COMMUNICATION

Inducing Molecular Reactions by Selective Vibrational Excitation of a Remote Antenna with Near-Infrared Light

Received 00th January 20xx,
Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

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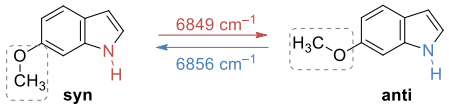
We demonstrate here that selective vibrational excitation of a moiety, remotely attached in relation to the molecular reaction site, might offer a generalized strategy for inducing bond-breaking/bond-forming reactions with exquisite precision. As a proof-of-principle, the electrocyclic ring-expansion of a benzazirine to a ketenimine was induced, in a cryogenic matrix, by near-IR light tuned at the overtone stretching frequency of its OH remote antenna. This accomplishment paves the way for harnessing IR vibrational excitation as a tool to guide a variety of molecular structure manipulations in unprecedent highly-selective fashion.

Since the invention of lasers in the 1960s, chemists have dreamt of using infrared (IR) laser radiation to manipulate matter in an unprecedented selective way.[1–4] The possibility of selectively manipulate a chosen molecular species in a complex mixture, including the manipulation of a specific conformation existing in a particular environment, has been demonstrated using vibrational excitation in conjugation with the matrix isolation technique.[5,6] In this context, narrowband IR-light is applied to selectively deposit energy in a vibrational state of a particular molecular system. If subsequent energy dissipation by intramolecular vibrational redistribution is partially channeled to a reaction coordinate, a transformation might be induced with a potential exquisite precision.[7,8]

In the last twenty years, this methodology has been employed to manipulate molecular conformations of different types of organic compounds, such as carboxylic acids,[9,10] alcohols,[11,12] amino acids,[13,14] and nucleic acid derivatives.[15] Most of the reported cases comprise the vibrational excitation of an OH moiety (typically at its first stretching overtone) and conformational isomerization at the same OH moiety or at an adjacent CC bond. A significant development was made in 2015, when the interconversion between two conformers was shown to be possible by selective vibrational excitation of a moiety (antenna), remotely located from the conformational isomerization coordinate (Scheme 1).[16,17]



Scheme 1. Conformational changes in 6-methoxyindole (Xe, 30 K) induced by vibrational excitation of the remote NH antenna at its first stretching overtone.[16]

In 2020, we demonstrated that, besides conformational isomerizations, bond-breaking/bond-forming reactions can also be induced by IR vibrational excitation under matrix isolation conditions.[18,19] In that breakthrough investigation, the bidirectional tautomerization (thione-enol ↔ thiol-keto) of thiotropolone was triggered by IR-irradiation of the corresponding reactant tautomeric form. A few other separate studies[20] have also reported examples of bond-breaking or bond-breaking/bond-forming reactions promoted by vibrational excitation of organic molecules in gas-phase at low-pressure[21–24] and in solution.[25–27] However, the use of IR vibrational excitation to induce transformations of organic molecules still remains vastly unexplored and hindered by the lack of a functioning approach.

Herein, we set the stage for a generalized approach aiming to induce bond-breaking/bond-forming reactions in organic molecules by IR vibrational excitation. Our envisioned strategy consists of using a vibrational antenna remotely located from the reaction center of the target molecule, following the principle previously established to control conformational changes. As a proof-of-principle of such approach, we demonstrate here that selective vibrational excitation of the OH moiety of benzazirine **3** successfully triggers its electrocyclic ring-expansion to cyclic ketenimine **4** (Scheme 2).

Benzazirines are highly reactive intermediates, with very low-energy barriers for ring-opening to phenylnitrenes and ring-expansion to cyclic ketenimines.[28–30] Therefore, they are particularly suitable species to be activated by IR vibrational excitation. The presence of two *ortho* fluorine atoms in a

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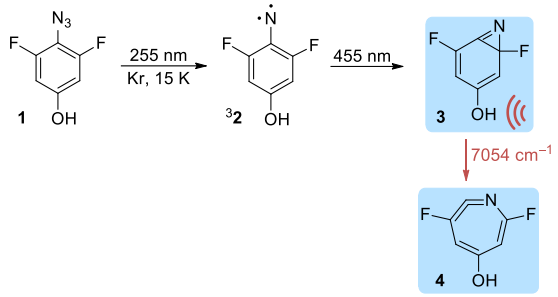
† Electronic Supplementary Information (ESI) available: For experimental and computational methods, additional figures and tables, and computational data see DOI: 10.1039/x0xx00000x

benzazirine is known to increase the reactions barriers enough to make the system stable against tunneling and allow its capture under cryogenic conditions.[31,32] In the present study, the introduction of a *para* OH substituent was conceived to act as a remote vibrational antenna. Thus, 4-hydroxy-2,6-difluoro-2*H*-benzazirine **3** resulted as an idealized target for the realization of this proof-of-principle study.



Scheme 2. Summary of the experimental results concerning the ring-expansion of benzazirine **3** to cyclic ketenimine **4** (Kr, 15 K) induced by vibrational excitation of the remote OH antenna at its first stretching overtone (7054 cm^{-1}).

The precursor, 2,6-difluoro-4-hydroxyphenylazide **1**, was synthesized as described in detail in the Supporting Information (SI). Cryogenic matrices of **1** were prepared by sublimating the sample at room temperature and co-deposited it with a large excess of Kr onto a CsI window at 15 K (Fig. S1). The UV-irradiation (λ = 255 nm) of matrix-isolated **1** leads to triplet 2,6-difluoro-4-hydroxyphenylnitrene ^{3}**2**. The bands that appear in the IR spectrum after irradiation of **1** are well reproduced by the B3LYP/6-311+G(2d,p) computed IR spectrum of ^{3}**2** (Fig. 1a,b). Particularly characteristic are the most intense IR bands observed at 1602/1599, 1468, 1220, 1139/1137 and 1018 cm^{-1}, which nicely match the most intense computed IR bands of ^{3}**2** at 1598 [ν(CC)], 1453 [ν(CC)], 1206 [δ(CH)], 1134 [ν(CO)] and 1007 [$\nu(CF)_{as}$] cm^{-1}. A detailed assignment of the IR spectrum of nitrene ^{3}**2** is provided in Table S1.

Subsequent visible-light irradiation of nitrene ^{3}**2**, at the low-energy edge of its first absorption band (λ = 445 nm),[33] was found to produce mainly *syn*-2,6-difluoro-4-hydroxy-2*H*-benzazirine **3s**. With the exception of a few minor bands of an unidentified product,[34] the bands that emerge in the IR spectrum after consumption of ^{3}**2** have a good correspondence with the B3LYP/6-311+G(2d,p) computed IR spectrum of **3s** (Fig. 1c,d). Most representative are the IR bands observed at 1620, 1316, 1201, 1144, 1118/1111 and 934/932 cm^{-1}, which are well reproduced by the high intensity computed IR bands of **3s** at 1614 [ν(C=C)], 1308 [δ(CH), ν(C-C)], 1185 [ν(CF)], 1134 [ν(CO)], 1095 [ν(CF)] and 918 [ν(C-C)] cm^{-1}. The characteristic absorption due to the ν(C=N) mode of **3s** is identified at 1685 cm^{-1}, near the absorption frequency previously reported for the 2,6-difluoro-2*H*-benzazirine analog (1679 cm^{-1}, Ar matrix at 10 K).[32] The presence of the *anti*-OH conformer **3a** was excluded, as some of its distinctive computed IR bands have no correspondence in the experimental IR spectrum (Fig. S2). A comprehensive assignment of the IR spectrum of benzazirine **3s** is given in Table S2, supported also by additional data addressed in the next section. According to our expectation, **3s** was found to be stable in a Kr matrix at 15 K (no trace of any transformation was detected after waiting 24 h).

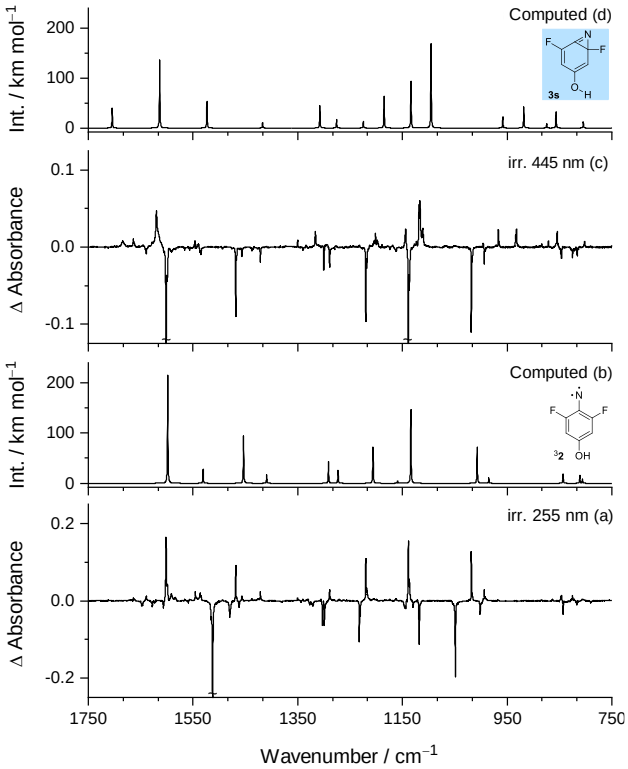


Fig. 1. Experimental difference IR spectrum showing changes that result from: (a) irradiation of azide **1** at 255 nm (8 min, 30 mW, Kr matrix at 15 K); (c) irradiation of triplet nitrene ^{3}**2** at 445 nm (50 min, 100 mW, Kr matrix at 15 K). B3LYP/6-311+G(2d,p) computed IR spectrum of: (b) triplet nitrene ^{3}**2**; and (d) benzazirine **3s**.

Relevant for the present investigation was the identification of the first OH stretching overtone in the near-IR spectra. Upon irradiation of matrix-isolated **1** at 255 nm, the IR bands due to the 2ν(OH) and ν(OH) modes of ^{3}**2** were identified at 7051 and 3612 cm^{-1}, in a reasonable match with the corresponding anharmonic B3LYP/SNSD computed absorptions at 7099 and 3634 cm^{-1} (Fig. 2; see also Fig. S3). After consumption of almost all ^{3}**2** by irradiation at 445 nm, the IR bands due to the 2ν(OH) and ν(OH) modes of **3s** were identified at 7054 and 3612 cm^{-1}, having the corresponding anharmonic B3LYP/SNSD computed absorptions at 7103 and 3636 cm^{-1} (Fig. 2). Although the ν(OH) absorption of **3s** and ^{3}**2** is practically coincident, the 2ν(OH) absorption of **3s** is shifted by +3 cm^{-1} in relation to ^{3}**2**, thus being fairly well reproduced by the anharmonic computations, which estimate a shift of +4 cm^{-1}.

The IR-induced chemistry of benzazirine **3s** was then explored by selective vibrational excitation of its OH antenna. A sample of **3s** (Kr, 15 K) was irradiated with narrowband (FWHM ≈ 0.2 cm^{-1}) IR-light, provided by an optical parametric oscillator pumped with a pulsed Nd:YAG laser, tuned at its 2ν(OH) frequency of 7054 cm^{-1}. Monitoring the process after 30 min, by IR spectroscopy, reveals a large-scale conversion (> 50 %) of **3s** into the cyclic ketenimine *anti*-3,7-difluoro-5-hydroxy-1-aza-1,2,4,6-cycloheptatetraene **4a**.[35] The negative and positive bands in the experimental difference IR spectrum are in excellent agreement with the B3LYP/6-311+G(2d,p) computed

IR spectra of **3s** and **4a**, respectively (Fig. 3). The depleted IR bands correspond to those previously identified for **3s** (assigned in Table S2); e.g. matching the most representative ones observed at 1620, 1316, 1201, 1144, 1118/1111, 934/932 cm^{-1}. The most intense emerging IR bands were observed at 1592/1584, 1542/1536, 1426, 1306, 1217 and 1139 cm^{-1}, which are in good correspondence with the most intense computed IR bands of **4a** at 1581 [ν(C=C)], 1525 [ν(C=C)], 1419 [δ(OH), ν(C-C), δ(CH)], 1293 [$\nu(C{=}C{=}N)_s$], 1196 [ν(CF)] and 1133 [ν(CO)] cm^{-1}. The characteristic absorption due to the $\nu(C{=}C{=}N)_s$ mode of **4a** is identified at 1823 cm^{-1}, near the absorption frequency previously reported for the 3,7-difluoro-1-aza-1,2,4,6-cycloheptatetraene analog (1830 cm^{-1}, Ar matrix at 10 K).[32] The 2ν(OH) and ν(OH) bands of **4a** were observed at 7038 and 3605 cm^{-1} (Fig. S4). The presence of the *syn*-OH conformer **4s** can be safely excluded, as some of its distinctive computed IR bands have no correspondence in the experimental IR spectrum (Fig. S5). A detailed assignment of the experimental IR spectrum of **4a** is provided in Table S3.

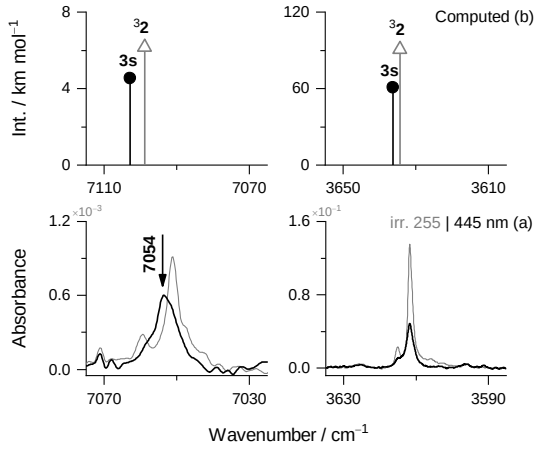


Fig. 2. (a) Selected regions of the experimental near-IR (left) and mid-IR (right) spectra: (gray line) after irradiation of azide **1** at 255 nm (8 min, 30 mW, Kr matrix at 15 K) and production of triplet nitrene ^{3}**2**; (black line) after irradiation of ^{3}**2** at 445 nm (50 min, 100 mW, Kr matrix at 15 K) and production of benzazirine **3s**. (b) Anharmonic wavenumbers and IR intensities computed at the B3LYP/SNSD level for the 2ν(OH) (left) and ν(OH) (right) modes of ^{3}**2** (triangles) and **3s** (circles).

To better understand the experimental observations, we computed the potential energy surface around benzazirine **3s** (Fig. 4). At the CCSD(T)/cc-pVTZ//B3LYP/6-311+G(2d,p) level, the OH-rotamerization barrier of **3a** to the most stable conformer **3s** is 1.8 kcal mol^{-1}, whereas the barrier of **4s** to the most stable **4a** is 3.5 kcal mol^{-1}. With such low-energy barriers, fast OH-rotamerization tunneling is expected to preclude the isolation of the higher-energy conformers **3a** and **4s**, as it has been reported for other phenol derivatives studied in noble-gas matrices.[36–39] Indeed, tunneling calculations using the Wentzel–Kramers–Brillouin model (see details in SI) estimate very short half-lives for **3a** [$\tau_{1/2}$ ~10^{-7} s] and **4s** [$\tau_{1/2}$ ~10^{-4} s], which justify the exclusive identification of benzazirine **3s** and ketenimine **4a** in the performed experiments. In this regard, it is likely that the IR vibrational excitation of **3s** induces ring-expansion to **4s**, which then undergoes fast OH-rotamerization tunneling to the observed product **4a**. At the CCSD(T)/cc-pVTZ//B3LYP/6-311+G(2d,p) level, the ring-expansion barrier of **3s** to **4s** is 10.1 kcal mol^{-1} (well below the ~20 kcal mol^{-1} of vibrational energy deposited in **3s**).

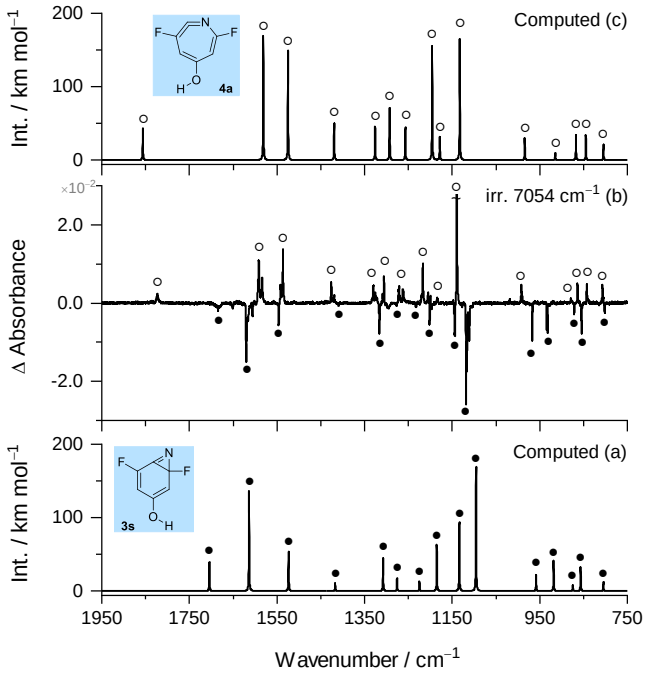


Fig. 3. B3LYP/6-311+G(2d,p) computed IR spectrum of: (a) benzazirine **3s**; and (c) cyclic ketenimine **4a**. (b) Experimental difference IR spectrum showing changes after irradiation at 7054 cm^{-1} (30 min, 100 mW, Kr matrix at 15 K), subsequent to the production of **3s** by irradiation of ^{3}**2** at 455 nm. The downward bands are due to consumed species assigned to **3s** (closed circles). The upward bands are due to the produced species assigned to **4a** (open circles).

Another possible bond-breaking/bond-forming reaction that could result from the vibrational excitation of **3s** is the ring-opening to open-shell singlet nitrene ^{1}A''-**2**, which subsequently should be followed by fast intersystem crossing to triplet ground state ^{3}**2**. Since ^{1}A''-**2** cannot be correctly described with a single-determinant wavefunction, computations were also carried out with multiconfigurational methods (see details in SI). At our best available MRMP/cc-pVTZ//CASSCF(8,8)/cc-pVTZ level, the ring-opening barrier of **3s** to ^{1}A''-**2** is 7.2 kcal mol^{-1}, whereas the ring-expansion barrier of **3s** to **4s** is 4.8 kcal mol^{-1} (such barriers are most probably underestimated by 3–5 kcal mol^{-1}, judging by the MRMP/cc-pVTZ//CASSCF(8,8)/cc-pVTZ underestimation of ~4 kcal mol^{-1} found for the reaction of the 2-fluoro-2*H*-benzazirine **3'** analog to ^{1}A''-**2'** and to **4'**; see Fig. S8).[40] Thus, computations indicate that the IR vibrational excitation of **3s** triggers exclusively the most favorable bond-breaking/bond-forming reaction, i.e. the ring-expansion to **4s**. On the other hand, it is clear that the competitive OH-rotamerization of **3s** to **3a** is a less energetic pathway. However, as mentioned above, **3a** should convert back to **3s** by fast tunneling, making its observation impossible. In any case, remarkably, the existence of this pathway does not preclude the energy deposited into the OH antenna of **3s** to be efficiently transferred to the remote ring-expansion reaction coordinate leading to **4s**.

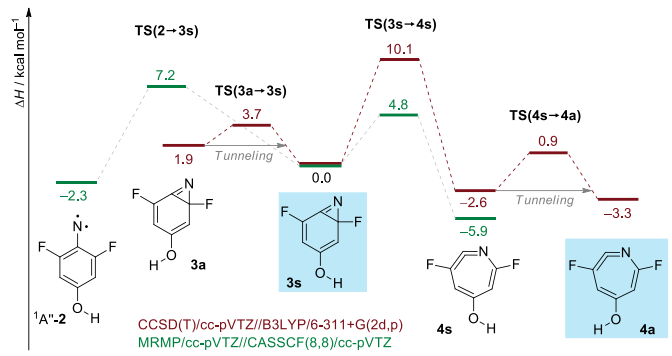


Fig. 4. Reaction pathways for benzazirine **3s** computed at CCSD(T)/cc-pVTZ//B3LYP/6-311+G(2d,p) + ZPVE (red) and MRMP/cc-pVTZ//CASSCF(8,8)/cc-pVTZ + ZPVE (green) levels of theory. ^{1}A'' = open-shell singlet state.

In summary, we demonstrated here 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. Harnessing the power of vibrationally induced chemistry creates unprecedented opportunities for highly-selective transformations, in ways not attainable by thermal or electronic excitation processes.

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 CQC is funded by the FCT through the projects UIDB/QUI/00313/2020 and UIDP/QUI/00313/2020. C.M.N. thanks the FCT for an Auxiliary Researcher grant. N.A.M.P. acknowledges the Project POCI-01-0145-FEDER-028973 for a Junior Researcher grant. L.P.V. acknowledges CQC for a Junior Researcher grant. José P. L. Roque is acknowledged for the participation in preliminary experiments.

Conflicts of interest

There are no conflicts to declare

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40 We have previously found that NEVPT2 computations also underestimated in 4–5 kcal mol^{-1} the ring-expansion barrier of a benzazirine to a cyclic ketenimine, whereas CCSD(T) computations provided a good rationalization for the experimental observations (see ref. 29). Here, we also found that CCSD(T) computations for the ring-expansion barrier of **3'** to **4'** is in excellent agreement with the experimental results (see Fig. S8).

