adiabatic-TST time-independent statistical approach:^[42-48] (i) the Landau-Zener (LZ);^[49,50] and (ii) the weak coupling (WC) formulation^[51,52] (details are provided in the Supporting Information). The calculated LZ rate constants are zero (considering $T = 10$ or 20 K) both at the multireference or DFT level. This is expected, since the LZ method neglects transitions between PESs caused by QMT for energies below the MECP; a thermal over-the-barrier process at the cryogenic temperatures considered is clearly not accessible. The calculated WC rate constants are given in Table 2 (see more details in the Supporting Information and in Table S6). The WC method accounts for contributions from tunneling below the MECP and from the classically allowed region above the MECP. Therefore, it is expected to correctly model heavy-atom QMT through crossing PESs occurring at cryogenic temperatures. The calculated WC rate constants using the MECP energy computed at the MRMP level of theory and all additional data taken from the CASSCF computations stay in the range of $6.9 \times 10^{-1} \text{ s}^{-1}$ (10 K) to 1.4 s^{-1} (20 K), which compare fairly well with the experimentally obtained results and, in particular, demonstrate the achievability of the heavy-atom QMT mechanism for the investigated chemical transformation. The calculated WC rate constants using the MECP energy computed at the M06-2X level of theory stay in the range of 1.5 to $3.2 \times 10^{-2} \text{ s}^{-1}$, only one order of magnitude higher (faster) than the experimental results. The WC results unambiguously show that QMT through crossing triplet to singlet PESs is solely responsible for the cyclization of **syn**-³**2** to **4** at cryogenic temperatures.

To the best of our knowledge, the WC formulation of non-adiabatic-TST has never been applied for calculating vibrational ground-state QMT reactions rates, although it has been applied quite successfully to calculate rates of spin-forbidden organic and organometallic/catalytic reactions.^[53-55] In order to further access the robustness and good performance of the WC method for modeling heavy-atom QMT through crossing PESs at cryogenic temperatures, rate constants were also calculated for the rearrangement of triplet nitrene ³**V** to singlet isocyanate **VI** reported by Abe and Zeng and co-workers (Scheme 1c).^[26] At the M06-2X/6-311++G(d,p) level of theory, the six calculated rate constants (considering temperatures in the range from 2.8 to 23.0 K) show that reaction occurs only due to heavy-atom QMT with an

Table 2: Weak coupling (WC) rate constants calculated for the cyclization of triplet **syn**-³**2** to singlet **4**.

Level of theory	$k_{wc} (10 \text{ K}) [\text{s}^{-1}]$	$k_{wc} (15 \text{ K}) [\text{s}^{-1}]$	$k_{wc} (20 \text{ K}) [\text{s}^{-1}]$
MRMP(10,10)/cc-pVDZ ^[a]	6.9×10^{-1}	1.1	1.4
M06-2X/6-311++G(d,p)	1.5×10^{-2}	2.4×10^{-2}	3.2×10^{-2}

[a] MRMP single point energies on CASSCF(10,10)/cc-pVDZ optimized geometries.



impressive agreement with the experimental observations in cryogenic matrices, essentially sharing the same 10^{-3} s^{-1} order of magnitude (Table S7).

Conclusion

In conclusion, we have presented here the discovery of a new heavy-atom QMT reaction, which has the distinctive feature of occurring through crossing surfaces from triplet to singlet. 2-Formyl-3-fluorophenylazide **1** was designed to achieve *syn*-aldehyde conformational stabilization. The IR spectrum of the room temperature vapor of **1**, quenched in an argon matrix (15 K), confirmed the presence of *syn*-aldehyde conformers in a significant ratio. The conformational tuning opened access to triplet *syn*-2-formylarylnitrene **syn**-**3**, which was successfully generated in a cryogenic matrix upon UV-irradiation of **1**. Triplet nitrene **syn**-**3** was then found to spontaneously cyclize to singlet 2,1-benzisoxazole **4** in the dark at 15 K. Monitoring the **syn**-**3** → **4** transformation by IR spectroscopy, rate constants of $\approx 1.4 \times 10^{-3} \text{ s}^{-1}$ (half-life of ≈ 8 min) were measured in argon matrix at 10, 15 and 20 K, providing clear evidence of heavy-atom QMT. A reaction mechanism involving heavy-atom QMT on the triplet surface was ruled out since triplet **3** is much higher in energy than triplet **syn**-**3**. Computations identified a minimum energy crossing point (MECP) between the triplet **syn**-**3** and singlet **4** surfaces at $\approx 12 \text{ kcal mol}^{-1}$, an insurmountably large energy requirement for any over-the-barrier process at the cryogenic temperatures. Non-adiabatic-TST computations, based on the weak-coupling (WC) formulation, estimate rate constants that display qualitative agreement with experimental measurements, unambiguously demonstrating that cyclization of **syn**-**3** to **4** at cryogenic temperatures takes place exclusively by heavy-atom QMT through crossing triplet to singlet PESs.

Although carbon-atom QMT is the predominant type of heavy-atom tunneling to be experimentally observed, oxygen-atom QMT has been hypothesized to contribute to reactions in atmospheric chemistry and astrochemistry.^[56–59] Interestingly, the heavy-atom QMT cyclization of **syn**-**3** to **4** involves considerable displacement of nitrogen and oxygen atoms. The direct experimental observation of a heavy-atom QMT reaction with significant contribution of oxygen-atom displacement represents an important new observation.

Acknowledgements

This work was supported by Project POCI-01-0145-FEDER-028973, funded by FEDER, via Portugal 2020—POCI, and by National Funds via the Portuguese Foundation for Science and Technology (FCT). The Coimbra Chemistry Centre is supported by the FCT through the projects UIDB/00313/2020 and UIDP/00313/2020, co-funded by COMPETE. C.M.N. acknowledges the FCT for an Auxiliary Researcher grant. L.P.V. acknowledges the Coimbra Chemistry Centre for the CQC-SER-C2-BPD research grant. J.P.L.R. acknowledges the Project POCI-01-0145-FEDER-028973 for a research grant. S.A.W. and R.J.M. gratefully acknowledge support

from the U.S. National Science Foundation (CHE-1954270, CHE-1664912).

Conflict of interest

The authors declare no conflict of interest.

Keywords: heavy-atom tunneling · IR spectroscopy · matrix isolation · nitrenes · non-adiabatic transition state theory

- [1] R. P. Bell, *Proc. R. Soc. London Ser. A* **1933**, *139*, 466–474.
- [2] E. M. Greer, K. Kwon, A. Greer, C. Doubleday, *Tetrahedron* **2016**, *72*, 7357–7373.
- [3] D. Ley, D. Gerbig, P. R. Schreiner, *Org. Biomol. Chem.* **2012**, *10*, 3781–3790.
- [4] “Quantum Mechanical Tunneling in Organic Reactive Intermediates”: R. S. Sheridan in *Reviews of Reactive Intermediate Chemistry* (Eds.: R. A. Moss, M. S. Platz, M. J. Jones), Wiley, Hoboken, **2006**, pp. 415–463.
- [5] J. P. Klinman, A. R. Offenbacher, *Acc. Chem. Res.* **2018**, *51*, 1966–1974.
- [6] J. P. Layfield, S. Hammes-Schiffer, *Chem. Rev.* **2014**, *114*, 3466–3494.
- [7] J. Meisner, J. Kästner, *Angew. Chem. Int. Ed.* **2016**, *55*, 5400–5413; *Angew. Chem.* **2016**, *128*, 5488–5502.
- [8] S. H. Bae, X.-X. Li, M. S. Seo, Y.-M. Lee, S. Fukuzumi, W. Nam, *J. Am. Chem. Soc.* **2019**, *141*, 7675–7679.
- [9] K. A. Haupa, G. Tarczay, Y. P. Lee, *J. Am. Chem. Soc.* **2019**, *141*, 11614–11620.
- [10] R. J. Shannon, M. A. Blitz, A. Goddard, D. E. Heard, *Nat. Chem.* **2013**, *5*, 745–749.
- [11] “Direct Observation of Tunneling Reactions by Matrix Isolation Spectroscopy”: C. M. Nunes, I. Reva, R. Fausto in *Tunneling in Molecules: Nuclear Quantum Effects from Bio to Physical Chemistry* (Eds.: S. Kozuch, J. Kästner), Royal Society of Chemistry, London, **2020**, in press.
- [12] P. R. Schreiner, *J. Am. Chem. Soc.* **2017**, *139*, 15276–15283.
- [13] P. R. Schreiner, H. P. Reisenauer, D. Ley, D. Gerbig, C.-H. Wu, W. D. Allen, *Science* **2011**, *332*, 1300–1303.
- [14] R. P. Bell, *The Tunnel Effect in Chemistry*, Springer, Boston, MA, **1980**.
- [15] W. T. Borden, *Wiley Interdiscip. Rev. Comput. Mol. Sci.* **2016**, *6*, 20–46.
- [16] S. Kozuch, A. Nandi, A. Sucher, *Chem. Eur. J.* **2018**, *24*, 16348–16355.
- [17] S. L. Buchwalter, G. L. Closs, *J. Am. Chem. Soc.* **1975**, *97*, 3857–3858.
- [18] M. B. Sponsler, R. Jain, F. D. Coms, D. A. Dougherty, *J. Am. Chem. Soc.* **1989**, *111*, 2240–2252.
- [19] A. M. Orendt, B. R. Arnold, J. G. Radziszewski, J. C. Facelli, K. D. Malsch, H. Strub, D. M. Grant, J. Michl, *J. Am. Chem. Soc.* **1988**, *110*, 2648–2650.
- [20] P. Zuev, R. Sheridan, *J. Am. Chem. Soc.* **1994**, *116*, 4123–4124.
- [21] P. S. Zuev, R. S. Sheridan, T. V. Albu, D. G. Truhlar, D. A. Hrovat, W. T. Borden, *Science* **2003**, *299*, 867–870.
- [22] R. A. Moss, R. R. Sauer, R. S. Sheridan, J. Tian, P. S. Zuev, *J. Am. Chem. Soc.* **2004**, *126*, 10196–10197.
- [23] H. Inui, K. Sawada, S. Oishi, K. Ushida, R. J. McMahon, *J. Am. Chem. Soc.* **2013**, *135*, 10246–10249.
- [24] M. Ertelt, D. A. Hrovat, W. T. Borden, W. Sander, *Chem. Eur. J.* **2014**, *20*, 4713–4720.
- [25] T. Schleif, J. Mierez-Perez, S. Henkel, M. Ertelt, W. T. Borden, W. Sander, *Angew. Chem. Int. Ed.* **2017**, *56*, 10746–10749; *Angew. Chem.* **2017**, *129*, 10886–10889.

- [26] Z. Wu, R. Feng, H. Li, J. Xu, G. Deng, M. Abe, D. Bégué, K. Liu, X. Zeng, *Angew. Chem. Int. Ed.* **2017**, *56*, 15672–15676; *Angew. Chem.* **2017**, *129*, 15878–15882.
- [27] C. M. Nunes, I. Reva, S. Kozuch, R. J. McMahon, R. Fausto, *J. Am. Chem. Soc.* **2017**, *139*, 17649–17659.
- [28] C. M. Nunes, A. K. Eckhardt, I. Reva, R. Fausto, P. R. Schreiner, *J. Am. Chem. Soc.* **2019**, *141*, 14340–14348.
- [29] T. Schleif, J. Mieres-Perez, S. Henkel, E. Mendez-Vega, H. Inui, R. J. McMahon, W. Sander, *J. Org. Chem.* **2019**, *84*, 16013–16018.
- [30] T. Schleif, J. Tatchen, J. F. Rowen, F. Beyer, E. Sanchez-Garcia, W. Sander, *Chem. Eur. J.* **2020**, <https://doi.org/10.1002/chem.202001202>.
- [31] C. Doubleday, R. Armas, D. Walker, C. V. Cosgriff, E. M. Greer, *Angew. Chem. Int. Ed.* **2017**, *56*, 13099–13102; *Angew. Chem.* **2017**, *129*, 13279–13282.
- [32] C. S. Michel, P. P. Lampkin, J. Z. Shezaf, J. F. Moll, C. Castro, W. L. Karney, *J. Am. Chem. Soc.* **2019**, *141*, 5286–5293.
- [33] A. Nandi, D. Gerbig, P. R. Schreiner, W. T. Borden, S. Kozuch, *J. Am. Chem. Soc.* **2017**, *139*, 9097–9099.
- [34] X. Li, T. Liao, L. W. Chung, *J. Am. Chem. Soc.* **2017**, *139*, 16438–16441.
- [35] S. Karmakar, A. Datta, *J. Phys. Chem. B* **2016**, *120*, 945–950.
- [36] C. Castro, W. L. Karney, *Angew. Chem. Int. Ed.* **2020**, *59*, 8355–8366; *Angew. Chem.* **2020**, *132*, 8431–8442.
- [37] S. Henkel, M. Ertelt, W. Sander, *Chem. Eur. J.* **2014**, *20*, 7585–7588.
- [38] E. Mendez-Vega, M. Maehara, A. H. Raut, J. Mieres-Perez, M. Tsuge, Y. P. Lee, W. Sander, *Chem. Eur. J.* **2018**, *24*, 18801–18808.
- [39] R. J. McMahon, O. L. Chapman, *J. Am. Chem. Soc.* **1987**, *109*, 683–692.
- [40] C. M. Nunes, S. N. Knezz, I. Reva, R. Fausto, R. J. McMahon, *J. Am. Chem. Soc.* **2016**, *138*, 15287–15290.
- [41] K. L. Gannon, M. A. Blitz, C. H. Liang, M. J. Pilling, P. W. Seakins, D. R. Glowacki, J. N. Harvey, *Faraday Discuss.* **2010**, *147*, 173–188.
- [42] J. B. Delos, *J. Chem. Phys.* **1973**, *59*, 2365–2369.
- [43] Q. Cui, K. Morokuma, J. M. Bowman, S. J. Klippenstein, *J. Chem. Phys.* **1999**, *110*, 9469–9482.
- [44] J. N. Harvey, M. Aschi, *Phys. Chem. Chem. Phys.* **1999**, *1*, 5555–5563.
- [45] J. C. Lorquet, B. Leyh-Nihant, *J. Phys. Chem.* **1988**, *92*, 4778–4783.
- [46] E. J. Heller, R. C. Brown, *J. Chem. Phys.* **1983**, *79*, 3336–3351.
- [47] G. E. Zahr, R. K. Preston, W. H. Miller, *J. Chem. Phys.* **1975**, *62*, 1127–1135.
- [48] J. C. Tully, *J. Chem. Phys.* **1974**, *61*, 61–68.
- [49] L. D. Landau, *Phys. Z. Sowjetunion* **1932**, *2*, 46.
- [50] C. Zener, *Proc. R. Soc. London Ser. A* **1932**, *137*, 696–702.
- [51] P. V. Coveney, M. S. Child, A. Barany, *J. Phys. B* **1985**, *18*, 4557–4580.
- [52] L. D. Landau, L. M. Lifshitz, *Quantum Mechanics. Nonrelativistic Theory*, Pergamon, Oxford, **1965**.
- [53] J. N. Harvey, *Wiley Interdiscip. Rev.: Comput. Mol. Sci.* **2014**, *4*, 1–14.
- [54] A. O. Lykhin, D. S. Kaliakin, G. E. Depolo, A. A. Kuzubov, S. A. Varganov, *Int. J. Quantum Chem.* **2016**, *116*, 750–761.
- [55] J. N. Harvey, *Phys. Chem. Chem. Phys.* **2007**, *9*, 331–343.
- [56] L. Reboussin, V. Wakelam, S. Guilloteau, F. Hersant, *Mon. Not. R. Astron. Soc.* **2014**, *440*, 3557–3567.
- [57] M. Minissale, E. Congiu, S. Baouche, H. Chaabouni, A. Moudens, F. Dulieu, M. Accolla, S. Cazaux, G. Manicó, V. Pirronello, *Phys. Rev. Lett.* **2013**, *111*, 1–5.
- [58] S. Hattori, J. A. Schmidt, D. W. Mahler, S. O. Danielache, M. S. Johnson, N. Yoshida, *J. Phys. Chem. A* **2012**, *116*, 3521–3526.
- [59] J. L. Chen, W. P. Hu, *J. Am. Chem. Soc.* **2011**, *133*, 16045–16053.

Manuscript received: May 7, 2020

Accepted manuscript online: June 17, 2020

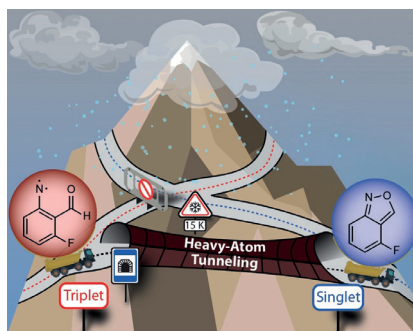
Version of record online: ■ ■ ■ ■ ■ ■ ■ ■ ■ ■

Research Articles

VIP Tunneling Reactions

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



Heavy-atom tunneling: The discovery of a new and distinct heavy-atom quantum mechanical tunneling (QMT) reaction is presented. Triplet *syn*-2-formyl-3-fluorophenylnitrene spontaneously cyclizes to singlet 4-fluoro-2,1-benzisoxazole under cryogenic conditions. Computational and experimental rate constants are in fair agreement and provide evidence for a mechanism involving heavy-atom QMT through crossing triplet to singlet potential energy surfaces.