Direct measurement of the energy thresholds to conformational isomerization in Tryptamine: Experiment and theory

Jasper R. Clarkson, Brian C. Dian, and Loïck Moriggi
Department of Chemistry, Purdue University, West Lafayette, Indiana 47906

Albert DeFusco, Valerie McCarthy, and Kenneth D. Jordan
Department of Chemistry, University of Pittsburgh, Pittsburgh, Pennsylvania 15260

Timothy S. Zwier
Department of Chemistry, Purdue University, West Lafayette, Indiana 47906

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The methods of stimulated emission pumping-hole filling spectroscopy (SEP-HFS) and stimulated emission pumping population transfer spectroscopy (SEP-PTS) were applied to the conformation-specific study of conformational isomerization in tryptamine [TRA, 3-(2-aminoethyl)indole]. These experimental methods employ stimulated emission pumping to selectively excite a fraction of the population of a single conformation of TRA to well-defined ground-state vibrational levels. This produces single conformations with well-defined internal energy, tunable over a range of energies from near the zero-point level to well above the lowest barriers to conformational isomerization. When the SEP step overcomes a barrier to isomerization, a fraction of the excited population isomerizes to form that product. By carrying out SEP excitation early in a supersonic expansion, these product molecules are subsequently cooled to their zero-point vibrational levels, where they can be detected downstream with a third tunable laser that probes the ground-state population of a particular product conformer via a unique ultraviolet transition using laser-induced fluorescence. The population transfer spectra (recorded by tuning the SEP dump laser while holding the pump and probe lasers fixed) exhibit sharp onsets that directly determine the energy thresholds for conformational isomerization in a given reactant-product conformer pair. In the absence of tunneling effects, the first observed transition in a given X→Y PTS constitutes an upper bound to the energy barrier to conformational isomerization, while the last transition not observed constitutes a lower bound. The bounds for isomerizing conformer A of tryptamine to B(688–748 cm⁻¹), C(1)(860–1000 cm⁻¹), C(2)(1219–1316 cm⁻¹), D(1219–1282 cm⁻¹), E(1219–1316 cm⁻¹), and F(688–748 cm⁻¹) are determined. In addition, thresholds for isomerizing from B to A(<1562 cm⁻¹), B to F(562–688 cm⁻¹), and out of C(2) to B(<747 cm⁻¹) are also determined. The A→B and B→A transitions are used to place bounds on the relative energies of minima B relative to A, with B lying at least 126 cm⁻¹ above A. The corresponding barriers have been computed using both density functional and second-order many-body perturbation theory methods in order to establish the level of theory needed to reproduce experimental results. While most of the computed barriers match experiment well, the barriers for the A→F and B→F transitions are too high by almost a factor of 2. Possible reasons for this discrepancy are discussed. © 2005 American Institute of Physics. [DOI: 10.1063/1.1924454]

I. INTRODUCTION

Molecules with several torsional degrees of freedom undergo conformational isomerization on highly corrugated, multidimensional potential-energy surfaces containing many minima and an even greater number of transition states separating them. When there are local minima close in energy to the global minimum, they can acquire significant population, even when the molecule is cooled in a supersonic expansion.

Building off a foundation of conformation-specific infrared and ultraviolet spectroscopies, we have recently been studying the conformational isomerization dynamics of such molecules using a new experimental protocol developed expressly for this purpose. As shown schematically in Fig. 1 this protocol involves (i) initial cooling of the molecules of interest to their zero-point levels, (ii) selective laser excitation of a single “reactant” conformation in the mixture while the molecules are still in a high-density region of the expansion where collisions are prevalent, (iii) isomerization and recooling of the molecules, followed by (iv) selective detection of a single “product” conformation downstream in the collision-free region of the expansion with a probe laser.

The initial studies that used this cool-excite-cool-probe scheme employed infrared excitation of a single conformation via the amide NH stretch fundamentals to initiate con-
formational excitation. Conformation-selective excitation and detection steps provide a means of dissecting the complex set of isomerization processes into individual reactant-product pairs. When the infrared laser is fixed and the probe laser tuned, one can determine which products are formed. This scheme is called IR-UV hole-filling spectroscopy because the "hole" created in the ground-state population of the excited conformer is used to fill in population in product conformers. On the other hand, when the IR laser is tuned while the UV probe laser is fixed to monitor a given product conformer population, the resulting spectrum called an IR-induced population transfer spectrum records the fractional population change induced by the infrared laser. By piecing together the results of a series of IR-population transfer spectra, it is possible to determine the isomerization quantum yields following conformation-selective infrared excitation.

One of the nonideal aspects of the infrared excitation scheme is that absorption of one infrared photon in the hydride stretch fundamental region puts 10 kcal/mol of energy into the excited conformation, well above many of the lowest-energy barriers to isomerization. Recently, we reported first results of a variation of the hole-filling method that employs simulated emission pumping (SEP) rather than infrared excitation. SEP is a powerful spectroscopic technique which has been utilized in a number of ways. With SEP, it is possible to tune widely over ground-state vibrational energies ranging from the vibrational zero-point level to well above the lowest-energy barriers to isomerization. In doing so, it is possible to directly measure the energy thresholds to isomerization for individual reactant-product pairs. Thus, the SEP-PT spectra provide a spectroscopic means of placing bounds on the barrier heights to conformational isomerization. This is an exciting prospect because spectroscopy almost always characterizes the minima on the potential-energy surface rather than the barriers.

The SEP hole-filling scheme was carried out first on tryptamine [TRA, 3-(2-aminoethyl)indole]. In the initial report, we demonstrated the ability of the method to measure the barriers to conformational isomerization, even in a case where there are several isomers present. In this respect, TRA is quite a challenge because it possesses seven conformational isomers with significant population, even under conditions of supersonic expansion cooling. As a result, there are 42 individual reactant-product pairs. Of course, the $X \rightarrow Y$ and $Y \rightarrow X$ pairs measure the same barrier from either direction. The difference in these energy thresholds then constitutes a measure of the energy differences between the minima; that is,

\[ E_{\text{thresh}}(X \rightarrow Y) - E_{\text{thresh}}(Y \rightarrow X) = E_{\text{min}}(Y) - E_{\text{min}}(X). \]

Thus, the combined results from all 42 $X \rightarrow Y$ pairs could in principle constitute a complete characterization of the energies of the relevant stationary points on the potential-energy surface for isomerization.
In the present paper, we provide a complete account of the SEP hole-filling studies of tryptamine. In addition to a more detailed exposition of the full experimental data set, we have now carried out an extensive set of \textit{ab initio} and density-functional theoretical (DFT) calculations of the transition states for conformational isomerization in TRA, for comparison with the experimental data. As we shall see, the experimental data match well with calculations for most of the reactant-product pairs measured. However, the thresholds into conformer well $F$ are computed to be about a factor of 2 higher than the experiment. The effect of tunneling on the measured isomerization thresholds has been explored by using tryptamine deuterated at the amino site.

The study of TRA presented here is followed up in an adjoining paper by an analogous study of conformational isomerization in 3-indole propionic acid (IPA) and its water-containing complexes.\textsuperscript{23}

II. METHODS

A. Experiment

The laser-induced fluorescence (LIF) chamber used in these experiments has been described in detail elsewhere.\textsuperscript{11} Those aspects of the experiment that are unique to the SEP hole-filling method are described here. The three UV laser beams enter the chamber through CaF$_2$ windows mounted at the Brewster’s angle before passing through a set of baffles containing $2 \times 10$ mm slits to allow easy spatial movement of the laser beams intersecting the supersonic expansion. The laser beams intersect the supersonic expansion at right angles while the fluorescence is collected by a filtered photomultiplier tube (PMT) (ETI 931QB with WG320 and WG305 cut-off filters) perpendicular to both the jet and the excitation beam. TRA (Aldrich) was resistively heated to 400 K in a stainless-steel sample holder. The sample was entrained in helium (commercial grade, 99.995\%) at a total pressure of 7 bars and expanded through a 20-Hz pulsed valve (Parker General, Series 9, 2-mm orifice) into a vacuum chamber pumped with a roots blower (Leybold, WS-1001) backed by two rotary vane mechanical pumps (Sargent-Welch) to supersonically cool the molecules into their conformational-specific zero-point levels. Total flow rates of $2 \times 10^{-3}$ bar L/s in a 1.0–1.5-ms gas pulse were used, leading to a vacuum chamber pressure of $\approx 5 \times 10^{-3}$ bar.

Three independent Nd:YAG- yttrium aluminum garnet pumped (Continuum 7000 series and NY-61) doubled dye lasers (Lumonics HD-500, Lambda Physik Scanmate 2E and FL3002) were employed. Foundational to all methods was laser-induced fluorescence excitation spectroscopy, in which a single ultraviolet laser ($\sim 0.1$ mJ/pulse) was tuned through the $S_1 \rightarrow S_0$ origin region of jet-cooled tryptamine. LIF spectroscopy was carried out at a distance ($\chi$) 12 mm downstream from the 2-mm-diameter expansion orifice ($D$) (corresponding to $x/D = 6$). SEP spectra were recorded at this same spatial position, with the pump laser $\lambda_1$ fixed on the $S_1 \rightarrow S_0$ origin band of a specific conformer. In the dump step, the excited-state population was transferred to a particular vibrational level in the ground state $[S_0(v)]$ via stimulated emission induced by a second tunable laser (the “dump” laser). Under optimal conditions, as much as 30\%–40\% of the population in the $S_1$ state of a particular conformation of TRA can be driven back to $S_0(v)$. The magnitude of this population transfer depends on (i) the laser powers in both pump and dump steps, (ii) the lifetime of the $S_1$ state, (iii) the delay between pump and dump lasers, (iv) the oscillator strength and Franck–Condon factors for the dump transitions, and (v) the rate of collisional removal from the lower level.

The SEP spectra were recorded using the active baseline subtraction mode of a gated integrator (SRS 250). The dump laser (10 Hz) was pulsed every other time the pump laser (20 Hz) fires. A negative signal indicates that the dump laser has depleted the fluorescence signal. Typical pulse energies for the pump and dump steps were $0.1$–0.2 and 0.5–1.0 mJ, respectively. Focusing conditions were chosen to ensure that the dump laser beam was larger than the pump laser, with the pump and dump lasers focused with 50- and 70-cm focal length lenses, respectively.

In order to detect the SEP dump transition, the two lasers were delayed somewhere in the range of 2–10 ns, determined by a compromise between maximizing the dip in the fluorescence signal and minimizing the interference from scattered light from the dump laser. The gated signal was delayed as far from the scattered light as possible while collecting sufficient fluorescence to detect the depletion in fluorescence signal created by the dump laser.

The triple-resonance methods presented here share the pump-dump-probe excitation scheme with the studies of Kable and Knight\textsuperscript{24} and Burgi et al.\textsuperscript{25,26} The unique aspect of the present work is the place of SEP excitation, sufficiently downstream so that SEP excitation could be cleanly carried out from the vibrational zero-point levels of the conformational isomers, but in a collisional regime where sufficient collisional cooling occurred subsequent to the SEP step to recollect the population into the zero-point levels of the various conformers prior to probing downstream. The lasers used for SEP excitation typically intersected the expansion at $x/D = 2$–2.5, while the probe laser was set to $x/D = 6$, producing a delay between pump/dump and probe of 1.8–2.0 $\mu$s for optimal signal, determined by the terminal velocity of a helium expansion ($1.8 \times 10^3$ cm/s). We estimate a collision rate for tryptamine with helium at $4 \times 10^9$ s$^{-1}$ at the SEP excitation point in the expansion under typical expansion conditions, falling off as $(x/D)^2$.

Two schemes, differing in terms of which lasers were tuned and which were fixed in wavelength, were employed for the infrared excitation.\textsuperscript{11} In SEP-population transfer spectroscopy, the pump and probe lasers were fixed on the $S_1 \rightarrow S_0$ origin transitions of two conformational isomers (e.g., $A$ and $B$, respectively), while the dump laser was tuned. As its name implies, population transfer (PT) spectroscopy monitors the amount of population transferred from $A$ to $B$ as a function of the internal energy placed in $A$ by the dump laser:

$$A^*(E_{\text{int}}) \rightarrow B.$$  

In order to selectively highlight the population transfer due to the dump laser, the pump and probe lasers operated at
20 Hz, while the dump laser operated at 10 Hz. The difference in signal between successive probe pulses was recorded using active baseline subtraction. By recording the LIF signal size due to conformer $B$ before and after the PT spectrum, the ordinate can be recorded as a fractional change in the population of the product $B$ induced by the dump laser.

A second variation, SEP hole-filling spectroscopy (HFS), has both the pump and dump wavelengths fixed; thereby selectively exciting a particular conformational isomer to a ground-state vibrational level with well-defined internal energy. In HFS, the probe laser was scanned to determine where the population went, with gains in the probe signal occurring whenever transitions due to energetically open product channels were encountered.

Since PT and HF spectroscopies require careful spatial and temporal controls of three laser beams, two laser checks were developed to assist in setting up the experiment. The proper timing and spatial arrangement between pump and probe lasers could be set by pulling back the nozzle so that collisional refilling could not occur, and then maximizing the SEP dip in the fluorescence signal from conformer $A$ produced by the pump laser fixed on the same transition. Maximizing the SEP dip was used to maximize the spatial overlap between pump and dump. These two checks were typically sufficient to observe some signal in the three-laser experiment. Final optimization of the delay and spatial overlap between pump and dump was carried out on the three-laser signal under hole-filling conditions.

TRAs deuterated at the NH$_2$ and indole NH sites [TRA($d_3$)] was prepared in order to test for the effects of tunneling involving the NH$_2$ hydrogen on the measured energy thresholds for isomerization. Because TRA is relatively insoluble in pure D$_2$O, the sample was dissolved in excess tetrahydrofuran in the presence of D$_2$O. The exchange was allowed to occur for several hours before removal of the solvent with a rotary evaporator. The procedure was repeated three times to bring the sample to near-complete deuteration at the ND$_2$ site. The resulting purity and further experimental details concerning the deuterated sample will be presented in the Results section.

### Table I. Dihedral angles (degrees) of local minima of tryptamine

For each conformer, with the exception of G, there is a second structure differing only by exchange of the two NH$_2$ H atoms. Results from Becke3LYP/6-31+G($d$) calculations.

<table>
<thead>
<tr>
<th>Conformer</th>
<th>$\alpha$</th>
<th>$\beta$</th>
<th>$\psi$</th>
<th>$\epsilon$</th>
</tr>
</thead>
<tbody>
<tr>
<td>$A$</td>
<td>-76.13</td>
<td>-64.04</td>
<td>122.77</td>
<td>76.13</td>
</tr>
<tr>
<td>$B$</td>
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<td>74.43</td>
</tr>
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<td>$H$</td>
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<td>-121.53</td>
<td>149.79</td>
</tr>
<tr>
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<td>65.68</td>
<td>-125.62</td>
<td>85.08</td>
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<tr>
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<td>82.57</td>
<td>133.11</td>
<td>68.60</td>
</tr>
<tr>
<td>$F$</td>
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<td>61.40</td>
<td>2.10</td>
<td>91.15</td>
</tr>
<tr>
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<td>176.27</td>
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<td>178.73</td>
<td>125.48</td>
<td>177.92</td>
</tr>
</tbody>
</table>

### B. Calculations

The minimum-energy structures were optimized using the Becke3 Lee–Yang–Parr ($\text{LYP}$) density-functional method with both the 6-31+G($d$) (Ref. 29) and augmented correlation consistent polarized valence double zeta (aug-cc-pVDZ) basis sets. Transition state structures were then optimized at the Becke3LYP/6-31+G($d$) level and employing the quadratic synchronous transit (QST3) (Ref. 33) algorithm. These calculations were followed up with the resolution of the identity second-order Møller-Plesset (RIMP2) (Refs. 34 and 35) single-point calculations at the Becke3LYP/6-31+G($d$) geometries. In addition, all local minima and a subset of the transition states were reoptimized at the RIMP2/aug-cc-pVDZ level. For selected minima and transition state structures, single-point RIMP2/augmented correlation consistent polarized valence triple zeta (aug-cc-pVTZ) and second-order Møller–Plesset (MP2)/aug-cc-pVDZ energies were calculated using RIMP2/aug-cc-pVDZ geometries, and in some cases, MP2/aug-cc-pVDZ geometry optimizations were performed as well. The results for these calculations are presented in their entirety in supplementary material and will be referred to throughout the text as necessary.

The RIMP2 procedure uses a resolution of the identity operator approach to reduce the computational effort associated with MP2-level calculations. Several studies have shown that the errors introduced in relative energies due to the use of this approximation is generally 0.1 kcal/mol or less. The main advantage of the MP2 and RIMP2 procedures over the computationally faster Becke3LYP method is the proper treatment of long-range dispersion interactions.

The Becke3LYP and MP2 calculations were carried out using the GAUSSIAN 03 program$^{37}$ and the RIMP2 calculations were carried out using the TURBOMOLE program. All Becke3LYP calculations used the ultrafine grid and tight convergence criteria as implemented in GAUSSIAN 03.

As will be discussed below, there are significant differences in some of the relative energies obtained from the Becke3LYP and RIMP2 calculations. To gain insight into the origin of these differences we also carried out coupled clus-
Conformational isomerization in tryptamine


FIG. 2. (a) LIF excitation spectrum of tryptamine in the region of the \( S_1 \rightarrow S_0 \) origins. Seven conformations are observed under supersonic conditions. The ethylamine side chain adopts several positions relative to the indole ring as shown and labeled in the inset. (b) Tryptamine dihedral angle definitions used in this work. Note that atom 25 is a “dummy” atom used to simplify the motions of the amino rotation.

FIG. 3. (a) Schematic PES of the nine calculated minima of tryptamine and their abbreviated structural designations plotted along two flexible coordinates \( \Psi \) and \( \beta \) corresponding to an amino internal rotation (C17–N20) and a C16–C17 rotation, respectively. (b) The calculated energies of the minima and all associated transition states interconnecting all minima about the two internal coordinates. All energies are in kcal/mol from B3LYP/6-31 +G(d) optimizations employing the QST3 algorithm for the transition state structures.

III. CONFORMATIONAL ASSIGNMENTS AND CALCULATED STATIONARY POINTS ON THE POTENTIAL-ENERGY SURFACE OF TRYPATMINE

The present work on conformational isomerization dynamics of TRA builds off previous studies that have assigned the observed \( S_1 \rightarrow S_0 \) vibronic transitions to particular conformational isomers.\(^3\),\(^18\)–\(^22\) The recent high-resolution study of the origin bands of the isomers by Nguyen et al.\(^22\) have provided convincing evidence for the assignments given in Fig. 2(a). The labels in the figure make use of a shorthand notation for the conformers which designates the position of the amino group relative to the indole ring: Anti, gauche on the phenyl (Gph), and gauche on the pyrrole (Gpy) side of indole.\(^3\) The label in parentheses refers to the direction of the amino nitrogen lone pair relative to the indole ring.

ter singles, doubles (triples) [CCSD(T)]\(^39,40\) coupled cluster single point calculations for the various minima using the 6-31+G(d) basis set and the RIMP2 geometries.
A. Conformational minima

The flexible ethylamine side chain present in TRA has a total of four coordinates along which large-amplitude motion can occur [Fig. 2(b)]. These include internal rotation about the C17–N20 (dihedral angle $\phi$), C16–C17 (dihedral angle $\beta$), and C15–C16 (dihedral angle $\alpha$) bonds and inversion of the NH$_2$ group. Table I summarizes the computed Becke3LYP values of these torsional angles for all minima located on the potential-energy surface. The geometrical parameters obtained at the RIMP2 level are reported in Table A in the supplementary material.

The seven lowest-energy minima (as determined from the Becke3LYP calculations) share a common configuration about the C15–C16 bond that points the C16–C17 bond approximately perpendicular to the indole ring ($\alpha = \pm 90^{\circ}$). The inversion of the NH$_2$ group has a barrier high enough that it is safe to conclude that the lowest-energy conformers differ primarily in the angles of internal rotation about the C16–C17 and C17–N20 bonds ($\beta$ and $\phi$). As a result, it is useful to consider the potential-energy surface as a function of $\beta$ and $\phi$ shown in Fig. 3. The threefold character of the potential along each of these coordinates produces nine conformational minima, seven of which are observed experimentally. The structures associated with these minima are shown in Fig. 3(a), and the computed energies of the minima and transition states (first-order saddle points) are given in Fig. 3(b). The two unobserved conformers are those in which the nitrogen lone pair points in toward the indole $\pi$ cloud [Gpy(in)/H and Gph(in)/J], which destabilizes these minima relative to the others. In conformer $H$, this leads to a substantial distortion of the structure in which the side chain rotates to about $-150.0^{\circ}$ about the C15–C16 bond so that the nitrogen lone pair is stabilized by interaction with an aromatic C–H group. One could argue that the distortion is so large that structure $H$ does not actually belong on the two-dimensional (2D) potential-energy surface depicted in Fig. 3.

Two other minima, labeled $G$ and $I$ in the tables, have the heavy atoms of the ethylamine side chain lying in or close to the plane of the aromatic ring [Fig. 4(a)]. These minima are formed by internal rotation of each of the three “anti” structures $E, C(1)$, and $D$ about the C15–C16 bond. These structures highlight the possibility that pathways to isomerization could swing the ethylamine side chain from one side of the indole plane to the other. As Fig. 4(b) shows, each of the conformational minima has a mirror image isomer. These enantiomers (labeled a and b) are spectroscopically indistinguishable, but could play a role in isomerization pathways that swing the ethylamine side chain from one side of the indole ring to the other.

Finally, a combination of inversion and internal rotation of the NH$_2$ group swaps the positions of the two hydrogens. These spectroscopically indistinguishable isomers [labeled with and without a prime (‘)] are relevant to isomerization pathways that involve these coordinates.

The relative energies of the minima computed at several levels of theory are given in Table II. The relative energies at the Becke3LYP/6-31+G(d) and Becke3LYP/aug-cc-pVDZ levels of theory are in fairly good agreement. Stress is placed on the Becke3LYP/6-31+G(d) level since the transition state optimizations with the Becke3LYP method were carried out only with the same basis set. Inspection of these results reveals that $A, B, C(2)$, and $F$ are preferentially stabilized by 0.6–1.8 kcal/mol relative to the other minima when going from the Becke3LYP to the RIMP2 method.

For all minima the relative energies from the RIMP2/ aug-cc-pVDZ and MP2/6-31+G(d) are in fairly good agreement, which indicates that basis set superposition error$^{31}$ is not the origin of the discrepancies between the Becke3LYP and MP2 results. In order to determine the origin of the inconsistencies between the RIMP2 and Becke3LYP results, we also carried out CCSD(T)/6-31+G(d) calculations at several of the local minima using the Becke3LYP/6-31 +G(d) and RIMP2/aug-cc-pVDZ geometries. In all cases the relative energies obtained from the CCSD(T) calculations are in good agreement with the RIMP2 results. This leads us to conclude that the stabilization of $A, B, C(2)$, and $F$ relative to the other conformers is a consequence of a greater importance of dispersion interactions in the former set of minima. Further support for this conclusion is provided by the results of the Hartree–Fock calculations, namely, the energy lower-

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**Fig. 4.** Two minima not shown on the schematic PES which have the ethylamine side chain in or near the plane of the aromatic ring. (b) Each of the minima has a mirror image isomer. Conformer $B$ of tryptamine is highlighted as an example. These isomers and their mirror images could play a role in isomerization pathways.
ing in going from the Hartree–Fock to the MP2 method is appreciable greater for $A$, $B$, $C_2$, and $F$ than for the other conformers.

Figure 5 summarizes the energies of the various conformers calculated at the different levels of theory, with conformer $I$ being chosen as the zero of energy. This figure underscores the close agreement between the RIMP2 and CCSD results and the fact that the Becke3LYP method is giving relative energies roughly intermediate between the Hartree–Fock and CCSD results. Further it is seen that the dispersion in the relative energies predicted by the various methods grows as one proceeds from the structures with the chain “in the plane” (right-hand side) to the structures with one of the amino NH bonds pointed toward the ring system (left-hand side).

B. Transition states

Searches for transition states connecting the minima were carried out at the Becke3LYP/6-31+G(d) level of theory. Structural parameters associated with the transition states are given in Table B of the supplementary material, while their energies relative to the lowest-energy minimum (conformer $A$) are collected in Table III.

For the most part, the transition state energies obtained from the Becke3LYP and RIMP2 methods are in fairly good agreement, with the largest changes being in those cases for which one is proceeding from one of the minima $A, B, C_2$, or $F$ to one of the other minima. In these cases the energies calculated at the RIMP2 level tend to be about 1 kcal/mol higher than the corresponding values calculated at the Becke3LYP level. The predictions from theory serve as a point of comparison for the experimental results described in Sec. IV.

IV. EXPERIMENTAL RESULTS AND ANALYSIS

A. “Upstream” LIF spectra

The hole-filling experimental protocol (Sec. II A) calls for SEP excitation of a single conformer to take place out of the vibrational zero-point level of that conformer. In doing so, the initial internal energy available to the conformer for isomerization has a single, well-defined value determined by the difference in the wavelengths of the pump and dump lasers. Much of this selective excitation is achieved by the choice of pump wavelength, which is fixed on the $S_0$-$S_1$ origin transition of the conformer of interest. In addition, we seek to carry out excitation at a point in the expansion where

![FIG. 5. Energies of the various conformers calculated at the different levels of theory, with conformer $I$ being chosen as the zero of energy. The results labeled CCSD(T)/aug-cc-pVDZ were estimated using: $E_{\text{CCSD(T)/aug-cc-pVDZ}} = E_{\text{CCSD(T)/6-31+G(d)}} - E_{\text{MP2/6-31+G(d)}} + E_{\text{MP2/aug-cc-pVDZ}}$.](image-url)
the vast majority of the populations of the conformers have
been collapsed into their vibrational zero-point levels. Figure
6 proves that this is the case. There, a LIF excitation spec-
trum of TRA recorded at the point where SEP excitation
occurs \( x/D = 2 \) is compared with a downstream spectrum at
the probe position \( x/D = 6 \). Apart from the broader rota-
tional band contours at \( x/D = 2 \), hot bands are very weak.
The band at 34 911 cm\(^{-1}\), marked with an asterisk, is a
\( v_9 = 1 - v_8 = 0 \) hot band of conformer \( A \). By comparing the in-
tensity of this hot band with the corresponding \( v_9 = 0 \)
! \( v_8 = 1 \) vibronic band of TRA\(_d\), we estimate that greater than
95% of the population at \( x/D = 2 \) is in the ground-state zero-
point level.

B. Single conformation SEP spectra

SEP scans of TRA\(_d\), \( B \), and \( C \) are shown in Figs. 7(a)–7(c), respectively, acquired with the pump laser fixed on
the selected \( S_1 \leftarrow S_0 \) origin in Fig. 2(a) while the dump laser
was tuned over the range from 440 to 1580 cm\(^{-1}\) above the
zero-point level in the ground state. SEP scans over this en-
ergy region produced vibrationally excited TRA conformers
with energies ranging from below to well above the thresh-
olds to isomerization. The SEP scan shows a dense vibronic
structure throughout this energy range, allowing narrow
bounds to be placed on the isomerization barriers. The strik-
ing similarities between the spectra are due to the Franck–
Condon activity isolated primarily in indole ring vibrations,
which are effected only slightly by the conformation of the
ethylamine side chain. The spectrum of band \( C \) [Fig. 7(c)] is
not, in fact, a single conformation spectrum, but rather a
composite of the two unresolved transitions \( C(1) \) and \( C(2) \) in
the origin region [Fig. 2(a)].

TABLE III. Relative energies (kcal/mol) of the transition states of tryptamine.

<table>
<thead>
<tr>
<th>Transition state</th>
<th>B3LYP/6-31+G(d)//B3LYP/6-31+G(d)</th>
<th>RIMP2/aug-cc-pvDZ//B3LYP/6-31+G(d)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>From lowest-energy minima</td>
<td>From higher-energy minima</td>
</tr>
<tr>
<td>AaBa</td>
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FIG. 6. (a) LIF excitation spectra taken “upstream” at \( x/D = 2 \). (b) LIF excitation spectrum taken “downstream” at \( x/D = 6 \). The asterisk (*) marks a hot band of conformer \( A \) at 34 911 cm\(^{-1}\) due to incomplete cooling.
C. SEP-PT spectra

SEP-induced population transfer spectrum obtained by carrying out SEP excitation on TRA(A) while monitoring transitions B, D, E, and F with the probe laser are shown in Figs. 8(b)–8(e), respectively. The abscissa in these scans is the difference in the wave number between the pump and dump lasers as the dump laser is scanned, which is equivalent to the initial internal energy of conformer A. Positive-going signals indicate an increase in the population of the indicated conformer downstream in the expansion. A comparison of the population transfer spectra with the SEP spectrum in Fig. 8(a) shows a sudden turn on of each spectrum at a particular threshold energy that is unique to each conformer.

The analogous scan monitoring transition C in the LIF spectrum with the probe laser [Fig. 9(c)] contains contributions from both the A → C(1) and A → C(2) conformer pairs. This spectrum has a threshold at 1000 cm\(^{-1}\), but it is impossible to know from this spectrum which conformer is responsible for the lowest-energy threshold, nor where the second threshold is to be found. Despite their overlapping origin transitions, conformers C(1) and C(2) have slightly different vibronic transitions 413 and 422 cm\(^{-1}\) above the C origin [Fig. 9(a)], which can be used to separate out the thresholds to isomerization for the two conformers.\(^3\) The population transfer spectra taken while monitoring these nonoverlapped transitions determine the threshold for C(1) at 1316 cm\(^{-1}\) [Fig. 9(d)], while that for C(2) occurs at 1000 cm\(^{-1}\) [Fig. 9(e)].

These spectra illustrate several important features of the experimental method. First, the obvious primary results to be derived from the data in Figs. 8 and 9 are the clear energy thresholds for isomerizing conformer A [Gpy(out)] to all six product wells. These thresholds for isomerization are located at 750 (A → B), 1316 [A → C(1)], 1000 [A → C(2)], 1280 (A → D), 1316 (A → E), and 750 cm\(^{-1}\) (A → F). Second, above threshold, the transitions in the PT spectra have relative intensities commensurate with the corresponding transitions in the SEP spectra of A. This argues against any modespecific effects in the isomerization process. Third, a lower bound on each threshold for A → X isomerization can be determined by identifying the last transition in the SEP spectrum of A that should have been seen in the A → X PT spectrum. It is likely that the upper and lower bounds on the energy threshold are bounds on the classical barrier height separating the particular A → X reactant-product pair. However, we need to take into account the possible effects on these bounds of tunneling (producing too low an upper bound to the barrier) or a kinetic shift (producing too high a lower bound). These effects will be considered in the Discussion section. Finally, these data raise the prospect of measuring similar thresholds for all 42 X → Y product pairs in TRA, leading to a complete characterization of all the stationary points of consequence on the potential-energy surface for TRA. Not surprisingly, such a complete characterization is not possible. The spectra in Figs. 8 and 9 involve observing the population transfer from a large population conformer (A) to small population conformers (B–F). The reverse process, namely, pumping a small population con-
former into a large population well, becomes increasingly hard to observe as the population in the initial conformer well decreases in size.

Despite this difficulty, the thresholds for several other $X \rightarrow Y$ product pairs were measured. SEP-induced population transfer spectra pumping TRA($B$) monitoring transitions $A,F$, and $C$ with the probe laser are shown in Figs. 10(b) and 10(c), respectively. Both TRA $C(1)$ and $C(2)$ are being probed when monitoring transition $C$ in the LIF spectrum of Fig. 2(a). However, based on the lower threshold for $A \rightarrow C(2)$ than $A \rightarrow C(1)$, we tentatively assign this threshold to the $B \rightarrow C(2)$ process. Similarly, the threshold for pumping conformers $C(1)/C(2)$ [whether $C(1)$ or $C(2)$ is not known] back to $B$ was also measured at 750 cm$^{-1}$, with the likely $X \rightarrow Y$ pair being $C(2) \rightarrow B$. Due to signal-to-noise constraints, only in the $B \rightarrow F$ case was it possible to establish a clear lower bound for the threshold.

The combined experimental data on the thresholds for isomerization are summarized on a 2D potential-energy surface in Fig. 11. The comparison with theory isomerization are summarized on a 2D potential-energy surface. The lower bound for the threshold.

An interesting consequence of these three sharp thresholds is that they can be used to exert some control over which isomerization products are formed by the SEP step. This is best observed in a hole-filling spectrum, in which the SEP laser wavelengths are fixed to selectively excite a particular conformer to a well-defined vibrational energy while the probe laser is scanned. As Fig. 12(a) shows, when the dump laser is fixed at a wavelength corresponding to an energy of 750 cm$^{-1}$ above the zero-point level of $A$, only conformers $B$ and $F$ are formed as products. At 1219 cm$^{-1}$ [Fig. 12(b)], conformer $C(2)$ appears in the product spectrum, while at 1411 cm$^{-1}$ [Fig. 12(c)], $C(1), D$, and $E$ are added as well. In Fig. 12, the population gain in the hot band of $A$ results from incomplete cooling of a small fraction of the population of $A$ during the recooling step.

Because the scans in Fig. 12 are taken with a 20/10/20-Hz configuration, the SEP hole-filling signal in transition $A$ reflects the population difference between population reaching the ground state via fluorescence versus SEP. The fluorescing molecules produce a ground-state population dictated by the Franck–Condon factors from the fluorescing level, while SEP produces a population only in a single level. When SEP is to a low-energy state, SEP will be more efficient than fluorescence at recooling into the reactant well, producing a gain on transition $A$, as is observed in Fig. 12(a). When the dump laser reaches to levels with higher internal energy [Figs. 12(b) and 12(c)], SEP will be more efficient at isomerization than fluorescence, leading to a depletion on transition $A$.
E. Studies of deuterated TRA

Two of the four flexible coordinates in TRA involve internal rotation and inversion of the NH$_2$ group. These motions are implicated in the high-resolution studies of TRA by Nguyen et al.,$^{22}$ which have revealed small tunneling splittings (95 MHz) in the origin bands of C(1) and D. In the present studies of isomerization dynamics, tunneling through the barrier could produce an energy threshold below the classical barrier height. One way to test for the effects of tunneling on the isomerization is to compare the isomerization thresholds for the NH$_2$ and ND$_2$ isotomers of TRA.

TRA has three exchangeable hydrogens: the two amino hydrogens and the indole NH, with the former more easily exchanged than the latter. Despite repeated exchange cycles, complete deuteration at all three sites was never achieved, probably due to exchange back in the sample compartment. The degree of isotopic substitution was assessed using resonant two-photon ionization spectroscopy (R2PI). The arrows signify all of the conformational isomerization reactant-product pairs probed experimentally. The numbers associated with the arrows denote the lower and upper bounds to the energy threshold.

FIG. 11. Schematic PES for TRA along two flexible internal coordinates. The arrows signify all of the conformational isomerization reactant-product pairs probed experimentally. The numbers associated with the arrows denote the lower and upper bounds to the energy threshold.

Because conformers A and B differ primarily in the orientation of the NH$_2$ group, suggesting that tunneling might play a role in the isomerization pathway connecting them. The other two pairs have $F$ as their product, and therefore represent pathways where the barriers computed on the 2D potential energy surface (PES) ($\sim$1300 cm$^{-1}$, Fig. 3) are significantly higher than the experiment ($<750$ cm$^{-1}$, Fig. 11).

The SEP-PT spectrum of TRA($A,d_3$)$\rightarrow$TRA($B,d_3$) exhibits a threshold to isomerization [742 cm$^{-1}$, Fig. 14(b)] that is identical to the measured threshold in the nondeuterated system [750 cm$^{-1}$, Fig. 8(b)]. Therefore, under the conditions of this experiment, tunneling does not shift the threshold for isomerization of TRA $A \rightarrow B$.

The corresponding PT scan for $A \rightarrow F$ is shown in Fig. 14(c). A comparison of this scan with the undeuterated ana-

FIG. 12. SEP-HF spectra after selective excitation of conformer A to vibrational levels with energies of (a) 748, (b) 1219, and (c) 1411 cm$^{-1}$.

FIG. 13. The mass-selected R2PI excitation spectra of deuterated tryptamine in the (a) triply deuterated mass channel, (b) doubly deuterated mass channel, (c) singly deuterated mass channel, and (d) the undeuterated tryptamine. The $S_1\rightarrow S_0$ origin transition of tryptamine A is 34 920 cm$^{-1}$ and the excitation wavelength for the deuterated tryptamine A is marked at 34 927 to ensure no interference from the other species in the LIF excitation scheme.
The experimental protocol employed in this work uses stimulated emission pumping to initiate conformational isomerization in a single conformational isomer with a well-defined internal energy. SEP excitation is an important extension of an earlier work that used infrared excitation in the hydride stretch region of the infrared.11–13 As noted earlier, the principle drawback of \( \text{XH stretch infrared excitation} \) is that many of the lowest-energy barriers to isomerization are well below the typical \( \text{XH stretch} \) \( \nu = 1 \) level \((\sim3500 \text{ cm}^{-1} = 10 \text{ kcal/mol})\). As such, near-IR excitation never directly probes the barriers to isomerization in the threshold region. By comparison, the principle advantage of SEP excitation is that it offers a wide tuning range that stretches from well below the lowest barriers to isomerization up to energies well in excess of these thresholds.

A. SEP as a vibrational excitation scheme

The experimental protocol employed in this work uses stimulated emission pumping to initiate conformational isomerization in a single conformational isomer with a well-defined internal energy. SEP excitation is an important extension of an earlier work that used infrared excitation in the hydride stretch region of the infrared.\(^{11–13}\) As noted earlier, the principle drawback of \( \text{XH stretch infrared excitation} \) is that many of the lowest-energy barriers to isomerization are well below the typical \( \text{XH stretch} \) \( \nu = 1 \) level \((\sim3500 \text{ cm}^{-1} = 10 \text{ kcal/mol})\). As such, near-IR excitation never directly probes the barriers to isomerization in the threshold region. By comparison, the principle advantage of SEP excitation is that it offers a wide tuning range that stretches from well below the lowest barriers to isomerization up to energies well in excess of these thresholds.

As a result, by observing the onset of a particular \( \text{X} \rightarrow \text{Y} \) population transfer, SEP population transfer spectra provide direct experimental measurements of the energy thresholds for isomerization in individual \( \text{X} \rightarrow \text{Y} \) reactant-product pairs. Furthermore, in cases where the thresholds for both \( \text{X} \rightarrow \text{Y} \) and \( \text{Y} \rightarrow \text{X} \) pairs can be measured, their difference constitutes a measure of the relative energies of minima \( \text{X} \) and \( \text{Y} \). Thus, in principle, step-by-step characterization of all \( \text{X} \rightarrow \text{Y} \) thresholds constitutes a complete characterization of the rate-limiting stationary points on the potential-energy surface for isomerization.

SEP excitation also offers exceptional selectivity in the excitation step. Any vibronic transition that is not overlapped in the ultraviolet spectrum can be used to selectively excite a particular conformation. With supersonic expansion cooling, vibronic bands typically have rotational band contours with widths of \(1–2 \text{ cm}^{-1} \), so different conformers need only shift...
the electronic origin by this amount in order to enable selective excitation, a very small fraction of the excitation energy (≈30,000 cm\(^{-1}\)).

Finally, SEP offers the versatility of carrying out SEP using vibronic bands above the origin in the pump step. In principle, selection of different \(S_1(v)\) levels offers a powerful means of changing the Franck–Condon intensities to the ground state in the dump step. These changed Franck–Condon factors could be used to narrow the bounds on the threshold for isomerization. This potential advantage is more one in theory than practice and, in fact, was not utilized in the present experiment. If intramolecular vibrational redistribution (IVR) is fast compared to the time delay between pump and dump, then the oscillator strength in the dump transition is spread over many transitions that reduce the SEP intensity in any one band considerably. In TRA, we were not able to carry out SEP effectively on bands more than 200 cm\(^{-1}\) above the \(S_1\) origin.

The principle disadvantage of SEP in the context of this experimental protocol is that it turns a two-laser IR pump/UV probe experiment into a three-laser experiment (SEP pump-dump, UV probe). Furthermore, in order to use this scheme, the molecule of interest must have an ultraviolet chromophore capable of efficient SEP, with a sufficiently long lifetime to stimulate a significant fraction of the excited-state population back down to the ground state. With the nanosecond lasers employed here, this requires excited-state lifetimes of several nanoseconds. The tryptamine conformers have excited-state lifetimes of 15 ns.\(^{18,22}\) In addition, the method is not easily adapted to the quantitative measurement of product quantum yields\(^{11,13}\) because the SEP pump step removes population that is not entirely brought back to the ground state by the dump step.

**B. The comparison between experiment and calculations**

In this section, we compare the experimentally determined energy thresholds for isomerization (Fig. 10) with computed barrier heights, corrected for zero-point energy effects (Fig. 3). This comparison is justified provided that the experimental upper and lower bounds bracket the computed classical barrier height. In order for the upper bound on the threshold to be an upper bound on the classical barrier height, tunneling must not play a significant role. The experimental lower bound is a firm lower bound only if the isomerization rate at threshold is fast compared to the vibrational cooling rate, producing a negligible kinetic shift in the threshold.

The measurements on TRA show no evidence for a significant kinetic shift. If vibrational cooling were competing effectively with isomerization, then the bands near threshold in the PT spectra should show a reduced intensity (compared to the SEP spectrum) that depends on the cooling conditions. In TRA, the intensities of transitions above threshold in the PT spectra faithfully reflect those in the SEP spectra, consistent with isomerization occurring on a time scale fast compared to cooling. This is consistent with Rice–Ramsperger–Kassel–Marcus (RRKM) estimates for the rate constants for isomerization (>10\(^9\) s\(^{-1}\) at threshold) which are fast compared to the anticipated cooling rate by helium (2–3 cm\(^{-1}\)/collision at a collision rate of 4×10\(^8\) s\(^{-1}\)). A more detailed discussion of the competition between isomerization and collisional cooling will be taken up in the adjoining paper on 3-indole propionic acid (IPA).\(^{4}\)

The data on TRA\(\delta_d\) (Sec. IV E) indicate that tunneling does play a role in isomerization in certain regions of the potential-energy surface; notably, in pathways leading into well \(F\). Recall that the threshold for \(A\rightarrow B\) isomerization was unchanged by deuteration at the amino group, while the thresholds for the \(A\rightarrow F\) and \(B\rightarrow F\) channels were raised by small but measurable amounts (~100 cm\(^{-1}\)). Because this shift is small, it could arise from some other effect than tunneling; perhaps due to zero-point energy (ZPE) shifts in the threshold or an increased kinetic shift to the measurement. However, the computed shift in the barrier height due to ZPE differences between TRA\(h_i\) and TRA\(\delta_d\) is less than 10 cm\(^{-1}\). Furthermore, the computed RRKM rate constants at threshold for isomerization of TRA\(\delta_d\) are only reduced by about 20% by deuteration, and are still large compared to the rate for cooling. Therefore, tunneling is the most likely explanation for the observed shift in the \(A\rightarrow F\) and \(B\rightarrow F\) isomerization thresholds in TRA\(\delta_d\). The relationship between the observed thresholds for \(A\rightarrow F\) and \(B\rightarrow F\) and the classical barrier height depends on the tunneling pathway, an issue to which we shall return shortly. In other measured \(X\rightarrow Y\) thresholds, we assume that tunneling plays an insignificant role, and treat the observed energy threshold as an upper bound to the classical barrier height.

**1. Relative energies of the minima**

A first test of the calculated potential-energy surface is to compare the relative energies of the minima with the observed relative populations of the conformers in the expansion in the absence of SEP excitation. One must be careful not to put too much weight on these populations reflecting energy differences alone, because it is possible that the cooling in the expansion can remove population out of the higher-energy minima into the lower ones if the barriers are not too great. In the case of TRA, we do not observe significant changes in these relative populations as a function of distance downstream in the expansion (Fig. 6), and therefore see some merit in correlating the relative intensities of the observed \(S_0-S_1\) origins with their relative energies. The high-resolution spectra of Nguyen et al. show that the intensity of the \(C(2)\) origin is about twice that of the \(C(1)\) origin. Sorting these intensities from large to small yields, \(I(A) > I(B) > I(C(2)) > [I(C(1)), I(D), I(E), \text{and } I(F)]\), where the bands in brackets have similar intensities. This suggests that the experimental energy ordering is

\[
E(A) < E(B) < E([C(2)]) < [E(C(1)], E(D), E(E), \text{and } E(F)].
\]

This energy ordering matches reasonably well with the DFT
energies, while the RIMP2 results would predict greater populations in C(2) and F than observed experimentally. It is possible that the low experimental barriers separating these minima from B (Fig. 11) provide a pathway for removing population from these minima into B early in the expansion (x/D < 2).

2. Barrier heights

For most of the measured A→X thresholds, the calculated barrier heights, including ZPE corrections, are within a couple of hundred wave numbers of experiment. For instance, the experimental barriers separating A [Gpy(out)] from any of the three anticonformers [C(1), D and E] are \(E_{\text{thresh}} \sim 1300 \text{ cm}^{-1} = 3.7 \text{ kcal/mol}\), consistent with the computed barrier heights for AD and BE (\(\sim 1300 \text{ cm}^{-1}\) for DFT and 1600–1700 cm\(^{-1}\) for RIMP2). The A→B threshold is somewhat lower experimentally (688 < \(E_{\text{thresh}} < 748 \text{ cm}^{-1}\)) than predicted by theory (\(E_{\text{barrier}} = 930 \text{ cm}^{-1}\) by both methods), but still within this 200 cm\(^{-1}\) spread.

The glaring exceptions to this general correspondence between experiment and theory are the A→F and B→F thresholds. As Fig. 3 shows, the computed barriers into well F are all up in the 1300–1500 cm\(^{-1}\) range, almost a factor of 2 higher than the experiment. These are the same pathways that show some evidence for tunneling, and it is possible that tunneling accounts for the entire discrepancy between experiment and theory. However, the small shift in threshold induced by deuteration seems to argue against such a simple resolution. Furthermore, since A and F differ along at least two of the flexible coordinates, one would like to pin down the isomerization pathway, whether tunneling or classical in nature.

3. Isomerization pathways

The experimental thresholds (Fig. 15) that connect A→B, A→F, and B→F are particularly low, suggesting that there is an efficient isomerization pathway connecting these minima. As just noted, this pathway may involve tunneling, but if so, the tunneling penetrates some of the highest computed barriers on the surface, those that surround minimum F. As noted in the initial communication, the observed thresholds are consistent with a pathway from A→F (688 < \(E_{\text{thresh}} < 748 \text{ cm}^{-1}\)) that passes from A→B (688 < \(E_{\text{thresh}} < 748 \text{ cm}^{-1}\)) and then from B→F (566 < \(E_{\text{thresh}} < 688 \text{ cm}^{-1}\)).

The computed potential-energy surface possesses a low-energy trough that connects wells A, H, and C(2) via the AH and HC(2) barriers. A possible way to resolve these differences would be to simply swap the assignments of conformers C(2) and F. These two conformers are both Gph conformers, differing only in the orientation of the NH\(_2\) group. As a result, they have rotational constants which are very close to one another. If this swap in assignments were made, the calculations would predict an A→F barrier of 672 cm\(^{-1}\) based on a pathway that goes from Gpy(out) to Gpy(in) (\(E_{\text{barrier}} = 672 \text{ cm}^{-1}\)) and then on to Gph(out) (\(E_{\text{barrier}} = 527 \text{ cm}^{-1}\)). While such a swap is tempting, the arguments that Nguyen et al. used to arrive at the assignments for C(2) and F are quite persuasive, and are consistent with previous assignments based on infrared and vibronic level data.\(^{22}\)

With or without such a swap in assignments, it is surprising that tunneling would lead to a shift in the A→F and B→F thresholds, but produce no shift in A→B, since the pathways from A or B into F necessarily involve motion of the entire NH\(_2\) group from the Gpy to the Gph position (with an effective tunneling mass of \(~16\) amu), while A→B isomerization [Gpy(out)→Gpy(up)] can be accomplished merely by an internal rotation and/or inversion of the NH\(_2\) group (\(~2\)-amu tunneling mass). Of course, this difference in mass of the tunneling group could be compensated for by a narrower width to the barrier. Since the likely isomerization pathway for either A→F or B→F involves motion of the NH\(_2\) group over the top of the phenyl ring, one wonders whether the interaction of the NH\(_2\) group with the indole \(\pi\) cloud could provide a low-energy tunneling pathway that inverts the NH\(_2\) group as it sweeps across the \(\pi\) cloud. A final resolution of these issues will require theoretical methods that can directly model the tunneling contribution to the isomerization dynamics.

Finally, even in a molecule the size of tryptamine, we are quickly losing our ability to use chemical intuition to identify the important isomerization pathways on the potential-energy surface. The transition states identified in this work are likely only a subset of those needed to fully describe the isomerization dynamics. In particular, isomerization pathways that involve swinging the ethylamine side chain from one side of the indole ring to the other may play a significant role in the
isomerization dynamics. The anticonfiguration supports minima $G$ and $I$ in which the ethylamine side chain is nearly in plane. The barriers into and out of these minima are quite low ($\sim 100$ cm$^{-1}$). Analogous pathways involving motion of the ethylamine group from the Gpy or Gph positions around the edges of the pyrrole or phenyl rings deserve further exploration.

VI. CONCLUSIONS

Despite its modest size, tryptamine possesses a potential-energy surface for conformational isomerization that is a challenge to characterize via experiment and theory. The population of TRA molecules is spread over seven conformational minima, even with supersonic expansion cooling. A complete characterization of the isomerization process would then require measurement of 42 independent $X \rightarrow Y$ conformer pairs, illustrating the need for new experimental tools capable of studying the process in a conformation specific way. The present paper describes measurements of the energy thresholds for isomerization using conformation-specific SEP excitation, followed by collisional cooling of the products prior to conformation-specific detection via laser-induced fluorescence. The method of SEP-induced population transfer spectroscopy provides a means for measuring the energy thresholds for isomerization of individual $X \rightarrow Y$ conformer pairs free from interference from others present in the expansion.

The application of this method to TRA has demonstrated the power of the method, but it has also raised many unanswered questions, providing a stimulus for future work. First, since the method uses collisions as an integral part of the experimental scheme, isomerization is always viewed in competition with collisional cooling. Ideally, this competition can be used as a means to quantify the energy-dependent rate of isomerization for individual $E \rightarrow Y$ pairs. It is hoped that such studies can provide critical new tests of RRKM theory, which is undergoing close scrutiny by theory, which suggests that in many circumstances, IVR into the torsional modes may limit the rate of isomerization near threshold. Second, as just discussed in the preceding section, theoretical methods that can explore the isomerization pathways more completely, and include the effects of tunneling, are needed. Third, it is important to compare the results of the present study with analogous studies of isomerization in the absence of collisions, using methods such as those employed by Pate and co-workers. Finally, hole-filling methods can be applied to the study of isomerization in a much wider range of contexts. In the adjoining paper, we will probe the effect of a bound solvent water molecule on the barrier to intramolecular isomerization in 3-indole propionic acid.

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