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Perturbation of Pyridinium CIVP Spectra by N₂ and H₂ Tags: an Experimental and BOMD Study

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This contribution is dedicated to Prof. Dr. Josef Michl

Abstract

In cryogenic ion vibrational predissociation (CIVP) spectroscopy, the influence of the tag on the spectrum is an important consideration. Whereas for small ions there have been several studies showing that the tag effects can be significant, these effects are less understood for large ions, or for large numbers of tags. Nevertheless, it is commonly assumed that if the investigated molecular ion is large enough, the perturbations arising from the tag are small, and can therefore be neglected in the interpretation. In addition, it is generally assumed that the more weakly bound the tag is, the less it perturbs the CIVP spectrum. Under these assumptions, CIVP spectra are claimed to be effectively IR absorption spectra of the free molecular ion. Having observed unexpected splittings in otherwise unproblematic CIVP spectra of some tagged ions, we report Born-Oppenheimer molecular dynamics (BOMD) simulations that strongly indicate that mobility among the more weakly bound tags leads to the surprise splittings. We compared the behavior of two tags commonly used in CIVP spectroscopy (H₂ and N₂) with a large pyridinium cation. Our experimental results surprisingly show that the more weakly bound tag can, under the appropriate circumstances, perturb the CIVP spectra more than the more strongly bound tag, by not just shifting, but also splitting the observed bands. The more weakly bound tag had significant residence times at several spectroscopically distinct sites on the molecular ion. This indicates that the weakly bound tag is likely to sample several binding sites in the experiment, some of which involve interaction with the reporter chromophore.

Introduction

During the past couple of decades, electrospray ionization mass spectrometry (ESI-MS) has proven to be a useful tool for mechanistic studies, due to its ability to transfer ions of interest from solution into the gas phase under soft conditions.¹ Remarkable progress in the advanced mass spectrometry tools, such as infrared (IR) ion spectroscopy, has added greatly to the confidence of the structural assignment of gaseous ions and helped in the investigation of many organic and organometallic reactions.²⁻⁵

One way to study IR spectroscopy of gaseous ions is cryogenic ion vibrational predissociation (CIVP) spectroscopy. It requires the use of weakly binding so-called messenger tags (e.g., He, Ne, Ar, H₂, or N₂),^{6,7} which associate with the ion of interest at low temperatures, and dissociate due to an increase in

the internal energy when the ion absorbs an IR photon. The absorption-induced dissociation can be monitored by a customized mass spectrometer, which allows recording the relative intensities of tagged and untagged ions as a function of the IR wavelength. This produces a spectrum which should, in the best case scenario, mimic the conventional gas-phase IR spectrum of the ion; in other words, a CIVP spectrum is a surrogate for the IR spectrum. The CIVP method was first described in 1986 by the Lee group, who recorded IR spectra of small protonated water clusters with H₂ tags.⁸ In that study, they noted that the greatest uncertainty in their spectra was the possible perturbation by the tag, which was, however, reckoned to be small.

We have recently started studying IR spectra of large ions in the gas phase by CIVP. In our first publication on the topic, we showed that the CIVP spectrum of [Ag(PPh₃)₂]⁺ was relatively insensitive to the type of tag,⁹ as commonly expected. We recently reported a CIVP study of a gas-phase molecular torsion balance (an *ortho*-substituted pyridinium ion), which similarly gave consistent results with several tags.¹⁰ However, in the same study, we noted that the tag appeared to be not completely innocent in the case of at least one *meta*-substituted pyridinium ion. Namely, we observed a red shift of ~25 cm⁻¹ in the signal of the N-H stretching vibration when we changed the tag from H₂ to N₂. In the course of investigating this effect, we found an unexpected, "capricious" splitting in some of the CIVP spectra of the H₂- and D₂-tagged pyridinium ion **1** (Figure 1), which, given our intended use of the CIVP spectra to probe conformational dynamics, demanded an explanation. We report Born-Oppenheimer molecular dynamics (BOMD) simulations for the calculation of the IR spectrum for pyridinium ion **1** with one or more H₂ or N₂ tags. Specifically, we choose BOMD simulations because they are suited for fluxional systems or, more generally, systems with multiple close-lying minima, of which non-covalent complexes, in general, or tagged pyridinium **1** ions, in particular, are examples.

Scheme 1. Structure of pyridinium **1**.

We find that, contrary to our expectations, the more weakly bound tag also appears to perturb the spectrum of the molecular ion more strongly: this perturbation splits the N-H stretching frequency, in contrast to the more strongly bound tag, which merely shifts it. We explain this finding semi-quantitatively by analysis of BOMD trajectories.

Methods

Chemicals. The synthesis of 3,5-bis(3,5-di-*tert*-butylbenzyl)pyridine, used in the gas-phase studies here, was reported in our previous work.¹⁰ The ions of interest were prepared upon electrospray ionization of a 10^{-6} M methanol solution of the 3,5-bis(3,5-di-*tert*-butylbenzyl)pyridine. HPLC-grade methanol was purchased from Sigma-Aldrich and used without further purification.

Ion spectroscopy. The mass-selected ions **1** (m/z 484) were cooled in a temperature-controlled ICR ion trap that was described in detail previously.⁹ The temperatures were as follows: 11 K for H₂, 8 K for D₂ and 31 K for N₂ tagging. Data collection and evaluation were done using the procedure described previously.¹¹ Briefly, we measure the change in the relative intensity of the MS signal between the tagged and untagged species as a function of the laser wavelength. In the case of absorption, the population of tagged and untagged species is changed which can be observed using MS: a tagged complex loses its intensity, while the untagged ion gains intensity. Here, we report the spectra that resulted from the evaluation of singly and doubly tagged species; the evaluation of multiply tagged species can be found in the SI (Figures S3-S4).

Computational studies

In a first approach to map the overall topology of the potential for interaction of a tag molecule with the pyridinium cation **1**, the most stable conformer of *untagged* **1** was located with the CREST (version 2.7.1) program, which implements the so-called MTD-GC workflow,^{12,13} which we used with the GFN1-xTB¹⁴ method. MTD-GC involves metadynamic sampling (MTD) followed by a genetic Z-matrix crossing (GC) approach for the generation of conformer ensembles. The CREST run for *untagged* **1** yielded 335 structures lying within a 4.9 kcal mol⁻¹ window. We then used the most stable structure in the ensemble for creating approximate binding energy maps to visualize the potential energy surface on the compound. To this end, we generated a molden file of **1** with GFN1-xTB, optimized with the same method. We used MultiWFN (version 3.7)¹⁵ on the molden file to generate points on the electron density isosurface with the isovalue of 10^{-6} au and a spacing of 0.5 Bohr between the points. One of the atoms of the tag molecule was then placed on each of those points. To relax the orientation of the tag molecule, all the coordinates except the second atom of the tag were then constrained, and the location of the unconstrained atom was optimized with GFN1-xTB. The final energies from the optimization were taken as binding energies on the defined electron density isosurface. The binding energy maps were plotted with PyMol (version 1.7.4).¹⁶ This workflow is based on the tagit code;¹⁷ the modified code is available in the SI (Section S4.1) and on GitLab.¹⁸

In a second approach to identify possible tagged ion structures, the preferential tag position was evaluated, again, with the CREST program. The conformer search of the mono- and doubly-tagged pyridinium **1** structures was performed with the *nci* mode (which excludes the genetic structure crossing) and the GFN1-xTB¹⁴ method. We will further refer to these species as **1**@tag or **1**@2tag,

respectively. This procedure yielded between 600 and 3000 structures depending on the type and number of tag molecules, lying within a 6 kcal mol⁻¹ window. We will further refer to these tagged structures as “tagomers”. The five most stable tagomers were then subjected to the subsequent semi-empirical BOMD simulations. They were also re-optimized using static density functional theory (DFT) calculations with more accurate methods.

DFT calculations were performed using Gaussian 09 suite¹⁹ with the default calculation settings. The structures were optimized with four commonly used functionals: B97D3,²⁰ BP86,²¹ TPSS²² and B3LYP^{23–26}; def2-TZVP²⁷ basis set was used with all functionals. For BP86, TPSS, and B3LYP, dispersion was treated with Grimme’s D3 correction with Becke–Johnson damping.^{28,29} Density fitting with W06 auxiliary basis set was used to speed up the calculations.³⁰ Harmonic frequencies were calculated analytically. The frequency data confirmed the optimized structures as local minima on the potential energy surfaces and provided the zero-point energy (ZPE) corrections. For spectra visualization, Gaussian broadening with a FWHM of 5 cm⁻¹ was applied to spectral lines to facilitate the comparison of calculated spectra with the experimental ones.

BOMD simulations were performed with Atomic Simulation Environment (ASE)³¹ 3.18.1 using the GFN1-xTB method *via* the Python API implemented in xTB 6.2.2.³² We chose the GFN1-xTB method over the newer GFN2-xTB³³ method because the calculated N-H stretching frequency, upon which we focus, matches the DFT result better with GFN1-xTB than with GFN2-xTB (see SI Figure S5 for a representative example). Each calculation started from an optimized structure with a 5 ps NVT simulation using Langevin dynamics, with a friction coefficient of 0.02 a.u., at the target temperature for equilibrating the atomic positions and velocities. The final structure from the NVT simulation was used as the starting point for a 20 ps NVE production simulation. Although the experiments to which these results are compared were performed either at 11 K or at 31 K, a higher temperature was chosen for the BOMD simulations to better sample the nuclear motion of interest. A higher effective temperature, at which a classical simulation is run, represents a crude way of accounting for ZPE, which is missing in classical MD simulations. This approach has been successfully implemented previously for MD simulations in solid Ar cages,³⁴ and has been empirically noted to produce spectra that better match the experiment.³⁵ Hence, we chose a temperature of 20 K higher than that of the experiment: BOMD simulations for **1**@H₂ were run at 30 K and for N₂ tagged **1** at 50 K. A timestep of 0.5 fs was used in the simulations, as has been recommended for calculating vibrational spectra from MD.³⁶ In total 10 trajectories were run for each structure. For each tagged species, the resulting IR spectra were obtained by averaging over 50 trajectories, i.e., 10 trajectories per initial tagomer selected from CREST. Selected MD simulation trajectories were visualized for each 10th frame with VMD-program (version 1.9.3).³⁷

For calculating the IR spectra from the MD trajectories, the dipole moment vector was extracted at each frame during the simulation. The autocorrelation function of the velocity of the dipole moment was calculated from this data, and the Blackman-Harris window was applied. The IR spectrum was obtained by using discrete fast Fourier transform on the resulting data.³⁸ We will further refer to this method as FT-DAC. The Python codes used for running the simulations and calculating the spectra are provided in the SI (Sections S4.2 and S4.3) and are also accessible at GitLab.³⁹

Results

Experimental CIVP spectra

Because the initial observation of splittings was unexpected and "capricious" in that the splittings appeared for some tagging situations and not for others, with no obvious regularity, we investigated the effect of H₂, D₂, and N₂ tags on the CIVP spectrum of **1** systematically. To this end, we recorded the CIVP spectra of **1** with different messenger tags at different temperatures (H₂ at 11 K, D₂ at 8 K, and N₂ at 31 K). These spectra are shown in Figure 1. Whereas the spectra recorded with the N₂ tag (Figure 1a-b) show one peak at the N-H stretching region, we observed a different behavior, reproducibly, with the weaker-binding messenger tags, specifically: H₂ and D₂.

Depending on how we evaluated the spectrum (see Methods) either one or two sharp bands were observed in the N-H stretching region. We confirmed that this feature was not an artifact by repeating the experiment with either H₂ or D₂ tags. Mass spectra used for evaluation and additional spectra for H₂-tagged **1** are provided in the SI, Figures S1-S4.

Figure 1. Experimental CIVP spectra of **1** recorded with H_2 , D_2 or N_2 as neutral tag evaluated with respect to the change in the intensity of the bare ion peak and the peak with a) one N_2 tag (m/z 512), b) two N_2 tags (m/z 540), c) one H_2 tag (m/z 486), d) two H_2 tags (m/z 488), e) one D_2 tag (m/z 488), f) two D_2 tags (m/z 492). The spectrum of **1** looks similar to d) and f) also when evaluated with more H_2 or D_2 tags (see SI, Figure S4).

Calculations

The approximate binding energy maps for both tags investigated (H_2 and N_2), according to the first approach in Methods, are shown in Figure 2 (top). One can easily identify the binding site with the tag residing in close proximity to the N-H moiety (site A). We also decided to investigate binding sites in which the tag interacts either with the π -system of the pyridinium ring (site B) or with the *t*-Bu substituents (site C).

We calculated the relative energies of tagomers at the binding sites A, B, and C with GFN1-xTB as well as four commonly used DFT functionals. The B97D3-optimized structures, from the second approach in Methods, correspond nicely to the binding sites A, B and C, identified by the first approach. The relative energies of the tagomers are shown in Table 1, and the optimized structures of each N_2 -tagomer with B97D3 functional are shown in Figure 2 as representative examples. The ZPE-corrected relative energies can be found in the SI, Table S1; the tag binding energies are provided in Tables S2 and S3.

----- Binding maps -----

----- Optimized structures -----

Figure 2. Top: Approximate binding energy maps calculated with GFN1-xTB for **1**@H₂ and **1**@N₂, shown in two different orientations (indicated with the background color to show which orientation in the binding maps, top, correspond to which optimized structures, bottom). The tag binding sites A, B, and C are indicated on the binding maps. The color map spans a width of 1 kcal mol⁻¹ from the lowest binding energy for each tag. Bottom: Optimized structures (B97D3/def2-TZVP) of **1**@N₂(A), **1**@N₂(B), and **1**@N₂(C). N₂ is colored dark pink for clarity. The pyridinium core of the structures is oriented as in the corresponding binding maps.

Table 1. Relative (not ZPE-corrected) energies of the tagomers A, B, and C in kcal mol⁻¹, calculated with GFN1-xTB and several DFT methods. The basis set used in DFT calculations is in each case def2-TZVP. The energy of the most stable tagomer is set to 0. The **1** + tag values refer to the the computed energy of the cation **1** with the tag fully dissociated.

	GFN1-xTB	B97D3	BP86-D3	TPSS-D3	B3LYP-D3
1 @H ₂ (A)	0	0	0	0	0.23
1 @H ₂ (B)	0.14	0.44	0.90	0.13	0
1 @H ₂ (C)	0.88	0.27	0.52	0.55	0.80
1 + H ₂ (dissociated)	1.36	1.42	1.63	1.28	1.60
1 @N ₂ (A)	0.19	0	0.02	0	0.20
1 @N ₂ (B)	0	0.00	0	0.38	0
1 @N ₂ (C)	0.93	0.48	1.06	1.01	1.12
1 + N ₂ (dissociated)	3.78	3.35	3.79	3.48	3.69

We used harmonic frequency calculations with DFT in our preliminary investigation of the tag effect on the N-H stretching frequency, reasoning that a harmonic analysis, even with its known limitations for weakly bound, fluxional systems, would give information on the direction and magnitude of spectral shifts. The harmonic spectra of tagomers with the tag molecule remote from the N-H moiety matches the harmonic spectrum of untagged **1** well (see SI, Figure S6). However, we observed a pronounced red shift in the spectra of structures A (see Figure 2) where the tag interacts with the N-H moiety (Figure 3). We observed a similar effect in our experimental spectra. Namely, the experiment shows that the N-H peak for **1**@N₂ is red-shifted by about 30 cm⁻¹ compared to that of **1**@H₂. Note that the “more strongly interacting” N₂ tag produces the larger red shift when the tag resides in close proximity to the N-H chromophore. We reason that the N₂ tag interacts more strongly with the N-H chromophore than the H₂ tag because it binds to **1** ca. 2 kcal mol⁻¹ more strongly (see Table 1).

Figure 3. Overlay of calculated (B97D3/def2-TZVP) harmonic IR with the experimental CIVP spectra for a) unperturbed pyridinium **1**; and **1** with either b) H_2 or c) N_2 tag in the close proximity to the N-H moiety. The calculated harmonic spectra are scaled by a factor of 0.97 to match the sharp band at 2972 cm^{-1} corresponding to the C-H stretching mode in the *t*-butyl groups.

In order to understand the unusual splitting of the N-H stretching frequency caused by multiple H_2 tags, BOMD simulations were performed. The resulting IR spectra, calculated via FT-DAC, are shown in Figure 4.

Figure 4. Spectra calculated via FT-DAC averaged over 10 MD trajectories for a) **1** at 30 K, and 50 MD trajectories for b) **1@H₂**, c) **1@2H₂**, d) **1@N₂**, e) **1@2N₂**. Each trajectory was run for 20 ps at 30 K for H₂- and at 50 K for N₂-tagged **1**. The resulting IR spectrum for **1** at 50 K looks very similar to a) (see SI, Figure S8).

Discussion

Current state-of-the-art mass spectrometry techniques usually allow detection and characterization of ions either solely based on the m/z ratio (high-resolution MS) or by means of collision-induced dissociation (CID) experiments, which are based on the monitoring of fragmentation patterns of the ion of interest. Usually, especially for small ions, the knowledge about m/z ratio combined with the CID

technique is sufficient for determination of connectivity. However, they do not enable analysis of conformational properties of the ion, or unimolecular isomerizations, in general, which can be of great interest, especially for large ions.

In order to resolve this ambiguity, structure-sensitive methods need to be employed. Most of the commonly used structure-sensitive spectroscopic methods, such as X-ray crystallography or NMR spectroscopy, are well suited for condensed phase studies, which do not necessarily provide accurate insight into gas-phase structures due to environment effects. However, there are several spectroscopic techniques that can be applied to gas-phase structure elucidation: gas-phase electron diffraction,⁴⁰ NMR spectroscopy,^{41,42} rotational spectroscopy,^{43,44} UV/Vis spectroscopy,⁴⁵ and IR spectroscopy.⁴ The first two methods are currently only applicable to small molecules, whereas the latter three are more generally applicable. Only UV/Vis and IR spectroscopy have been coupled with mass spectrometry. Of those two methods, IR spectroscopy is undoubtedly more informative with regards to molecular structure.

IR-MS spectroscopic methods can be divided into single-photon and multiphoton processes. There are two multiphoton spectroscopic methods that allow infrared investigation of trapped ions: infrared multiphoton dissociation spectroscopy (IRMPD) and double-resonance IR-UV spectroscopy.⁴⁶ IRMPD is based on fragmentation induced by sequential absorption of several IR photons with rapid intramolecular vibrational redistribution between each absorption event.⁴⁶ Alternatively, double-resonance IR-UV spectroscopy, pioneered by Rizzo and co-workers,⁴⁷ employs a UV photon to induce dissociation subsequent to absorption of an IR photon. Both of these schemes share certain disadvantages, though. The IR-UV double-resonance scheme is not universally suitable for any ion as it requires the presence of a UV chromophore.⁴⁸ IRMPD studies suffer from saturation and nonlinear effects, causing a mismatch between relative intensities of the experimental IRMPD bands with those predicted by theory.^{49,50} These effects are especially pronounced for large ions, which are subject to a considerable kinetic shift.⁵¹ With increasing size of the ion, its vibrational degrees of freedom, in which the absorbed energy can be stored, also increase. According to statistical rate theory, observation of a dissociation in the timeframe of the experiment requires an excess of energy above the thermodynamic threshold.⁵² Lastly, both double-resonance IR-UV, and IRMPD spectroscopy are destructive methods in the sense that the ions themselves are fragmented at each laser shot, the constant replenishment, with concomitant thermalization of new ions, impacting the duty cycle of the measurement negatively.

CIVP is a single-photon method, and it has two main advantages to the aforementioned multiphoton methods: 1) it can, unlike IR-UV double resonance, be applied to any molecular ion, because the attractive ion-induced dipole interactions, which bind the tags to the ion, are universal; 2) in contrast to IRMPD, it is less sensitive to kinetic shifts because of the much lower dissociation energy, resulting in better resolution and signal-to-noise ratios. The employment of tags—weakly binding inert gas atoms

or molecules—gives a much lower dissociation barrier compared to that of breaking a covalent bond, concentrating the photodissociation process into one channel, namely the loss of the tag.⁶ In addition, the CIVP experiment, at least in our incarnation, recycles the same ions repeatedly, raising the duty cycle of the experiment. Employment of tags does, however, have drawbacks. Firstly, the formation of ion-neutral complexes with the tag requires cryogenic temperatures, which complicates the experimental setup. Secondly, tags introduce the issue of perturbation of the observed vibrational modes due to the interaction of the tag with the ion, although one would expect frequency shifts in CIVP to be less than those in cryogenic matrix isolation spectroscopy, for example, where they are generally no more than a few cm^{-1} .⁵³ In extreme cases, tags have been observed to undergo reactions with highly reactive molecular ions. For example, it has been shown that carbocations can form covalent bonds with the rare gas atoms.^{54,55} In addition, H_2 tagging of coordinatively unsaturated metal complexes can lead to the oxidative addition of H_2 to the metal center.⁵⁶ For most organic ions, however, the perturbation of the spectrum is generally due to weak electrostatic or London dispersion interactions of the tag with the ion. We will discuss this perturbation effect in detail below.

Multiple CIVP studies have shown that small ions are more likely to suffer from the so-called “tag effect”, which is caused by interaction of the tag with the IR chromophore leading to the perturbation of the resulting IR spectrum.^{57,58} Such perturbations have been reported with several organic cations: protonated water dimer,⁵⁹ protonated water-acetonitrile complex,⁶⁰ various carbocations,^{57,61,62} and small peptides.^{63,64} The general trends that emerge from these studies are: a) less polarizable tags usually affect the spectrum less; b) the type and magnitude of the perturbation depend on the binding site of the tag; c) the perturbation may additionally depend on the number of bound tags. Accordingly, one expects that tags that interact more strongly with the chromophore should perturb the IR spectra more. Among the many messenger tags being used (e.g., He, H_2 , N_2 , Ne, Ar), He has been shown to be the most innocent towards CIVP investigations of small ions.^{5,65} On the other hand, He tagging is also the most difficult to achieve. The very small binding energy of He to an investigated ion requires temperatures below 4 K in order to observe He-tagged species, and quite high pressures of the He buffer gas inside the cryogenic trap.^{5,7} Therefore, other messenger tags such as Ar, H_2 , Ne and N_2 are used widely.⁶

The increase in polarizability of the messenger tag amplifies the question of the tag’s innocence with respect to the measured IR spectrum. Although direct interaction of a tag with the chromophore leads to perturbation,⁶² these effects can become smaller for large ions, where the tag is less likely to be bound to the measured chromophore, and can bind on the periphery of the ion instead. Even though one can argue that the small tag molecules should not perturb a large molecular ion too much, and hence change the spectra, we execute extensive control experiments to investigate the effects of different tags on our spectra. To our surprise, we found that the more weakly bound H_2 or D_2 tags can, in some instances, perturb the infrared spectrum of the pyridinium **1** more severely (see Figure 1), which in our context means that the peak in the CIVP spectrum is not merely shifted slightly, which one expects, but is also

unexpectedly split into more than one peak, which cannot be explained under the assumption that the tag is innocent.

The influence of the tags to X-H stretching vibrations, specifically, have been reported by Johnson and coworkers for several compounds. In 2005, they found that the CIVP spectrum of H_5O_2^+ with Ne resembled that of a bare complex, whereas the Ar-tagged ion had an increased number of signals,⁵⁹ similarly to a previously measured H_2 -tagged complex.⁶⁶ They rationalized that the more strongly interacting tags break the symmetry of the dimer, resulting in more unique vibrations; these changes in the spectra were later also reproduced by simulations.⁶⁷ Three years later, the Johnson group reported a change in the IR spectrum of protonated acetonitrile-water complex, depending on whether the complex was tagged with one or two Ar atoms.⁶⁰ As the Ar tags appeared to introduce a $\sim 50\text{ cm}^{-1}$ red shift in the OH stretching signal, they concluded that the Ar tags were sequentially binding to the OH groups of water. In more recent studies, Johnson and coworkers have published CIVP spectra of small protonated peptides.^{63,64} Two observations relevant for this study were that: a) measuring the complex with one H_2 tag produced three N-H stretch signals (above 3000 cm^{-1}), more H_2 tags produce two (in both cases, one of them was an internal amide N-H signal); b) measuring with N_2 tag resulted in a more red-shifted and broader N-H stretch signal. Based on these changes in the N-H stretching signals, they postulated that the tags were bound to the terminal protonated NH_3 moiety. The overarching message from these studies is that tags appear to bind preferentially to polar X-H bonds, and that the resulting symmetry breaking can cause IR signals to split. Common to all of these explanations is a discussion in terms of “static” structures.

In all the studies mentioned above, the ions had several X-H bonds, which enabled the number of observed signals to change due to symmetry breaking. Pyridinium **1**, however, has only one N-H bond that seems to give one clean signal in most cases (i.e., it is not inherently split by a Fermi resonance, for example, which we investigated in a previous report for isomeric pyridinium cations¹⁰). On the other hand, pyridinium **1** is a larger ion, compared to those investigated by Johnson *et al.* It has large aliphatic substituents (*t*-Bu groups) and aromatic rings that may serve as favorable binding sites for a tag molecule, due to the London dispersion interactions. We discuss how signal splitting could occur in such a case by first analyzing the tag effects on the calculated harmonic frequencies, and then by studying the BOMD-derived spectra and trajectories. Static (harmonic) IR spectra calculated with DFT (Figure 3) show that the interaction of the tag with the N-H moiety red-shifts the N-H stretching frequency, and that this effect is more pronounced, as expected, with N_2 than with H_2 . Relative shifts of similar magnitude have been experimentally observed for the N-H stretching frequencies of protonated diglycine, where the tags were assumed to be located on the protonated terminal ammonium group.⁶⁴ Our experimental observation that the N-H stretching frequency in the IR spectra of **1**@ N_2 is more red-shifted compared to that of **1**@ H_2 suggests that the tags might also reside in close proximity to the N-H moiety. In addition, because different binding sites would correspond, in principle, to

different N-H frequencies, the splitting of the N-H signal with higher number of H₂ tags suggests that H₂ behaves differently than N₂ under the conditions of our experiment. Specifically, the splitting could be caused by: a) the tags residing at several binding sites under the conditions of our experiment, or b) the tags wandering around a flat surface on the timescale of the measurement. Indeed, the binding energy surface of **1**@H₂ appears to be rather flat, more so than that of **1**@N₂ (Figure 2). However, we note that, not only the relative energies, but also the relative ordering of the tagomers seems to be method-dependent, as visible from our comparison of the four chosen DFT functionals as well as xTB (Table 1). This uncertainty in relative energies as well as the large number of possible tagomers complicates the analysis of tagomer distributions, and their effect to the IR spectra, by statistical methods. We note further that, even with the differences between the computed binding energies when different methods are used, they all agree that the absolute binding energy is approximately 1 kcal mol⁻¹ for H₂ and 3–4 kcal mol⁻¹ for N₂. We therefore take the computational results to be permissive, rather than definitive, with regard to the conclusions we make.

An alternative approach to static statistical analysis is molecular dynamics (MD). It is advantageous because MD simulations can sample large volumes of phase space based on the equations of motion, and the resulting properties converge to ensemble averages under (quasi-)ergodic conditions. The biggest disadvantage is that converged results require about 10⁴–10⁵ force calculations, which necessitates usage of cheap methods. For the compounds in the size category of **1** (>80 atoms), even DFT is generally prohibitively slow. For this reason, we used the fast semi-empirical GFN1-xTB method. Although the energies from xTB are likely to be not very accurate (xTB was not parametrized for accurate energies), the relative energies lie in a similar range to the respective DFT values (Table 1). Therefore, we expect to be able to extract at least qualitative, or semi-quantitative, insight about the behavior of tags from xTB MD simulations, even though they probably do not converge to accurate averages. In addition, the BOMD simulations allowed us to utilize a more sophisticated computational treatment of the CIVP spectra, which includes anharmonicity, even to the extreme case of conformational or configurational isomerization, via [FT-DAC](#), which we obtained from the simulations (see Methods). We emphasize again the caveat that we consider the computational modeling, at least at the level of theory we employed, to be permissive rather than definitive, pending, at the very least, a better electronic structure model. Figure 4 shows the averaged IR spectra that result from the 50 BOMD simulations of the respective **1**@tag and **1**@2tag species. The MD simulations show the appearance of two peaks in the N-H stretching frequency region for both tags. In order to understand the observed splitting of the N-H signal, we analyzed the individual MD trajectories of the tagomers of **1**@N₂ and **1**@H₂ in more detail. We found that the splitting of the N-H signal could be observed regardless of whether the simulation started with tagomer A or B (see Figure 2). We further analyzed the dynamics of the tag in these simulations by plotting the time evolution of the distance between the N-H moiety and tag centroid ($r_{\text{NH-tag}}$). Our analysis of individual trajectories suggests that there exists a preferential

tagomer for **1**@N₂, with N₂ being in close proximity to the N-H moiety, presumably to maximize the charge/induced dipole interaction strength (the time evolution of $r_{\text{NH-N}_2}$ from individual trajectories can be found in the SI, Section S5.2). On the other hand, the H₂ tag appears to be able to switch between at least two distinct tagomer structures, even at cryogenic temperatures. The resulting representative plots for **1**@H₂ are shown in Figure 5 (other individual trajectories **1**@N₂ and **1**@H₂ can be found in the SI, Section S5). The particular trajectory in Figure 5c shows, that for the first 10 ps of simulation, the N-H...tag (centroid) distance stays at around 3.25 Å, and then changes to around 2.50 Å during the last 10 ps of the simulation. It is imperative to note that the H₂ tag also displays mobility in the opposite direction, meaning that it can reversibly switch the binding site; Figure 5d depicts a trajectory in which the tag is initially in close proximity to the N-H moiety, travels away at around 6 ps and returns at 12 ps.

Figure 5. Spectra calculated via FT-DAC from two selected MD trajectories of **1**@H₂, at 30 K together with the time evolution of the N-H...H₂ (centroid) distance.

To investigate the effect of the moving tag on the resulting IR spectrum, we split the trajectory shown in Figure 5c in two parts (10 ps + 10 ps) and plotted FT-DAC for both parts. To visualize the tag motion, all tag positions from the trajectory were superposed. The resulting IR spectra, together with the visualization of the tag motion, are shown in Figure 6. During the first 10 ps of the simulation, the tagomer structure stays similar to that of structure B (see Figure 2). During the last 10 ps of the simulation, the tag moves closer to the N-H moiety, resembling structure A, which causes a red shift of the N-H stretching frequency by about 30 cm⁻¹. Hence, the wandering of the tag around the N-H moiety results in the splitting of the N-H stretching frequency. The 30 cm⁻¹ red shift agrees with the static DFT frequency calculations of the different tagomers: when the tag molecule is remote from the N-H moiety, the harmonic spectra match those of the untagged **1**, however, a pronounced red shift is observed when the tag resides in close proximity to the N-H moiety (see Figure 3 and the SI, Section S2, for harmonic DFT spectra). Although we take the simulations at this level to be permissive, we suggest that this behavior also occurs at the cryogenic temperature of the experiment. Specifically, the observed splitting is caused by the motion of the H₂ tag around the N-H chromophore due to the almost equal relative

energies of the corresponding tagomers, and thereby comparable populations of these tagomers on average.

Figure 6. Spectra calculated via FT-DAC from the MD trajectory of **1**@H₂ corresponding to in Figure 5c plotted for: the full simulation (20 ps); the first 10 ps of the simulation; the last 10 ps of the simulation. The trajectory visualizations exhibit a side view of the superposition of tag molecule during the full 20 ps simulation, the first 10 ps of simulation and the last 10 ps of simulation. Color represents the relative position of the tag with respect to its distance to the N-H moiety (red—further away from N-H, blue—in close proximity to the N-H). The motion of **1** is not shown for clarity.

Averaged IR spectra of **1**@N₂ also give rise to two peaks (although with a distinct intensity difference) in the N-H stretching frequency region (see Figure 4a for details). However, the two peaks, in the case with N₂, arise from “static” sampling of different tagomers, as a detailed analysis of the trajectories showed the presence of one tagomer in each case. We do not observe a splitting in our N₂-tagged experiments, which points out that, most likely, only one tagomer with the N₂ residing in the proximity to the N-H is present under our experimental conditions. Ironically, the N₂ tag, whose higher polarizability results in a deeper electrostatic well in its interaction with **1**, presumably remains localized in that deeper well, giving only the usual shift of the CIVP band, whereas, the more weakly bound H₂ tag finds multiple, similarly weakly bound positions, from which it can cause the much more troublesome splitting of peaks. This interpretation can be visually followed in Figure 2—within a 1 kcal mol⁻¹ window with respect to the deepest well, the binding energy varies smoothly across the surface of **1** in the case of H₂, but displays discrete binding sites in the case of N₂, which are, therefore, separated by at least a 1 kcal mol⁻¹ barrier. Lastly, the experimental observation of the splitting in the CIVP

spectrum of **1**@2H₂, but not **1**@H₂ may arise because the first tag occupies the “best” binding site, leaving the second tag to wander among multiple “next-best” sites. Indeed, the experimental spectra and the BOMD simulations strongly suggest that weak binding may not always be best when one seeks the least perturbed spectrum.

Conclusion

In the course of our experimental investigation of tag effects on pyridinium cations, we observed, in addition to the expected red shift of the N-H stretching frequency of the pyridinium **1** with N₂ as a tag, a surprising splitting of that signal, when H₂ or D₂ tags were used under the cryogenic conditions of the experiment. We used BOMD simulations to investigate the mobility of the H₂ and N₂ tags, as well as to calculate IR spectra. Based on the higher observed mobility of H₂ between different binding sites of **1**, and the respective simulated IR spectra, we propose that the observed splitting of the N-H stretching frequency in case of H₂ tagging is due to the presence of at least two spectroscopically distinct tagomers under cryogenic conditions.

Associated content

Supporting Information

CIVP spectra; additional IR harmonic spectra; Python and Shell scripts for running the calculations, single MD trajectories evaluation (PDF)

Cartesian coordinates of all optimized structures, together with their total and ZPE-corrected energies in Hartree (XYZ)

Cartesian coordinates of all starting structures for the MD simulations, together with their total energies in Hartree (XYZ)

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Notes

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