Bond Dissociation Energies in the Gas Phase for Large Molecular Ions by Threshold Collision-Induced Dissociation Experiments: Stretching the Limits
Bond dissociation energies in the gas phase for large molecular ions by threshold collision-induced dissociation experiments: a benchmarking study

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Abstract

Accurate bond dissociation energies for large molecules are difficult to obtain by either experimental or computational methods. The former are hampered by a range of physical and practical limitations in gas-phase measurement techniques, while the latter require incorporation of multiple approximations whose impact on accuracy may not always be clear. When internal benchmarks are not available, one hopes that experiment and theory can mutually support each other. A recent report found, however, a large discrepancy between gas-phase bond dissociation energies, measured mass spectrometrically, and the corresponding quantities computed using DFT-D3, and DLPNO-CCSD(T) methods. With the widespread application of these computational methods to large molecular systems, the discrepancy needs to be resolved. We report a series of experimental studies that validate the mass spectrometric methods from small to large ions, and find that bond dissociation energies extracted from threshold collision-induced dissociation experiments on large ions do indeed behave correctly. The implications for the computational studies are discussed.

Introduction

The fundamental understanding of structure and reactivity in organic chemistry requires accurate thermochemical data to test and validate models for intra- and intermolecular interactions. The data can, in principle, come from experimental measurements, or, alternatively, from quantum chemical calculations. While in some circumstances, independent experimental measurements with cross-validation may provide a high degree of certainty for the reliability of the derived thermochemical data, as exemplified splendidly by the Active Thermochemical Tables, there are now instances, particularly for increasingly large molecules in the gas phase, where the range of experimental measurements is sparse, due to technical limitations, making independent cross-validation difficult. In the best of worlds, one would hope that the new generation of quantum chemical calculations that purport "chemical accuracy" could provide yet another independent axis for a quantitative comparison to those experiments on the edge of feasibility, and, by their mutual concurrence, validate both the experimental determination and the computational method.

Scheme 1. Schematic representation of the London dispersion interactions in different proton-bound pyridinium dimers, and their contribution to the bond dissociation energy.
In an earlier investigation that probed the contribution of London dispersion\textsuperscript{4,5} to the bond dissociation energy (BDE) of increasingly large proton-bond dimers of substituted pyridines, quinolines, and tertiary amines with threshold collision-induced dissociation (T-CID) measurements in an electrospray ionization tandem mass spectrometer,\textsuperscript{1} we observed that London dispersion\textsuperscript{6} added a chemically significant increment, meaning up to tens of kcal/mol, to the BDE when the interacting substituents became large enough. Energy decomposition analysis,\textsuperscript{7} in the specific instance, SAPT,\textsuperscript{8} indicated that the variation of the BDE within a series of structurally homologous gas-phase dimers derived primarily from London dispersion, in complete agreement with arguments from qualitative theory. Nevertheless, a size-dependent discrepancy in the quantitative comparison between the BDEs derived from experiment, and the same BDEs, computed with at least some of the dispersion-corrected quantum chemical methods, proved troubling. For example, as may be seen in Scheme 1, the experimentally-derived gas-phase BDE of the proton-bound dimer of the parent pyridine, a typical "small" pyridine, agreed well with an independent gas-phase measurement,\textsuperscript{9} as well as with DFT-D3,\textsuperscript{10} M06-L\textsuperscript{11} and DLPNO-CCSD(T) calculations,\textsuperscript{12} to within declared or expected uncertainty bounds. On the other hand, the gas-phase BDE for the proton-bound dimer of 2,5-bis(3,5-di-tert-butylphenyl)pyridine, a "large" pyridine, was found to be $35.7 \pm 0.9$ kcal/mol experimentally, as compared to the significantly higher value ~ 45 kcal/mol, produced by B97-D3 or, surprisingly, DLPNO-CCSD(T).\textsuperscript{1} A control experiment, based on an intramolecular competition, indicated that the high value, i.e. the 45 kcal/mol, is unlikely to be correct.\textsuperscript{1} We have reported a further, independent experimental investigation of dispersion interactions, based on gas-phase molecular torsion balances, and it also finds that the dispersion-corrected quantum chemical methods appear to overbind significantly.\textsuperscript{13} Given the magnitude of the discrepancy, the universality of London dispersion interactions, and the centrality of the determination to the confidence in experiment, theory, or both, we judged it imperative to validate the T-CID method itself with increasingly large molecules in the gas phase.

\begin{center}
\begin{tabular}{c c}
\textbf{Scheme 2.} 3D representation of ortho- and meta-substituted conformers of proton-bound pyridinium dimers. & \\
\end{tabular}
\end{center}

Given that the BDE for proton-bound dimers of "small" pyridines, as determined by T-CID, agree well with the independent gas-phase equilibrium measurements on the same dimers, as well as the computed BDEs with B97-D3, M06-L, and DLPNO-CCSD(T), \textit{vide infra}, we take these values with considerable confidence to be physically correct. In this regard, we considered the T-CID measurement, and the subsequent data treatment to extract the BDE, to be already validated for small molecular systems. For large dimers, gas-phase equilibria cannot be measured, and the computations themselves involve further approximations, so we seek an experiment that extends the confidence in T-CID from small molecules to large ones. The difference between the small dimers in our previous work, and the large ones, consists in the additional increment in BDE due to London dispersion, which scales up rapidly with the number of atoms in the interacting substituents. For the present validation of the T-CID method, we choose an experimental design, Scheme 2, in which dimers are made increasingly large with substituents placed in positions where they \textit{cannot} interact with each other, so that we separate issues of size from issues of London dispersion. We reason that a confirmation that T-CID works reliably for large molecules, \textit{per se}, would mean that the T-CID determination of the London dispersion in those cases where interaction does indeed become important to BDE is, in fact, treated properly in the experiment. We report here the confirmation that the T-CID experiment, deconvoluted with the L-CID
program, properly treats bond dissociation energy in a series of test molecules ranging from small to large (>100 atoms).

Results

For the tabulation of Results, Scheme 3 gives designations for the dimers investigated in this study. The key result in the previous work concerned the bond dissociation energy in the dimer designated here as 5. The designations in Scheme 3 show composition, rather than structure of the dimers, as the actual structures in the mass spectrometric experiment can be ascertained only post facto by computation or experiment. For example, Figure 1 displays the B97-D3 optimized structure for two proton-bound dimer analogs of 5, overlaid on the x-ray crystallographically determined structure for their tetrakis 3,5-bis(trifluoromethyl)phenyl borate ([BAR$_4$]) salts, showing that the o,o'-substituted cases can adopt the expected proton-bound structure with the two pyridine rings bisected and the substituents packed together to optimize the attractive non-covalent interactions. In order to demonstrate the role of attractive London dispersion interactions in the formation of these complexes analysis based on the reduced gradient density and electron density was carried out (for details, see the Supporting Information, section S4). We designate this structure to be the normal H-bonded dimer. Further, Figure 2 shows the B97-D3 optimized structures for the dimers 5-7, indicating the possible structures: normal H-bonded structures for 5, 6, and 7, an anomalous H-bonded structure for 6, and π-stacked structures for 6 and 7, all found by conformer search routines implemented with the GFN-xTB model in the XTB program, plus a manual search for further conformers, and then re-optimized at the stated, higher level. The anomalous dimer for 6 is still proton-bound, but the pyridine rings are no longer bisected, and the N-H-N bond is bent out of linearity to permit an energetically favorable π-stacking of the aryl substituents. Conformational searches for 6-9 find π-stacked dimer structures for which the π-stacking is so energetically favorable that the dimers give up the N-H-N ionic hydrogen bond altogether so that the stacking can be made more optimal. For the cases where the normal proton-bound structure is not strongly enough bound, these structures, unwanted in our present study, can become the global minimum structures for dimers.

Scheme 3. Composition of pyridinium dimers investigated in this study.
Figure 1. X-ray structures of the proton-bound dimers of o,o'-dibenzylpyridine (left) and o,o'-bis(3,5-dimethylbenzyl)pyridine (right), overlaid on the computed structures optimized with B97-D3 and a triple-ζ basis set. Hydrogens, with the exception of the proton in the N-H-N bond are omitted for clarity.

Figure 2. B97-D3 optimized structures for the dimers 5, 6, and 7, showing the normal H-bonded structure, the anomalous H-bonded structure, and π-stacked structures with the pyridines oriented syn or anti.

As has been described in previous reports,\textsuperscript{17} we measured the bond dissociation energies, $E_0$, in this case for the proton- and silver-bound dimers 1-9, by means of energy-resolved collision-induced dissociation cross-sections, more often called threshold CID or T-CID. A representative sample of the
experimental measurements, extrapolation to zero-pressure (single-collision limit), and fit with the L-CID program, is shown for 3b in Figure 3 to illustrate the typical quality of the data and the goodness of the fit.

Figure 3. ESI-MS/MS spectrum of 3b (upper-left), peak intensities for $m/z = 378$ and $m/z = 243$, as a function of collision gas pressure (upper-right), extrapolation of the reactive cross-section to zero-pressure (lower-left) and fit of the extrapolated cross-section with L-CID, done with 23 different sets of initial parameters (lower-right), as representative for the T-CID data in the pyridine dimers bound with $\text{H}^+$ or $\text{Ag}^+$. The L-CID fits produce $E_0$, listed in Table 1, with uncertainty bounds derived from the variance of the L-CID fits.

Multiple fits, shown in Figure 3, with different starting conditions converge to give the $E_0$, with the statistical error bounds derived from the variance of the fits. The comparable data for the other proton- and silver-bound dimers are given in the Supporting Information, section S7. The tabulated $E_0$ values from the experimental fits, shown in Table 1, are not assigned \textit{a priori} to a particular structure for the proton- or silver-bound dimers, as mentioned above, and further explained in the Discussion, although we had admittedly, in our earliest expectations, thought innocently that the normal H-bonded dimer structure would always be canonical. Table 1 also lists the computed $E_0$ values for different dimer structures found in our conformational searches, and subsequently re-optimized, from which it may be seen clearly that the normal H-bonded dimer structure cannot be taken to be the lowest energy structure in all cases.

<table>
<thead>
<tr>
<th>Compound - Conformer</th>
<th>Experiment</th>
<th>B97D3</th>
<th>M06-L</th>
<th>DLPNO-CCSD(T)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1a normal H-bonded</td>
<td>26.1 ± 0.7</td>
<td>27.5</td>
<td>24.3</td>
<td>26.0</td>
</tr>
<tr>
<td>2a normal H-bonded</td>
<td>29.2 ± 1.4</td>
<td>27.8</td>
<td>24.7</td>
<td>26.9</td>
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<tr>
<td>3a normal H-bonded</td>
<td>30.1 ± 0.8</td>
<td>27.8</td>
<td>24.7</td>
<td>26.9</td>
</tr>
<tr>
<td>4a normal H-bonded</td>
<td>33.6 ± 0.9</td>
<td>27.9</td>
<td>24.8</td>
<td>27.0</td>
</tr>
<tr>
<td>1b normal Ag-bonded</td>
<td>44.4 ± 0.5</td>
<td>47.8</td>
<td>45.6</td>
<td>47.1</td>
</tr>
<tr>
<td>2b normal Ag-bonded</td>
<td>43.0 ± 1.2</td>
<td>49.9</td>
<td>47.7</td>
<td>49.1</td>
</tr>
<tr>
<td>3b normal Ag-bonded</td>
<td>43.8 ± 1.3</td>
<td>50.2</td>
<td>48.0</td>
<td>49.3</td>
</tr>
<tr>
<td>Compound</td>
<td>B97D3</td>
<td>M06-L</td>
<td>DLPNO-CCSD(T)</td>
<td>$E_0$ from experiment</td>
</tr>
<tr>
<td>----------</td>
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<td>-------</td>
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<td>----------------------</td>
</tr>
<tr>
<td>MeO-NO</td>
<td>41.9</td>
<td>40.5</td>
<td>38.9</td>
<td>42.2 ± 0.8$^a$</td>
</tr>
<tr>
<td>EtO-NO</td>
<td>41.5</td>
<td>40.4</td>
<td>39.4</td>
<td>44.3 ± 1.0$^a$</td>
</tr>
<tr>
<td>$t$-BuO-NO</td>
<td>41.5</td>
<td>41.7</td>
<td>40.7</td>
<td>42.1 ± 1.4$^a$</td>
</tr>
<tr>
<td>C6H5CH2O-NO</td>
<td>39.3</td>
<td>38.7</td>
<td>39.5</td>
<td>43.2 ± 2.8$^a$</td>
</tr>
<tr>
<td>PyC6H5NO (10)</td>
<td>43.4</td>
<td>41.6</td>
<td>40.0</td>
<td>42.5 ± 0.3$^b$</td>
</tr>
</tbody>
</table>

Table 2. Bond dissociation energies, $E_0$, for the RO-NO bond in the nitrites, including 10, computed with DFT or DLPNO-CCSD(T), versus bond energies experimentally measured with threshold CID for 10 after $E_0$ is

Table 1. Bond dissociation energies, $E_0$, for the dimers 1-9, computed with DFT or DLPNO-CCSD(T), versus experimentally measured with threshold CID, with $E_0$ deconvoluted by the L-CID program. Energies are given in kcal/mol. DFT energies for each computational method are for single-point calculations with the def2-QZVP basis set at geometries re-optimized with B97D3/def2-TZVP. The various conformers were found by combination of manual search and algorithmic search.15 DLPNO-CCSD(T) energies are reported for single-points at the CBS(2,3), for compounds 1a-4a and 5-9, or CBS(3,4), for compounds 1b-4b, with def2-XZVP basis sets, all done at the B97-D3/def2-TZVP geometries. All energies are ZPE corrected.

As will be treated further in the Discussion, we further benchmark the $E_0$, extracted from the T-CID experiment by the L-CID program with independent experiments. One of the key validation experiments tests, the "smoking gun," in ref. [1], involves an intramolecular competition between cleavages of two bonds in one molecule.19 The reference bond is the O-N bond in a pendant nitrite, for which $E_0$ may be computed. We measure this $E_0$ for the underlying structure, shown in Scheme 4, to show the consistency of computations and T-CID experiments. The available bond dissociation energies for simple alkyl nitrites from the literature20,21 are compared to $E_0$, computed with multiple methods, and the $E_0$ measured for the nitrite from protonated 4-pyridylmethyl nitrite, 10, are listed in Table 2.
deconvoluted by the L-CID program, or by other experimental methods. Energies are given in kcal/mol. DFT energies for each computational method are for single-point calculations with the pc-3 (quadruple-$
abla$) basis set at geometries optimized with B97-D3/pc-2-sp-(d). DLPNO-CCSD(T) energies are reported for single-points at the CBS(3,4) limit with pc-X basis sets, with the B97-D3/pc-2-sp-(d) geometries. All energies are ZPE corrected. The experimental values are taken from (a) ref [20], (b) ref [21], or (c) this work.

We have recently introduced cryogenic ion vibrational predissociation spectroscopy as an additional tool among the other tools in the mass spectrometric methods we employ. CIVP spectra can be considered to be very lightly perturbed infrared spectra of mass-selected molecular ions. While CIVP spectroscopy is not the main thrust of the present manuscript, a key result may be inferred from Figures 4 and 5. The dimer with a composition corresponding to 7 was electrospayed from methanol solution, selected by its m/z ratio, and then subjected to CIVP in the frequency range of 2840 to 3540 cm$^{-1}$, the tuning range we currently have accessible with our available lasers. The computed IR spectra for three potential conformers of 7 are shown in Figure 4. The C-H stretching region looks similar in all three conformers, but the N-H stretch was calculated to appear either around 3400 cm$^{-1}$ (unscaled), when the N-H is not H-bonded, or around 2000 cm$^{-1}$, when it is. While the CIVP spectra cannot distinguish between $\pi$-stacked anti and $\pi$-stacked syn conformers, and the assignment of the band must be regarded as tentative, we observe a band slightly below 3400 cm$^{-1}$, shown in Figure 5. While we cannot yet definitively exclude the possibility that the observed band is an unusually intense overtone of an in-plane C-H wag, for instance, the absence of any other strongly allowed vibrational band in the vicinity from which an otherwise forbidden overtone could borrow intensity argues against such an assignment. Assignment of the band to an N-H stretch would signal that some, if not all, of the ions corresponding to 7 in the gas phase at temperatures of 10-40 K have a $\pi$-stacked structure, presumably in preference to the normal H-bonded structure.

![Figure 4](image_url)  
**Figure 4.** IR spectra of 7, calculated with B97D3/def2-TZVP for three possible structures, all of which were found as minima in a conformation search, followed by re-optimization. Hydrogen-bonding shifts the N-H stretching frequency strongly to the red, from approximately 3500 cm$^{-1}$ to about 2000 cm$^{-1}$. Frequencies are unscaled.
Figure 5. Comparison of computed IR spectra (B97D3/def2-TZVP, frequencies scaled by 0.95 to align the aliphatic C-H bands) with CIVP spectra measured at approximately 30K in a FT-MS trap with a N2 tag and at 9 K with a D2 tag. For the dimer the computed N-H stretching band at 3375 cm\(^{-1}\) in the π-stacked dimer matches acceptably with an observed band at 3250 cm\(^{-1}\), indicating that some, if not all, has that structure.

Discussion

Background and the Discrepancy

London dispersion is a universal interaction between two electron densities which has recently been recognized as a potential handle for explaining, or more importantly, designing structures and reactivity in organic molecules.\(^6\) The concept of dispersion energy donors, DEDs, has even been invoked to explain stereoselectivity in a Cu-catalyzed hydroamination reaction, for example.\(^{24}\) Whereas the potential well due to London dispersion in argon dimer, for example, is only 0.3 kcal/mol deep,\(^{25}\) i.e. smaller than kT at room temperature, the interaction scales up quickly with size, reaching, in principle, tens of kcal/mol for interacting structures with on-the-order-of-100 atoms. Accordingly, the phenomenon, which can be quantified for small molecules in the gas phase by high-resolution spectroscopy, can be expect to become chemically significant as an influence on rates and equilibria in solution for organic molecules the size of many substrates, catalysts, and reagents. The quantification of the interaction for larger molecules becomes technically much more complicated,\(^{26}\) as suitable gas-phase experiments for large molecules are very rare, and accurate quantum chemical calculations for large molecules necessarily involve approximations whose impact on the accuracy is difficult to judge.

In fact, it had been hoped that gas-phase experiments, in particular, bond dissociation energy determinations by collision-induced dissociation threshold measurements of large proton-bound dimers in an electrospray tandem mass spectrometer, and dispersion-corrected quantum chemical calculations on molecules with ~ 100 or more atoms, would mutually reinforce each other to give confidence on the model assumptions on both sides. In the absence of any other credible validation, both the experimental method and the computational approach need auxiliary experiments or theory to gain sufficient credence so that they may act as reliable guides to molecular design.

The present work seeks to help resolve a discrepancy between bond dissociation energies determined by either experiment or computation in a model system designed to isolate and highlight the contribution of London dispersion.\(^1\) Proton-bound dimers of pyridines were expected, and often found, to have a linear, bisected structure, as may be seen in our x-ray crystal structures in Figure 1, which would place ortho substituents in an ideal position to interact with each other non-covalently. The central ionic hydrogen bond served to make the complex charged (for electrospray ionization and mass spectrometry), and pre-organize the complex for the additional non-covalent interactions (for details, see figures S5-S9 in the Supporting Information). SAPT analysis, breaking down the overall bond energy into components due to different effects, found that the central ionic hydrogen bond remained nearly constant as the ortho substituents were varied from small, e.g. H or CH\(_3\), to large, e.g. (3,5-di-
tert-butylbenzyl). Accordingly, the variation of the bond dissociation energies of the proton-bound dimers can be interpreted as primarily due to London dispersion, and perhaps other non-covalent, forces between the substituents. In fact, the bond dissociation energy, in the gas phase, for the proton-bound dimer of pyridine itself, BDE = 26 ± 2 kcal/mol represents the weakest bond in the series, with BDE increasing systematically as the ortho-substituents become larger. Whereas the qualitative conclusion, that increasingly large substituents give increasingly large London dispersion forces, is supported by both the experimental determinations and the computed bond dissociation energies, a significant, quantitative discrepancy necessitates a further experimental investigation to validate the method applied to the large proton-bound dimers. The discrepancy appears for the larger proton-bound dimers, of which the most prominent is 5, the proton-bound dimer of 2,6-bis(3,5-di-tert-butylbenzyl)pyridine, for which the experiment and M06-L/CBS//B97-D3/def2-TZVP deliver BDE around 35 kcal/mol while B97-D3/CBS//B97-D3/def2-TZVP and DLPNO-CCSD(T)/CBS//B97-D3/def2-TZVP give a higher value around 45 kcal/mol. Especially if quantum chemical calculations are to be used to make quantitative predictions of rates, equilibria, and selectivities, the 10 kcal/mol discrepancy, which would correspond to a seven orders-of-magnitude difference in a rate or equilibrium constant at room temperature, demands a resolution. In principle, either the experiment, or one or more of the calculations, or even both the experiment and the calculations, could be wrong. The present set of experiments are designed to validate (or not) the determination of bond dissociation energies in large molecules in the gas phase by threshold collision-induced dissociation experiments.

For experimental thermochemical determinations in the gas phase, there are, in principle, two classes of methods: Second Law and Third Law experiments. The latter is easier to explain, and consists in measuring relative number densities or concentrations of different species or states at thermodynamic equilibrium. Presuming, or course, that the species or states can be identified unambiguously by an appropriate spectroscopic method, the Third Law experiment provides a free energy of dissociation via the equilibrium constant which involves no assumption beyond that of a Boltzmann distribution and thermodynamic equilibrium. Unfortunately, Third Law measurements of association-dissociation equilibria in the gas phase are uncommon for anything but the smallest molecules, for practical reasons. Thermodynamic equilibrium means that both the monomers and dimers, in our case, must be volatile enough to establish a sufficient steady-state concentration, and thermally stable enough that they do not undergo a thermal reaction other than the reversible association. Consequently, high-temperature, high-pressure mass spectrometric determination of equilibria, as had been reported by Meot-Ner, can be used for a limited range of small molecules, or for unimolecular equilibria such as interconversion between conformers of a given ion. The temperature-dependent equilibria for pyridines/pyridinium ions versus their proton-bound dimers have provided bond dissociation energies for the parent pyridine and analogs with a limited range of small alkyl substituents. Within this range of sizes for the ortho substituents, our subsequent, independent Second Law (vide infra) measurement, the B97-D3, M06-L, and DLPNO-CCSD(T) calculations all agree satisfactorily to within the error bounds of the measurements. This is good, and it serves as an anchor point from which we start. Nevertheless, the largest molecules for which a Third Law determination could be done in our original experiment are still too small for the discrepancy to appear.

Second Law experiments, fundamentally, measure a rate from which one derives an activation energy. With a suitable assumption of no reverse barrier, which for the dissociation of molecular ions (the microscopic reverse is an ion-molecule association with a long-range electrostatic interaction) is a good assumption, the activation energy becomes a bond dissociation energy. Second Law experiments are much more general in their range of application, and they can be executed for labile species prepared in situ, or even reactive intermediates. Moreover, with electrospray ionization, molecular ions with m/z ratios even as high as 10⁶ can be transferred from solution to the gas phase. The thermochemical determinations on electrosprayed proton-bound dimers of pyridines with substituents large enough for London dispersion forces to contribute significantly to the bond dissociation energy are Second Law experiments.

In a typical Second Law experiment, energy is transferred to the (large) molecules or molecular ions in the gas phase by absorption of a photon, scattering of an electron, charge recombination, or collision with another atom or molecule. Dissociation of the molecule, observed, for example, in a mass spectrometer, should appear, in principle, if the energy transferred is sufficient for the molecule to surmount the transition state for dissociation. In the simplest conception of the experiment, a threshold collision-induced dissociation in our case, one might have thought naively that the energetic threshold for observing the product ion of a dissociation reaction would define the activation energy, and hence the bond dissociation energy, according to the assumptions of a Second Law experiment. In practice, however, competing physical processes, ranging from emission of blackbody radiation to removal of the molecule (or molecular ion) by collision with a wall, collision with the detector, or simple transport
out of the spatial area of observation, complicates the interpretation of the experimentally observed threshold. For a CID experiment in our rf triple-quad, or a similar mass spectrometer, the timescale for competing removal of the energetized ion is on the order of $10^5$ seconds. Given that the rate of dissociation of the proton-bound dimer exactly at threshold is vanishingly small, one can already surmise that one must add enough energy above threshold until the rate of dissociation exceeds approximately $10^5$ s$^{-1}$ before one may observe the dissociation at all, as depicted schematically in Figure 6.

**Figure 6.** Schematic representation of the relationship between the thermochemical threshold for CID, $E_0$, and the observed threshold in a T-CID experiment, showing the kinetic shift.

The extra energy above threshold is termed the kinetic shift, identified already by Chupka in 1958, and further reviewed by Lipshitz in 1982. For a given activation energy for dissociation, the kinetic shift scales up rapidly with the number of internal degrees-of-freedom in a molecule, as one would expect from statistical rate theory. For threshold CID of ions with perhaps 10 atoms, the kinetic shift is smaller than the uncertainty bounds of the experiment itself, and can be safely ignored. On the other hand, for threshold CID of an ion with 200 atoms, the kinetic shift can be as large as, or larger than, the bond dissociation energy that one seeks to determine, which means that the demand for accuracy of the kinetic model for dissociation rates becomes increasingly stringent as the molecule or molecular ion increases in size. All Second Law methods share this limitation because they are all variations on the same principle by which one measures the threshold at which the rate of dissociation exceeds something like $10^5$ s$^{-1}$. It should be noted that the rates are microcanonical rates, $k(E)$, rather than the more familiar canonical rates, $k(T)$, used in a van't Hoff or Arrhenius analysis. Although there are other practical, technical issues difficulties in the mass spectrometric measurements of dissociation thresholds for large ions, the principal, fundamental difficulty is the kinetic shift. Accordingly, one should always remain cognizant that the "experimental" bond dissociation energy in a Second Law measurement contains implicitly a kinetic model, whose failure in the worst case could invalidate the bond dissociation energy.

The thermodynamic barrier for dissociation, $E_0$, is extracted from the threshold CID experiment by the program L-CID. Along with the related CRUNCH program from Armentrout and coworkers, L-CID treats the kinetic shift with statistical rate theory. The particular implementation corresponds roughly to a phase space theory treatment, which is the most basic variant of RRKM theory, for which one needs the density-of-states function, $\rho(E)$, for the starting and the energized complexes. The assumption of statistical behavior in the dissociation of large ions has been tested extensively over several decades, and this assumption can be judged to be good, there being admittedly some rare exceptions. For statistical rate theory, approximations enter in the calculation of $\rho(E)$. Translational and rotational degrees-of-freedom can be treated classically, or even altogether neglected (if the moments-of-inertia of the starting complex and the transition state are sufficiently similar, for example), but vibrational (and librational) degrees-of-freedom become the principal problem. While CRUNCH implements a Beyer-Swinehart direct state count, which has the advantage of using computed frequencies for the starting complex and transition states, it carries the necessary disadvantage that one needs to compute the transition state that one is purporting to measure experimentally, which carries, in turn, a curiously circular logic when the experimental result is then used to validate a
calculation. Moreover, the Beyer-Swinehart algorithm, at least in its common implementation, assumes harmonic oscillators, i.e. evenly spaced vibrational levels, which is most certainly a poor approximation for energies at a dissociation threshold. L-CID makes a seemingly radical approximation of all frequencies with a single "effective" frequency, which itself serves as a fit parameter. Together with the number of vibrational degrees-of-freedom, 3N-6 for a molecular ion with N atoms, \( \nu_{\text{eff}} \) plays the role of entropy to \( E_0 \)'s enthalpy, to the extent that one can draw an analogy to canonical terms in a microcanonical ensemble. The effective frequency absorbs structural effects, anharmonicity, and other non-idealities; the approximation is central to L-CID, and hence to the extraction of the chemically relevant \( E_0 \) value from a threshold CID experiment.

**Anchoring a benchmark**

While one may be tempted to attempt a theoretical justification of any particular set of approximations, it is perhaps more germane to validate the methods by cross-comparison to independent methods for which one or more of the approximations has not been made. Comparison of \( E_0 \) for the collision-induced dissociation of crown-ether complexes of alkali metal cations, for example, shows excellent agreement between CRUNCH and L-CID, which suggests that the treatment of \( \rho(E) \) for those systems is close enough to equivalent, despite the somewhat different underlying assumptions.\(^{18}\) Perhaps more relevant to the present problem is the comparison of \( E_0 \) for the dissociation of proton-bound dimers of the pyridines with small ortho substituents. The Second Law determinations of \( E_0 \) by threshold CID, deconvoluted from the admittedly modest kinetic shift by L-CID,\(^{1\textprime}}\) and the third Law determinations of \( E_0 \) by high temperature, high pressure mass spectrometry, reported by Meot-Ner,\(^{9\textprime}}\) agree to within the stated experimental error bounds. In the same sense that the thermochemical data in the ATcT database are validated by cross-comparison to independent thermochemical cycles with different physical methods,\(^{2\textprime}}\) the threshold CID measurements, deconvoluted with L-CID, may be claimed to be reliable for the small-to-medium-sized ions for which there are overlapping determinations with other methods. Also, in the same way, small calibration systems, for example the nitrites for which independent bond strengths are known from gas-phase thermolysis and conventional Arrhenius/van't Hoff analysis or gas-phase thermochemical cycles, may be used to cross-check the reliability of the Second-Law T-CID methodologies, deconvoluted with L-CID. Specifically for our case, the Second-Law determination for the BDE in (4-pyridinium)methyl nitrite 10, BDE = 42.5 ± 0.3 kcal/mol, agrees more-than-satisfactorily with that for benzyl nitrite, BDE = 43.2 ± 2.8 kcal/mol, determined from a thermochemical cycle with independent data,\(^{21\textprime}}\) as well as the well-known RO-NO bond strengths, 42-44 kcal/mol, for methyl nitrite, ethyl nitrite, and t-butyl nitrite,\(^{20\textprime}}\) all listed in Table 2. Important for the latter case are the computed BDEs for the nitrites, which range from 36 to 41 kcal/mol, all not far from the experimental numbers. The level of agreement in the proton-bound dimers of small-to-medium-sized pyridines, as well as in the nitrites, for which the departing NO moiety is small enough that London dispersion's contribution to the BDE falls within the uncertainty bounds of the determination (or calculation!), indicates that the Second-Law thermochemical determination for 10, for example, by T-CID, as deconvoluted with L-CID, is reliable for molecules in the tested size range where multiple, independent methods may be brought to bear on the problem.

**Extending the benchmark and lessons learned from it**

Given that the bond dissociation energies for the proton-bound dimers of pyridines with small substituents, as well as the bond dissociation energy of alkyl and benzylic nitrites, are independently validated, a more general validation of the method for larger systems means stepping up the size systematically within a series of otherwise identical test molecules chosen so that the substituents that increase internal degrees-of-freedom do not increase the contribution of London dispersion to the bond dissociation energy. In a sense, the strategy is exactly the opposite of that in our previous study, where we chose to place substituents so that increasing size would lead to increasing interactions. In this present case, the experimental design, see Scheme 2, for example, would call for the Second-Law determination of bond dissociation energies of proton-bound dimers starting with the small pyridines which had been independently validated, but extending out to pyridines with increasingly large substituents placed remotely so that the ionic hydrogen bond in the proton-bound dimer is not affected. One would expect the extracted bond dissociation energies in a series of homologous ions to remain roughly constant if the L-CID deconvolution were to be functioning properly for small and large ions. In the former study, substituents were placed on the ortho positions. In the present study, the substituents were moved to meta- or para-positions on the pyridines with the expectation that the remote substitution would change nothing in the bonding other than the size of the system.
Even a superficial perusal of Table 1 finds that the proton-bound dimers with meta- and para-substitution display bond dissociation energies that differ significantly from those in the validated small pyridine cases. The BDEs vary comparatively widely, and furthermore, follow no immediately obvious, systematic trend. An ad hoc explanation, which we subsequently confirm, vide infra, presented itself when we examined the proton-bound dimers with different DFT methods. Whether the proton-bound dimers of pyridines with large ortho substituents reported in our previous work were bound, for example, by 35-36 kcal/mol, as we claimed from experimental measurement of 5, or 45 kcal/mol, as computed by B97-D3, one finds that the dimer is bound strongly, as expected from the experimental design. In a key observation, the structure of 5 and its analogs found by geometry optimization with B97-D3, furthermore matched the x-ray crystal structure of closely related salts of the proton-bound dimer, Figure 1.14 Examination of either the DFT-computed, or crystallographically determined, structure finds that the proton-bound dimer is compact, in the sense that the ortho substituents are packed together closely, leaving essentially no voids in the structure. The compact packing is indeed part of the original experimental design to maximize the non-covalent interactions. Accordingly, the dissociation energy of 5 is large, whether 35 or 45 kcal/mol, and the structure well-defined. For the proton-bound dimers of meta- and para-substituted pyridines, the expectation would be that the dissociation energy remains, however, around 26 kcal/mol, like it is for the proton-bound dimers of pyridine itself. In practice, the bond dissociation energies measured by T-CID for these proton-bound dimers are larger, meaning that the dimers present in the experiment are more stable than the one expected based on the normal H-bonded structure. A computational search for alternative bound structures formed from the meta-substituted pyridines and the corresponding pyridinium ions found, surprisingly, multiple low-lying structures, often with binding energies much larger than 26 kcal/mol, which would mean that these anomalous dimers are proton-bound with a distorted geometry which permits interaction of large meta substituents, or, in some case, not even proton-bound at all, as depicted in Figure 2. Given that the overall goal of the study required us to shut off non-covalent interactions, the ad hoc conclusion is that the dimers formed from meta-substituted pyridines and pyridiniums, proton-bound, or, indeed, otherwise-bound, may, in fact, be a poor choice for the purpose of validating Second Law T-CID experiments deconvoluted by L-CID. The observed discrepancies between computed and measured bond dissociation energies in Table 1 neither validate nor invalidate the original experiment or the computation. An experimental probe of the structure of dimer 7, shown in Figures 5 and 6, shows an only slightly perturbed N-H stretching vibration in the CIVP spectrum, if one accepts the assignment, which essentially corresponds to an IR absorption spectrum. Both computationally, and in a series of experiments, we have determined that the N-H stretching frequency of the gas-phase pyridinium cations appears around 3400 cm⁻¹,¹³ and that it is strongly red-shifted, by much more than 1000 cm⁻¹, in the proton-bound dimers. Accordingly, the CIVP spectrum of the tested dimer of a meta-substituted pyridine, with an observed band at 3250 cm⁻¹ suggests that the low-lying structure is not hydrogen-bonded at all, i.e. not the desired proton-bound dimer. The most likely structure, taken from the consensus of the calculations, is a face-to-face π-stacked structure, although the multiple aryl moieties would permit, in principle, many other structures consistent with the CIVP spectrum. While it is not the purpose of the present work to establish the structure of all of the anomalous dimers unambiguously, it is nevertheless unambiguous that the ad hoc explanation for the discrepancies in Table 1 is, in fact, highly likely to be correct. A low BDE for the normal, bisected proton-bound dimer means that there are other more favorable dimer structures, especially when the substituents on the pyridine are arené-rich.

The dimers take the most stable structure, whether that is the desired, linear, bisected, proton-bound structure, or some other structure which we call anomalous or π-stacked. If the proton-bound dimer of 5 were to have a BDE = 45 kcal/mol, as computed by B97-D3 and DLPNO-CCSD(T), but another, anomalous or π-stacked structure were to lie yet lower in energy, then the T-CID experiment would necessarily give an experimental BDE even higher than 45 kcal/mol, not lower as we had observed. Furthermore, one should note that, however one may regard the DFT-computed bond dissociation energy, all attempts to optimize geometries of the proton-bound dimer of the ortho-substituted pyridines, e.g. 5, converged to the same linear, bisected, H-bonded dimer (which we also found in the x-ray structure in closely related dimers, Figure 1), in distinct contrast to the case with the meta-substituted pyridines. Accordingly, we conclude with a high certainty that the ortho-substituted pyridines form proton-bound dimers—the global minimum energy structure—and that the discrepancy between the Second-Law experimental BDE for 5, and that calculated for the same structure with B97-D3 or DLPNO-CCSD(T), stubbornly persists.
A better experimental design

The experimental validation of the Second Law T-CID experiment for large ions proved inconclusive because the originally chosen proton-bound dimers were too weakly bound, relative to alternative binding modes. The molecules took more favorable, anomalous or π-stacked structures, and given the approximations in any of the computational methods, the relative ordering in some of the cases remained, in fact, ambiguous, different DFT methods tipping the delicate balance of interactions to favor one structure or another. More specifically, the BDE of the simple proton-bound dimer of pyridine itself, 26 kcal/mol, can be too easily trumped by other interactions, especially when the appropriate substituents make π-stacking possible. The concept for the validation remains nevertheless sound, if a series of dimers were to be bound strongly enough in the desired geometry so that the pendant substituents add degrees-of-freedom but no additional attractive interactions. We propose that the [Ag⁺]-bound dimers with aliphatic para-substituents, 1b-4b in Scheme 3 and Table 1, fulfill this requirement. Computational investigations of the bond dissociation energy of the [Ag⁺]-bound dimer of pyridine find that the BDE should be around 40-45 kcal/mol. Ag⁺ is a closed-shell, d¹⁰ cation for which decades of classical coordination chemistry show a favored linear 2-coordinate geometry. Moreover, 2:1 complexes of pyridines and Ag⁺ salts have been reported in ESI-MS studies, and, importantly, the [Ag⁺]-bound dimer of pyridines have been crystallographically characterized, showing the desired linear, bisected structure, even in cases where these subunits further assemble in the solid-state. We propose that the series of [Ag⁺]-bound dimers of pyridines with increasingly large para-substituents would extend the validation of the Second-Law T-CID experiment, deconvoluted with L-CID, from the small dimer regime, where we already have confidence that the determination is reliable, to the regime of large dimers where the validation would mean that we can tease out the contribution of London dispersion to the BDEs for the large ortho-substituted species.

Scheme 5. Silver-bound pyridinium ions investigated here and their expected BDEs, calculated at different levels of theory.
The experimental results, treated with L-CID, give an unambiguous answer. The [Ag\textsuperscript{+}]-bound dimers of pyridines with para-H, isopropyl, tert-butyl, and adamantyl, spanning a range where the number of degrees-of-freedom goes from 63 to 207, as indicated in Scheme 5. The lower end overlaps with the size regime where the experimental methodology has been validated, and, importantly, the computationally-derived BDEs produced by B97-D3, M06-L, and DLPNO-CCSD(T) all behave consistently in that, for each method by itself, the computed BDE remains approximately constant as the size of the [Ag\textsuperscript{+}]-bound dimer is increased. In other words, the stronger bond, as argued above, gives a preference for the desired, linear structure for the [Ag\textsuperscript{+}]-bound dimers, which, in turn, means that the increase in the number of degrees-of-freedom does not come with a concomitant increase in the contribution of London dispersion to the BDE. According to the experimental design, this should mean that an experimental BDE extracted from a threshold CID measurement, deconvoluted with L-CID, should remain constant along the series if the Second-Law experiment and L-CID behave properly. Examining the extracted BDEs in Table 1 and Scheme 5, one finds that the experimental BDE for all members of the series was found to be 45 ± 2 kcal/mol, which is effectively constant within the uncertainty limits. One can conclude that the L-CID deconvolution of the T-CID experiment operates correctly for both small and large ions, at least within the tested range. We elected not to pursue T-CID experiments with the [Ag\textsuperscript{+}]-bound analogs of 6-9 because of the well-known affinity of Ag\textsuperscript{+} for unsaturated moieties, especially for alkynes. While the pyridines themselves are arenes, the electron-poor \(\pi\)-system of pyridine is less likely to give unexpected structures than would the more electron-rich \(\pi\)-system in the 3,5-di(t-butyl)benzyl side-chains of 6 and 7, or the C=C bonds in 8 and 9, for example, which argues for the selection of 1b-4b, with only saturated, aliphatic substituents, as the test of L-CID's performance in a series from small to large molecules with all confounding factors suppressed or eliminated. One should note that the same logic applied to the series 1a-4a in Table 1, i.e. proton-bound para-substituted pyridine dimers. They also show a reasonably constant set of BDEs, but one also sees some evidence for a deviation, which could signal the onset of alternative structures for the dimers, presumably becoming competitive because the normal H-bond is weak.

Consequences and speculations

The constant BDE in a well-behaved series of complexes which systematically step up the size, but not the London dispersion contribution to the measured bond, indicates that, at least from the experimental methodology itself, there is no reason to doubt the measured BDE for the proton-bound dimers of ortho-substituted pyridines, even when the substituents become large. The result supports the conclusion from the intramolecular competition experiment previously published as a control which favored the (lower) Second Law BDE measurement over the (higher) computed BDE.\textsuperscript{1} In the meantime, we have also reported a Third-Law determination of London dispersion based on conformational equilibria in gas-phase ions, which also concludes that these dispersion-corrected quantum chemical methods appear to overbind significantly.\textsuperscript{13} The present work provides another line or argument in support of that conclusion. Consequently, we claim that the discrepancy with computed results derives from a problem in the computation, about which one can speculate as to the cause. The dispersion-corrected methods appear to model the interaction adequately for small molecular systems, but then they seem to diverge increasingly as the size of the system increases. We speculate about four areas where the methods could be examined:

1. The D3 methods have been constructed carefully to give an asymptotically correct behavior of the potential function at large distances,\textsuperscript{14} which has been cited as evidence that they would provide a reliable guide to structure and energetics in molecular systems with significant contributions of non-covalent interactions to bond dissociation energies, for example. One should note, however, that the actual potential attributed to London dispersion is the sum of the D3 correction and the opposing damping function,\textsuperscript{38} the latter being insignificant at longer distances. At the distances where non-covalent contacts play an important role, 2-4 Å, the damping function and the D3 correction sum up to the observed potential, which is the small difference between two much larger values. Even if the D3 correction is built to give the correct asymptotic behavior, a small change in the damping function, which is a substantially simpler, parameterized empirical function, will give chemically significant deviations from the actual, physical potential, which, furthermore, should rise rapidly with the "size" of the system, because the number of atom pairwise interactions necessarily rises faster than does the number of atoms. Validation of the combination of the damping function with the D3 correction for the interaction at long distances, and for the interaction in small molecules where the overall effect is relatively small, would not reveal a systematic discrepancy because that validation is done for long distances where the
damping function has gone to zero anyways. It would only appear when the molecular system grew much larger and the distances were intermediate.

(2) The D3 correction was constructed from CCSD(T)-computed molecular polarizabilities of diatomics, which themselves had been validated by comparison to experimentally measured polarizabilities in the cases where the data are available. Construction of the correction from diatomics, even in the case that the reproduction of the original data were to be exact, produces a correction which is necessarily atom-centered and isotropic. Whereas three-body corrections do, in fact, introduce an element of anisotropy in the overall London Dispersion Potential, one should be cognizant that parameters derived from the model are nevertheless inherently isotropic. Taking the Clausius-Mosotti equation, one sees a relationship between molecular polarizability and bulk refractive index. The phenomenon suggests that an isotropic C\(\pi\) coefficient in the D3 correction may itself cause unforeseen errors. As an indication that anisotropy may indeed be significant in the context of common organic functional groups, consider some of the Second Law measurements of dissociation energies in the anomalous dimers listed in Table 1. For the dimer 6, the lowest-lying computed geometries, an anomalous structure with extensive \(\pi\)-stacking of the meta-substituents, and the almost isoenergetic \(\pi\)-stacked isomer, make 6 unsuitable for inclusion in a test series because all members of the series would not be isostructural. The B97-D3-computed BDE for the anomalous structures agree, however, extremely well with the L-CID deconvolution of the T-CID experiment, even if the B97-D3-computed BDE for 5 does not. The agreement could, in principle, be coincidental, but it could also indicate that the particular orientation of the interacting substituents, in the case of 6, face-to-face parallel, corresponds to a direction for which the C\(\pi\) and C\(\delta\) coefficients in the D3 correction are, in fact, correct. One notes that D3-corrected methods reproduced strain energies in cyclophanes, in which the interaction is also face-to-face \(\pi\)-stacking, very well. Looking at Figure 1, one sees that 5 has no face-to-face \(\pi\)-stacking interactions at all, the important non-covalent interactions being rather CH-\(\pi\), or edge-to-face interactions of the rings. Further work with more systematically designed test molecules would be needed before this hypothesis would rise above ad hoc status, but it is a factor to ponder.

(3) For the DLPNO-CCSD(T) method, the challenge of rationalizing the results is more difficult. We suggest, tentatively, that the discrepancy for the larger molecular systems could possibly arise from the use of normal PNO cutoffs. In principle, DLPNO-CCSD(T) achieves its impressively better scaling with the number of basis functions, as compared to canonical CCSD(T), by choosing carefully which clusters are treated explicitly. The remaining ones are treated with LMP2, a local version of MP2. The transition is controlled by the PNO cutoff, which can be set to normal, tight, or extremely tight. For smaller molecules, validation studies show that the error introduced by the normal PNO cutoff, relative to extremely tight, or even canonical CCSD(T), is limited.

The scaling of the error with size is more difficult to predict. If one were to translate the PNO cutoff into a distance beyond which a non-covalent interaction is treated by LMP2 rather than explicit coupled-cluster theory, then one might speculate that the long-known tendency of MP2, not to speak of LMP2, to overbind may be the origin of the discrepancy between DLPNO-CCSD(T) results and our measurements for large systems with many non-covalent contacts in the 2-5 Å range. The large dimers, which means for us >100 atoms, would require tens of thousands basis functions, if one were to do the CBS extrapolation with basis sets of triple-\(\zeta\) quality or better. With present resources, they can be treated in DLPNO-CCSD(T) calculations only with normal PNO. A tighter PNO cutoff leads to increasingly unfavorable scaling of the calculation with the number of basis functions, which means that a fair test of the method for the larger systems in our series is presently out-of-reach with our computational resources.
(4) One further possibility may play a role in the discrepancy between DLPNO-CCSD(T) bond energies and the experimental determinations for the largest ions. In the computed BDEs, we extrapolated to the complete basis set (CBS) limit. While the extrapolation, in itself, is unquestioned, there are two practical issues. Ideally, in the case of a two-point extrapolation, one would use CBS(3,4), i.e. extrapolation based on triple-ζ and quadruple-ζ calculations. This is usually the case for the smaller ions in this, and our previous, study. For the larger ions, however, even normal PNO calculations with basis sets beyond triple-ζ are not yet practical, so CBS(2,3) extrapolations were executed. Slow convergence of the energies with increasing basis set size, especially if the convergence rate for the monomers and dimers is inconsistent, could introduce a significant error. Moreover, there is still an open debate among practitioners whether the extrapolation should be done with the counterpoise correction for basis set superposition error (BSSE) for the double-ζ, the double- and triple-ζ, or neither part of the CBS(2,3) calculation. Preliminary investigations find that the computed BDE at the CBS limit can be shifted by many kcal/mol in large molecules, depending on which of these variations one chooses.

Conclusions

Starting with a discrepancy between an experimentally-determined bond dissociation energy for a large molecular ion designed to emphasize the contribution of dispersion forces, and the corresponding computationally-derived bond energies, we have designed further series of structures whose trends in bond dissociation energies should test whether the discrepancy comes from the failure of approximations inherent to the experiment or failure of approximations made in the computation. Initial results were surprising, with the unexpected findings attributable to alternative structures for the ions, which we could confirm spectroscopically. More strongly bond test molecules provided a structurally well-defined series whose measured bond dissociation energies confirmed that the T-CID experiment, deconvoluted with the L-CID program, a typical “Second Law” experiment, treats the kinetic shift well enough to handle molecules with up to approximately 100 atoms. Accordingly, we conclude that the discrepancy in bond dissociation energy for the large molecular ions between values extracted from a T-CID experiment and those computed with DFT-D3 or DLPNO-CCSD(T) comes from problems in the calculations.

Experimental

Synthesis and Materials

4-Isopropylpyridine and 4-tert-butylpyrididine were purchased from commercial suppliers. 4-Adamantylpyridine was synthesized according to the published procedure. The meta-substituted pyridines were synthesized using the standard Pd-catalyzed coupling reactions, especially the Negishi, Suzuki and Sonagashira reactions. For more details, see the SI.

T-CID Measurements and L-CID Fitting

Stock solutions for all the measured systems were prepared by diluting the corresponding pyridine in MeOH with c ≈ 10⁻³ mol L⁻¹. Solutions for electrospraying were prepared by diluting the stock solutions 100-fold. For the weaker bound complexes such as 4-isopropylpyridine the stock solution was either diluted only 10 fold, or used as is. The silver-bound complexes were prepared by mixing the pyridine stock solutions with a stock solution of AgNO₃ in MeOH (c ≈ 10⁻³ mol L⁻¹). The protonated 4-pyridinylmethyl nitrite complex was prepared in situ by mixing and diluting a stock solution of (4-pyridinyl)methanol with a stock solution of tert-butyl nitrite (both in MeOH, c ≈ 10⁻³ mol L⁻¹). All the silver-bound dimers, the protonated (4-pyridinyl)methyl nitrite and proton-bound dimers were measured on the TSQ Quantum Ultra EMR and the data were worked up with a custom Python script. All the data were fitted using the L-CID software using at least 5 pressure curves and at least 15 fits. All the fittings used the loose transition state model.

Computational details

All of the computations were performed with the ORCA software suite (version 4.1.1) with the exceptions of the conformational searches, which were done with the CREST (version 2.7.1) and XTB (version 6.1) programs. Initial structures for the dimers were obtained from the CREST conformational searches using the nci setting and two different starting structures – linear and stacked. Structures that were not simply rotamers were then optimized with the B97-D3 functional and the def2-TZVP basis set. The optimization criteria were manually lowered to be stricter than the ones set by the TightOPT keyword. All the DFT calculations used the resolution of identity (RI) approximation with the def2-J basis set. Vibrational frequencies and the zero-point energy (ZPE) corrections were also
obtained from the B97-D3/def2-TZVP calculations. The final DFT BDEs were calculated as single points with the def2-QZVP basis set. No CBS was used for the DFT values, because the triple-\(\zeta\) and quadruple-\(\zeta\) values differed by less than 0.1 kcal mol\(^{-1}\). The DLPNO-CCSD(T)\(^{12,54}\) calculations were done using also the def2-XVP basis sets and the associated def2-XVP/C Coloumb fitting basis sets.\(^{55}\) The final BDE values were extrapolated to the CBS limit using the 2-point extrapolation scheme\(^{56}\) with double-\(\zeta\) and triple-\(\zeta\) basis sets.

**CIVP spectroscopy**

The ions were generated by electrospaying the MeOH solutions of the precursor pyridines. The ions of interested were than pre-selected with the quadrupole mass filter and guided into the FT-ICR cell where they are cooled with a buffer gas. Upon cooling the ions produce a distribution of untagged and multiply tagged species. The ions are then irradiated with an IR laser for several seconds and the absorption causes the tags to dissociate thus generating a new distribution of the tagged and untagged species. CIVP spectrum is then recorded by varying the frequency of the IR laser and comparing the change in ratio of the tagged and untagged species when the laser beamline is closed and open. For more details, see our recent publication.\(^{52}\)

**Acknowledgements**

The authors acknowledge assistance and discussions with Dr. Robert Pollice and Felix Fleckenstein. Dr. Larisa Miloglyadova provided support in setting up the CIVP spectroscopy. Financial support for this work from the ETH Zürich, the Swiss National Science Foundation, and the European Research Council is also gratefully acknowledged.

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For 5, attempts at crystallization have produced x-ray-quality crystals, but the crystals were of the the pyridinium salt itself, i.e. the protonated monomer rather than proton-bound dimer.


For benzyl nitrite, there is an old determination of the PhCH₂O-NO BDE in a gas-phase thermolysis, Gray, P.; Rathbone, P.; Williams, A. *J. Chem. Soc.* **1960**, 3932-3943; which reports 34 ± 2 kcal/mol, but whose reliability may have been compromised. The decomposition was not first-order, and it showed autocatalysis attributed to radical chain reactions. An alternative value for the BDE of 43.2 ± 2.8 kcal/mol for the RO-NO bond in benzyl nitrite may be constructed via a thermochemical cycle combining the measured proton affinity of benzyl alcohol, Bartmess, J.; Scott, J. A.; McIver, R. T. Jr. *J. Am. Chem. Soc.* **1979**, *101*, 6046-6056; with the electron affinity of benzyloxy radical, Moylan, C. R.; Dodd, J. A.; Han, C. C.; Brauman, J. I. *J. Chem. Phys.* **1987**, *86*, 5350-5357; as well as the ΔH[benzyl nitrite] = 7.8 ± 2.0 kcal/mol derived from the reported R-ONO BDE of benzyl nitrite, and ΔH[benzyl radical], NO, and NO₂, Luo, Y. R.; Holmes, J. L. *J. Phys. Chem.* **1994**, *98*, 303-312. The most important value derived in the thermochemical cycle, ΔH[benzyloxy radical] = 29.2 ± 2.0 kcal/mol, agrees extremely well with the computed G3 value, da Silva, G.; Bozzelli, J. W. *J. Phys. Chem. A* **2009**, *113*, 6979-6986; which further supports the result of BDE = 43.2 ± 2.8 kcal/mol for RO-NO.


