Transformations of Strained Three-Membered Rings a Common, Yet Overlooked, Motif in Heavy-Atom Tunneling Reactions

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Abstract: Quantum mechanical tunneling has long been recognized as an important phenomenon when considering transformations dominated by a lightweight hydrogen atom. Tunneling of heavier atoms like carbon, initially dismissed as negligible, has seen a quickly increasing number of computationally predicted and/or experimentally confirmed examples over the last decade, thus highlighting its importance for a wide variety of reactions. However, no common structural motif has been pointed out within these seemingly unconnected examples, strongly limiting the predictability of the impact of heavy-atom tunneling on a given reaction. This Concept article will provide this perspective and showcase how the recognition of the formation and cleavage of three-membered rings as common motif can inform the prediction of and research into heavy-atom tunneling reactions.

Introduction

Quantum mechanical tunneling describes the ability of a molecular system to penetrate the potential barrier separating reactants and products rather than overcome it under the influx of thermal energy. It thus serves as an important lower limit for the rates of (exothermic) decay of metastable molecules at cryogenic temperatures, whilst also contributing to the classical thermal decay from higher vibrational states.[1] However, the degree to which tunneling impacts reactions (and thus the necessity to even account for it) strongly varies as the tunneling probability P depends on the mass m, width w and activation energy E_A [Eq. (1)].[2]

$$P \approx \exp[-w\pi^2(2mE_A)^{1/2}/h] \tag{1}$$

The mass dependency means that tunneling processes involving heavier nuclei ("heavy-atom tunneling", HeavyAT) exhibit a much lower probability than hydrogen tunneling. As a result, few experimentally confirmed or even theoretically predicted cases of HeavyAT reactions were known until roughly a decade ago. Recent years have seen an increasing number of

studies demonstrating the influence of HeavyAT in a broad variety of reactions.[2,3] However, exactly this wide range of HeavyAT reactions also poses a challenge: can a common structural motif be identified that signals a likely contribution from HeavyAT to a given reaction? Can it be predicted which classes of molecules should warrant special attention when estimating their synthetic feasibility? This Concept article addresses this gap in the literature by providing a structural rationale for the retroactive analysis as well as future prediction of HeavyAT reactions and highlighting the persistence of such common structural motif throughout the literature from the beginnings of HeavyAT research up to the present day.

Three-Membered Rings as Ideal Arrangements

When surveying the reactions for which a strong contribution by HeavyAT has been shown experimentally or predicted computationally, as collected by Borden[2] as well Castro and Karney[3] in two excellent reviews, it becomes obvious that a large majority of reactions represent the (trans)formation of a three-membered ring. Such frequent occurrence of the same structural motif that is being formed or cleaved speaks to the suitability of this arrangement of nuclei to facilitate HeavyAT reactions.

In order to understand why three-membered rings are such ideal arrangements for HeavyAT, one should consider the factors determining tunneling probability as presented in Equation (1). With a low mass of the atom(s) whose motion dominates the tunneling reaction, the range for a combination of barrier width w and height E_A resulting in an impactful tunneling probability is relatively wide. Thus, hydrogen tunneling ($m \approx 1$ u) allows for more varied transformations in which a greater barrier height can be compensated for by a smaller width and vice versa (Figure 1), even allowing for the sequential occurrence of multiple tunneling isomerizations.[4]

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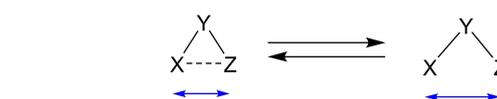
With HeavyAT, dominated by the motion of nuclei like carbon, nitrogen or oxygen ($m \approx 12$–16 u), the range of suitable barrier widths and heights resulting in non-negligible tunneling probabilities and thus observable tunneling rates is much more limited. Because the barrier width correlates with the distance that the "tunneling-determining" atom[5a] moves during the transformation, this translates to the heavy nucleus only moving by a very small distance during the reaction. As can be seen from the comparison in Figure 1, hydrogen atoms can travel over distances comparable to typical X—H bond distances despite noticeable barrier heights with tunneling probabilities that should allow for detection of such reaction under cryogenic conditions (as per estimates introduced by Kozuch).[5] Contrastingly, carbon atoms can only tunnel a fraction of the distance of a C—C bond length for almost any given barrier height.

As almost all reported HeavyAT reactions constitute unimolecular rearrangements, the two heavy nuclei (X and Z) should be attached to one another via a linker (Y; Scheme 1). In order for the change in geometries between reactant and product to be as small as possible, the linker should be of minimal length, that is, a single nucleus. These simple geometric considerations justify the common occurrence of three-membered rings as structural motifs in either the reactants or products of HeavyAT reactions. In the coming sections their contribution to individual examples for experimentally or computationally investigated tunneling reactions shall be showcased and analyzed within the context of ring closings, openings and expansions.
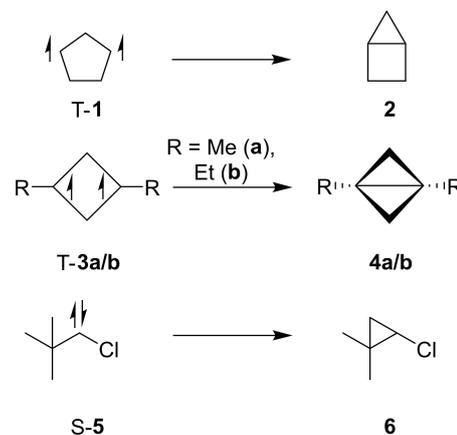
Ring Closing

Already the earliest experimentally confirmed cases of HeavyAT (with the notable exception of the automerization of cyclobutadiene)[11] constituted examples for the presence of a three-membered ring as a unifying structural motif (Scheme 2): Cyclopentane-1,3-diyl (T-**1**)[9a,b] and cyclobutane-1,3-diyls (T-**3a/b**)[9c] form strained bicyclic cyclopropanes (**2** and **4a/b**, respectively), similar to the formation of a substituted cyclopropane (**6**) from *tert*-butylchlorocarbene (S-**5**).[10] The strain energy built up in each of these three reactions is counter-balanced by the recombination of unpaired electrons or obtaining a full valence shell at the former carbene center,

Scheme 1. Schematic depiction of a HeavyAT reaction in which the distance between heavy nuclei X and Z changes over the course of the reaction (indicated by blue arrows), while they remain linked by a moiety Y.
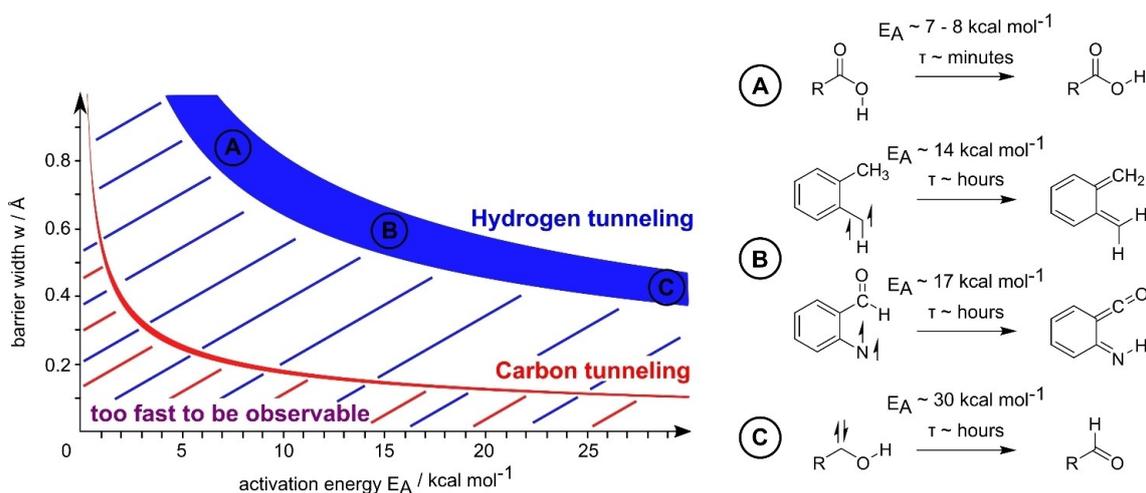

Scheme 2. Ring closing of diradicals T-**1** and T-**3a/b**[9] and *tert*-butylchlorocarbene (S-**5**).[10]

respectively. Such compensation provides these reactions with a great thermodynamic driving force that subsequently limits the barrier height, akin to the Bell–Evans–Polanyi principle, and thus contributes to a high tunneling probability.

Recent studies have shed some more light on these reactions: Sarkar et al. revisited the low-temperature chemistry of cyclopentane-1,3-diyl (T-**1**) and characterized its ring closing product for the first time in situ using matrix-isolation IR spectroscopy.[12] Meanwhile, Viegas et al. developed computational tools to address the simultaneous occurrence of intersystem crossing and tunneling in T-**1**.[13] Lastly, Schreiner in retrospect identified the ring closing of S-**5** as the first example of a reaction yielding a tunneling product, that is, a compound that can only be formed by tunneling while both thermodynamic and kinetic control would favor a 1,2-methyl shift.[14] Thus, interest in these classical examples of HeavyAT leading to the formation of three-membered rings proliferates till the current day.

Tim Schleif obtained his Ph.D. degree in 2019 under the guidance of Professor Wolfram Sander at the Ruhr-Universität Bochum. His research utilized matrix-isolation spectroscopy to study heavy-atom tunneling reactions and the influence of different (cryo)solvents on their kinetics. In June 2021, he joined the lab of Professor Mark A. Johnson at Yale University as a postdoctoral researcher, continuing his research on tunneling reactions by using cryogenic vibrational spectroscopy.

Ring Opening

More recent studies have found HeavyAT reactions opening cyclic structures and thus allowing for the release of ring strain (Scheme 3). The ring opening of cyclopropylcarbinyl (**7**), first predicted by Borden and co-workers,[19] could later be experimentally confirmed by analyzing the kinetic isotope effect in a collaboration of the groups of Borden and Singleton.[15] It also featured in a test set of 13 reactions that Doubleday et al. used to assess the relevance of HeavyAT in organic chemistry.[20] Two

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Figure 1. Comparison of reaction barriers in terms of height (activation energy E_A) and width (w) that would allow facile tunneling reactions at cryogenic temperatures. Areas colored in solid red (carbon tunneling, $m = 12$ u) or blue (hydrogen tunneling, $m = 1$ u) exhibit tunneling probabilities that fall within the spectroscopic window of matrix-isolation experiments, as estimated by the tunneling limit $2 \leq T_L \leq 2.6$ introduced by Kozuch;[5] areas shaded in red or blue represent regimes in which tunneling would occur too fast to be detectable with this technique. Different prototypical reaction types of intramolecular hydrogen tunneling are depicted to highlight their diversity (from top to bottom: rotamerization,[6] 1,4-H shift[7,4b] and 1,2-H shift[8]).
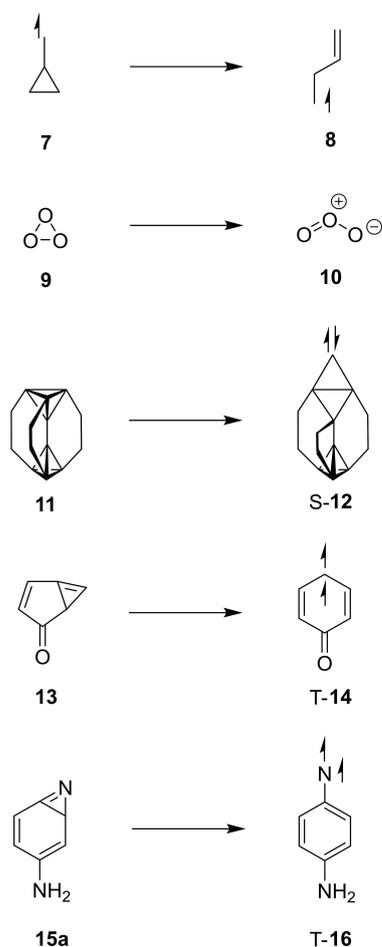
Scheme 3. Ring opening of cyclopropylcarbinyl (**7**),[15] cyclic ozone (**9**),[16] tetrahedryl-tetrahedrane (**11**),[5b] 1*H*-bicyclo[3.1.0]-hexa-3,5-dien-2-one (**13**)[17] and 4-amino-2*H*-benzazirine (**15a**).[18]

further computational predictions by Borden and co-workers address the effects of deuteration[21] or dimethylation[22] on the kinetics of this tunneling reaction. Unfortunately, a recent experimental study of the photolysis of (iodo)methylcyclopropane at $T \sim 10$ K did not detect **7**, but instead its rearrangement product **8**. This result likely indicates that the tunneling reaction proceeds too fast to be detected by matrix isolation.[23]

The most prototypical and instructive example for ring opening through HeavyAT concerns cyclic ozone (**9**). This O_3 allotrope had long attracted theoretical interest, all the while eluding experimental observation. For this reason, it featured prominently in the *Angewandte Chemie* editorial by Hoffmann, von Ragué Schleyer and Schaefer III calling for more stringent criteria when predicting the viability of a molecule.[24] While it does fulfill the criteria they set in terms of sufficiently high barriers to dissociation or isomerization, Chen and Hu computationally showed that the barrier of isomerization can be penetrated by facile oxygen tunneling, severely limiting the lifetime of **9**.[16] This case study resonates with a study by Kozuch who pointed out that the bridged tetrahedryl-tetrahedrane **11**, while theoretically possessing the shortest C—C bond on record, would also decay rapidly by tunneling at cryogenic temperatures.[5b] These reports highlight the importance to also check hypothetically feasible compounds for "tunneling instability",[25] especially when noticing the presence of a strained ring.

As evident from the ring opening of **11**, extreme ring strain can allow for the exothermic formation of a carbene despite its high reactivity. This point is further exemplified by the tunneling rearrangements of the strained **13**[17] or 4-amino-2*H*-benzazirine (**15a**),[18] yielding a triplet carbene and nitrene, respectively. Both reactants violate Bredt's rule by exhibiting a double bond at the bridgehead of a bicyclic system and thus

can overcome the thermodynamic penalty of forming highly reactive species. The ring opening of **13** was recently demonstrated to strongly accelerate in the presence of Lewis acids, offering a proof of concept for the catalysis of tunneling reactions.[26] 4-Amino-2*H*-benzazirine (**15a**), on the other hand, constitutes the only known example of a molecule in which two HeavyAT pathways compete at comparable timescales.[27] The strained azirine ring can either open to yield 4-aminophenylnitrene (T-**16**) or expand to form a ketenimine (**21a**, see Scheme 7, below), the latter being a common rearrangement of benzazirines that will be discussed in detail below. Both of these tunneling reactions are driven by the release of ring strain from the anti-Bredt benzazirine.

A debatable inclusion within this series of ring openings facilitated by HeavyAT concerns the (Curtius) rearrangement of trifluoroacetylnitrene (**17**, Scheme 4).[28] While its triplet ground state can hardly be called a three-membered ring, its singlet state on the other hand features a pseudo-oxazacyclopropane structure typical for singlet acyl nitrenes with $\alpha(N–C–O) = 90°$ and $d(N–O) = 1.80$ Å. The resulting ring strain presumably contributes significantly to the higher exothermicity as well as lower action energy of the [1,2]-CF$_3$-shift in **17** on the singlet surface ($E_A \sim 20$ kcal mol^{-1}) compared to the triplet surface ($E_A \sim 55$ kcal mol^{-1}), as calculated by Wu et al. These authors were also able to experimentally observe the HeavyAT rearrangement of T-**17** to (singlet) **18** with a minimum energy crossing point, that is, estimated effective activation barrier of ~ 14 kcal mol^{-1}. Thus it stems to reason that HeavyAT could also facilitate the ring-opening and simultaneous [1,3]-shift of a substituent in singlet acyl nitrenes though experimental evidence of such hypothesis is as of yet missing.
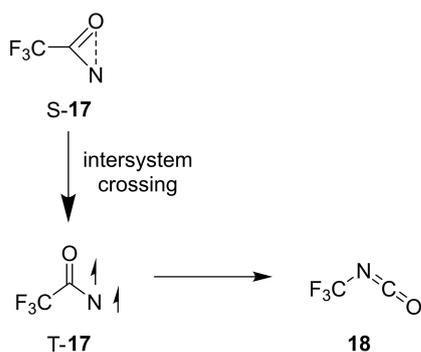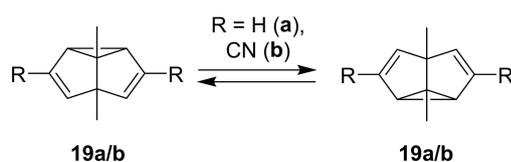
Simultaneous Ring Closing and Opening

The degenerate Cope rearrangement of 1,5-dimethylsemibullvalenes (**19a/b**, Scheme 5), predicted to be facilitated by HeavyAT by Borden and co-workers[30] and later experimentally investigated by the group of Sander,[29] poses an interesting conundrum: As a cyclopropyl ring is both formed and cleaved during this experimentally observed HeavyAT reaction, the ring opening or closing cannot provide any thermodynamic driving force, unlike the previous examples where the release of ring strain or radical recombination drove the reactions, respectively. Instead, the three-membered rings in reactant and product provide semibullvalene with a rigid boat-like conformation, favoring its Cope rearrangement and thus lowering the respective barrier (compared to the less rigid bullvalene and barbaralane[1]). During the tunneling reaction two pairs of carbon atoms have to move, opening the ring on one side of the molecule while simultaneously closing a ring on the other side.[30] Thus, the overall motion of the four carbon atoms mirrors the one allowing for the tunneling automerization of cyclobutadiene,[11] but in an antisymmetric fashion rather than the symmetric motion found in the latter case.

An intriguing computational result concerns the rearrangement of norbornadienylidene (**20**, Scheme 6): This highly reactive singlet carbene has been explicitly designed with the strain of three-membered rings in mind, as the carbene center approaches either of the double bonds as it would during the course of a cyclopropanation reaction. However, the enormous amount of ring strain that would result from this intramolecular cycloaddition keeps the carbene at an intermediary geometry (stabilized by a three-center two-electron bond with the alkene moiety), with the carbene center leaning to either of the two double bonds. This so-called foiled carbene[31] has the potential to exhibit "ping-pong tunneling",[32] with a single carbon atom swinging between the double-well minima, simultaneously ring closing and opening the partially formed three-membered rings. However, for the parent norbornadienylidene **20** the tunneling probability and subsequent reaction rate can be calculated to be negligible below 100 K, thus necessitating derivatization in order to aim for an experimentally observable automerization at cryogenic temperatures.[1]


Scheme 4. [1,2]-CF$_3$ shift of trifluoroacetylnitrene (**17**).[28]

Scheme 5. Degenerate simultaneous ring opening and closing in 1,5-dimethylsemibullvalenes **19a/b**.[29]
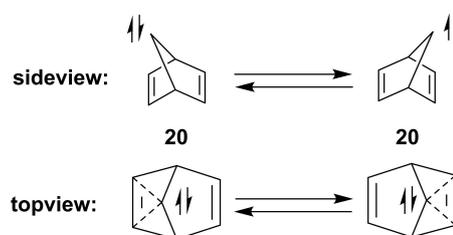
Scheme 6. Degenerate rearrangement of norbornadienylidene (**20**) viewed from the side (top) and top (bottom).[1]

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Ring Expansion

Within the last couple of years, HeavyAT research has extensively investigated ring expansions of three-membered heterocycles fused to cyclohexadienes (Scheme 7). The first report within this line of research found that 4-thiomethoxy-2*H*-benzazirine (**15 d**) rearranges at cryogenic temperatures while the corresponding 4-methoxy derivative does not react under these conditions.[33a] Nunes et al. expanded upon this study by investigating the 2-formyl derivative **15 b** whose ring expansion by tunneling could be greatly accelerated under the influx of IR radiation.[33b] Conformer-specific HeavyAT could be demonstrated for the first time by investigation of the four isomeric benzazirines accessible through the photochemistry of 4-methoxyphenylnitrene (among them **15 e**), while also reporting the tunneling rearrangement of 3,5-difluorobenzazirine (**15 c**).[33c] Lastly, as mentioned above, 4-amino-2*H*-benzazirine (**15 a**) could be shown to undergo two competing tunneling rearrangements, both cleaving its strained three-membered ring, as it can undergo ring expansion to ketenimine **21 a** in addition to the ring opening yielding nitrene T-**16** discussed earlier.[18] Ultimately, the diversity of these examples demonstrates the general propensity of benzazirines to undergo ring expansions through contribution from HeavyAT and likely points to similar chemistry for related anti-Bredt compounds, driven by the release of ring strain.

Less strained, but equally prone to ring expansion by tunneling are the bicyclic benzene oxide (**22**) and benzene imine (**24**). The ring opening of **24** to yield 1*H*-azepine (**25**) was investigated computationally, predicting tunneling contributions to both the ring opening as well as the subsequent *endo–exo* isomerization.[35] Meanwhile, a recent experimental investigation at cryogenic temperatures was instrumental in clarifying the energetics of the valence tautomerization between **22** and oxepin (**23**).[34] Furthermore, the direction of the interconversion between them through tunneling could actually be inverted by solvent interaction. This demonstrates once more the versatility of the three-membered ring in promoting both ring closure or opening through HeavyAT due to the close proximity of the atoms whose motion dominates the tunneling reaction.
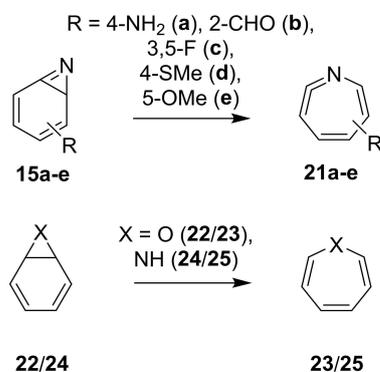
Scheme 7. Electrocyclic ring expansions of benzazirines **15 a–e**,[18,32] benzene oxide (**22**),[34] and benzene imine (**24**).[35]
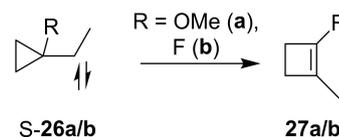
Scheme 8. Ring expansion of cyclopropylmethylcarbenes S-**26 a/b**.

The final example for HeavyAT promoting the ring expansion of a cyclopropane ring comes from a computational study by Kozuch et al. that investigated this reaction in cyclopropylmethylcarbenes S-**26 a/b** (Scheme 8) and contrasted it with their propensity to undergo hydrogen migration.[36] This reactivity resonates with similar, experimentally observed ring expansions of cyclobutyl- or noradamantylcarbenes.[37] The rearrangements barely relieve the ring strain as they result in similarly strained cyclic alkenes or, in the case of noradamantyl-chlorocarbene, even an anti-Bredt compound. However, the thermodynamic driving force comes from the high reactivity of the reactants, similar to the ring closing reactions discussed above.

Conclusion

Reactions involving three-membered rings make up a majority of computationally and/or experimentally demonstrated transformations involving heavy-atom tunneling. The close proximity of two heavy nuclei enforced by this structural motif allows for their minimal displacement, reflecting a narrow barrier width and thus high tunneling probability. Additionally, ring strain can provide a great thermodynamic driving force for ring opening or expansion, and thus guarantee a suitably small activation barrier, for example, in bicyclic (hetero)cyclopropenes violating Bredt's rule. On the other hand, a highly reactive species like a diradical can undergo rapid ring closing to a three-membered ring. These reaction types throughout the literature on heavy-atom tunneling have been surveyed and put into context to serve as a guideline for future research into this still underappreciated phenomenon. On top of that, this Concept article should inform computational predictions to take into account potential tunneling rearrangements of three-membered rings, which can severely limit the lifetime of a hypothetically proposed molecule.

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Conflict of Interest

The authors declare no conflict of interest.

Data Availability Statement

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

[1] S. Kozuch, T. Schleif, A. Karton, *Phys. Chem. Chem. Phys.* **2021**, *23*, 10888–10898.

[2] W. T. Borden, *Wiley Interdiscip. Rev.: Comput. Mol. Sci.* **2016**, *6*, 20–46.

[3] C. Castro, W. L. Karney, *Angew. Chem. Int. Ed.* **2020**, *59*, 8355–8366; *Angew. Chem.* **2020**, *132*, 8431–8442.

[4] a) P. R. Schreiner, J. P. Wagner, H. P. Reisenauer, D. Gerbig, D. Ley, J. Sarka, A. G. Császár, A. Vaughn, W. D. Allen, *J. Am. Chem. Soc.* **2015**, *137*, 7828–7834; b) T. Lohmiller, S. K. Sarkar, J. Tatchen, S. Henkel, T. Schleif, A. Savitsky, E. Sanchez-Garcia, W. Sander, *Chem. Eur. J.* **2021**, *27*, 17873–17879.

[5] a) S. Kozuch, *Phys. Chem. Chem. Phys.* **2014**, *16*, 7718–7727; b) S. Kozuch, *Org. Lett.* **2014**, *16*, 4102–4105.

[6] M. Tsuge, L. Khriachtchev, *J. Phys. Chem. A* **2015**, *119*, 2628–2635.

[7] C. M. Nunes, S. N. Knezz, I. Reva, R. Fausto, R. J. McMahon, *J. Am. Chem. Soc.* **2016**, *138*, 15287–15290.

[8] A. K. Eckhardt, F. R. Erb, P. R. Schreiner, *Chem. Sci.* **2019**, *10*, 802–808.

[9] a) S. L. Buchwalter, G. L. Closs, *J. Am. Chem. Soc.* **1975**, *97*, 3857–3858; b) S. L. Buchwalter, G. L. Closs, *J. Am. Chem. Soc.* **1979**, *101*, 4688–4694; c) M. B. Sponsler, R. Jain, F. D. Coms, D. A. Dougherty, *J. Am. Chem. Soc.* **1989**, *111*, 2240–2252.

[10] P. Zuev, R. S. Sheridan, *J. Am. Chem. Soc.* **1994**, *116*, 4123–4124.

[11] B. K. Carpenter, *J. Am. Chem. Soc.* **1983**, *105*, 1700–1701.

[12] S. K. Sarkar, E. Solel, S. Kozuch, M. Abe, *J. Org. Chem.* **2020**, *85*, 8881–8892.

[13] L. P. Viegas, C. M. Nunes, R. Fausto, *Phys. Chem. Chem. Phys.* **2021**, *23*, 5797–5803.

[14] P. R. Schreiner, *J. Am. Chem. Soc.* **2017**, *139*, 15276–15283.

[15] O. M. Gonzalez-James, X. Zhang, A. Datta, D. A. Hrovat, W. T. Borden, D. A. Singleton, *J. Am. Chem. Soc.* **2010**, *132*, 12548–12549.

[16] J.-L. Chen, W.-P. Hu, *J. Am. Chem. Soc.* **2011**, *133*, 16045–16053.

[17] a) M. Ertelt, D. A. Hrovat, W. T. Borden, W. Sander, *Chem. Eur. J.* **2014**, *20*, 4713–4720; b) W. Sander, G. Bucher, F. Reichel, D. Cremer, *J. Am. Chem. Soc.* **1991**, *113*, 5311–5322.

[18] C. M. Nunes, A. K. Eckhardt, I. Reva, R. Fausto, P. R. Schreiner, *J. Am. Chem. Soc.* **2019**, *141*, 14340–14348.

[19] A. Datta, D. A. Hrovat, W. T. Borden, *J. Am. Chem. Soc.* **2008**, *130*, 6684–6685.

[20] 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.

[21] X. Zhang, A. Datta, D. A. Hrovat, W. T. Borden, *J. Am. Chem. Soc.* **2009**, *131*, 16002–16003.

[22] X. Zhang, D. A. Hrovat, A. Datta, W. T. Borden, *Org. Biomol. Chem.* **2011**, *9*, 3142–3145.

[23] T. Schleif, W. Sander, *J. Phys. Org. Chem.* **2022**, *35(2)*, e4295.

[24] R. Hoffmann, P. v. R. Schleyer, H. F. Schaefer III, *Angew. Chem. Int. Ed.* **2008**, *47*, 7164–7167; *Angew. Chem.* **2008**, *120*, 7276–7279.

[25] H. Amlani, A. Frenklah, S. Kozuch in *Tunnelling in Molecules: Nuclear Quantum Effects from Bio- to Physical Chemistry* (Eds.: J. Kästner, S. Kozuch), The Royal Society of Chemistry, **2021**, pp. 61–87.

[26] S. Henkel, M. Prado Merini, E. Mendez-Vega, W. Sander, *Chem. Sci.* **2021**, *12*, 11013–11019.

[27] C. M. Nunes, A. K. Eckhardt, I. Reva, R. Fausto, P. R. Schreiner, *J. Am. Chem. Soc.* **2019**, *141*, 14340–14348.

[28] 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.

[29] a) T. Schleif, J. Tatchen, J. F. Rowen, F. Beyer, E. Sanchez-Garcia, W. Sander, *Chem. Eur. J.* **2020**, *26*, 10452–10458; b) T. Schleif, J. Mieres-Perez, S. Henkel, M. Ertelt, W. T. Borden, W. Sander, *Angew. Chem. Int. Ed.* **2017**, *56*, 10746–10749; *Angew. Chem.* **2017**, *129*, 10886–10889.

[30] X. Zhang, D. A. Hrovat, W. T. Borden, *Org. Lett.* **2010**, *12*, 2798–2801.

[31] R. Gleiter, R. Hoffmann, *J. Am. Chem. Soc.* **1968**, *90*, 5457–5460.

[32] a) A. Nandi, A. Sucher, S. Kozuch, *Chem. Eur. J.* **2018**, *24*, 16348–16355; b) A. Nandi, A. Sucher, A. Tyomkin, S. Kozuch, *Pure Appl. Chem.* **2020**, *92*, 39–47.

[33] a) H. Inui, K. Sawada, S. Oishi, K. Ushida, R. J. McMahon, *J. Am. Chem. Soc.* **2013**, *135*, 10246–10249; b) C. M. Nunes, I. Reva, S. Kozuch, R. J. McMahon, R. Fausto, *J. Am. Chem. Soc.* **2017**, *139*, 17649–17659; c) T. Schleif, J. Mieres-Perez, S. Henkel, E. Mendez-Vega, H. Inui, R. J. McMahon, W. Sander, *J. Org. Chem.* **2019**, *84*, 16013–16018.

[34] T. Schleif, M. Prado Merini, W. Sander, *Angew. Chem. Int. Ed.* **2020**, *59*, 20318–2032; *Angew. Chem.* **2020**, *132*, 20498–20502.

[35] N. Mandal, A. Das, C. Hajra, A. Datta, *Chem. Sci.* **2022**, *13*, 704–712.

[36] A. Nandi, D. Gerbig, P. R. Schreiner, W. T. Borden, S. Kozuch, *J. Am. Chem. Soc.* **2017**, *139*, 9097–9099.

[37] a) P. S. Zuev, R. S. Sheridan, T. V. Albu, D. G. Truhlar, D. A. Hrovat, W. T. Borden, *Science* **2003**, *299*, 867–870; b) R. A. Moss, R. R. Sauers, R. S. Sheridan, J. Tian, P. S. Zuev, *J. Am. Chem. Soc.* **2004**, *126*, 10196–10197.