

## Structural Selection by Microsolvation: Conformational Locking of Tryptamine

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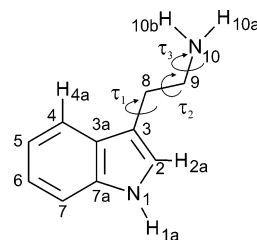
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**Abstract:** The conformational space of tryptamine has been thoroughly investigated using rotationally resolved laser-induced fluorescence spectroscopy. Six conformers could be identified on the basis of the inertial parameters of several deuterated isotopomers. Upon attaching a single water molecule, the conformational space collapses into a single conformer. For the hydrogen-bonded water cluster, this conformer is identified unambiguously as tryptamine A. In the complex, the water molecule acts as proton donor with respect to the amino group. An additional interaction with one of the aromatic C–H bonds selectively stabilizes the observed conformer more than all other conformers. Ab initio calculations confirm much larger energy differences between the conformers of the water complex than between those of the monomers.

### Introduction

Conformation of molecules plays an important role in reactions of organic and biochemically relevant molecules. Still, little is known about the effect of solvents on conformations, in particular, in small systems. The conformational landscape even of small aromatic molecules with an ethylamino side chain like tryptamine comprises many structurally different, but nearly equally stable conformations. Tryptamine possesses 27 conformers from three 3-fold rotations in and of the alkylamino side chain (cf. Figure 1): two around the C–C single bonds, and one around the C–N bond. In 9 of these 27 conformers, the C<sub>α</sub>H<sub>2</sub>–NH<sub>2</sub> tail of the alkylamino group is oriented perpendicular to the aromatic plane. These nine conformers have been calculated to have energies considerably lower than those of the remaining ones.<sup>1</sup> Surprisingly, the multitude of conformers reduces to a single one upon complex formation with just one water molecule.<sup>2</sup> In the present work, we study the reason for this locking of the conformational variety to a single structure. This is an interesting subproblem in the more general context of the induced fit principle,<sup>3</sup> which describes the predisposition of a flexible ligand toward a coordination partner or of the lock and key principle,<sup>4</sup> which describes the static behavior of a preorganized ligand toward one or more coordination partners. A more flexible model for describing these kinds of conformational complementarities has been proposed by Kumar et al.<sup>5</sup>



**Figure 1.** Atomic numbering and definitions of the geometry parameters used in the fit.  $\tau_1$  is the dihedral angle defined by the atoms C<sub>2</sub>, C<sub>3</sub>, C<sub>8</sub>, C<sub>9</sub>,  $\tau_2$  for C<sub>3</sub>, C<sub>8</sub>, C<sub>9</sub>, N<sub>10</sub>, and  $\tau_3$  for the dihedral angle C<sub>8</sub>, C<sub>9</sub>, N<sub>10</sub>, H<sub>10b</sub>, where H<sub>10b</sub> designates the hydrogen atom that is closest to the indole ring.

All three models have far reaching implications for molecular recognition processes.

Pioneering experimental work on the different conformers of tryptamine was performed in a molecular beam using rotationally resolved LIF spectroscopy by Philips and Levy at a spectral resolution of 0.07 cm<sup>-1</sup>.<sup>6</sup> The triply deuterated conformers were investigated by Wu and Levy<sup>7</sup> of the same group. The conformers were analyzed using the rotational constants<sup>8</sup> of undeuterated and deuterated tryptamines. Seven different conformers were identified on the basis of rotational contours and were named A, B, C(1), C(2), D, E, and F.<sup>9</sup> A conformational analysis of tryptamine was reported from

<sup>†</sup> Heinrich-Heine-Universität.

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(6) Philips, L. A.; Levy, D. H. *J. Chem. Phys.* **1988**, *89*, 85–90.

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(8) The rotational constants determine the structure of the molecule in a given electronic state since the rotational constant along the *g*-inertia axis of the molecule (*g* = *a*, *b*, *c*) is defined as  $A_g = h/8\pi^2 I_g$ , with  $I_g$  the moment of inertia along the *g*-axis.

(9) Park, Y. D.; Rizzo, T. R.; Peteanu, L. A.; Levy, D. H. *J. Chem. Phys.* **1986**, *84*, 6539–6549.

rotational coherence spectra taken by Connell et al.<sup>10</sup> Caminati published the microwave structure of the *A* and *B* conformer of tryptamine and made an assignment based on ab initio calculations.<sup>11</sup> A more thorough investigation of all seven conformers was given by Carney and Zwier based on resonant ion dip infrared (RIDIR) spectra in the region of the CH alkyl stretch vibrations and by UV–UV hole-burning spectroscopy.

Carney and Zwier<sup>1</sup> proposed a schematic nomenclature of the nine tryptamine conformers with the C<sub>α</sub>H<sub>2</sub>–NH<sub>2</sub> tail out of plane, based on the amino group positions relative to the indole ring and the orientations of the amino group lone pair. We use their nomenclature throughout this publication. The two conformations with the amino lone pair pointing downward to the aromatic ring were found to be much less stable than the other seven conformers. Recently, Dian et al. measured directly the energy thresholds between the different conformers of tryptamine using stimulated emission pumping-hole filling and stimulated emission pumping-induced population transfer spectroscopy.<sup>12</sup>

Microsolvated clusters of tryptamine have been less investigated than have the monomers. Park et al. found that the multitude of conformations of tryptamine collapses into one conformer upon complexation with methanol.<sup>9</sup> The binary water, methanol, and ethanol clusters were investigated by Sipior and Sulkes by LIF spectroscopy, and all were shown to collapse into one prominent conformer peak.<sup>2</sup> Peteanu and Levy investigated the water, methanol, chloroform, and dioxane complexes of tryptamine by two-color two-photon ionization spectroscopy.<sup>13</sup> They observed very different behavior of the dioxane cluster compared to the water and methanol clusters. Rotational constants for the cluster with one water molecule were reported by Felker<sup>14</sup> and Connell et al.<sup>15</sup> using rotational coherence spectroscopy on two isotopomers of the cluster. They deduced a bridged cluster for the cluster with one water molecule. The clusters with two and three water molecules were studied by Carney et al. using RIDIR spectroscopy.<sup>16</sup> They proposed that the preference for a certain conformer is due to a water bridge between the amino and the pyrrolic NH sites of the molecule for clusters with more than one water molecule. We report here a high-resolution laser-induced fluorescence study of the complex of tryptamine with a single water molecule and the origin of the conformational locking in this cluster.

## Techniques

**Experimental Procedures.** The experimental setup for the rotationally resolved LIF is described elsewhere.<sup>17</sup> Briefly, it consists of a ring dye laser (Coherent 899-21) operated with rhodamine 110, pumped with 6 W of the 514 nm line of an Ar<sup>+</sup> ion laser. Its output is coupled into an external folded ring cavity (Spectra Physics) for second harmonic generation (SHG). The molecular beam is formed by co-expanding tryptamine, heated to 160 °C and argon (250–500 mbar, see below) through a 100 μm nozzle into the vacuum. The molecular beam machine consists of three differentially pumped vacuum chambers that are

linearly connected by skimmers (1 and 3 mm, respectively) in order to reduce the Doppler width. The molecular beam is crossed at right angles in the third chamber with the laser beam 360 mm downstream of the nozzle, and the resulting fluorescence is collected perpendicular to the plane defined by laser and molecular beam by an imaging optics. The Doppler width in this setup is 25 MHz (fwhm). A photomultiplier tube detects the integrated molecular fluorescence, and its output is discriminated and digitized by a photon counter and transmitted to a PC for data recording and processing. Relative frequencies are determined with a quasi confocal Fabry–Perot interferometer with a free spectral range (FSR) of 149.9434(56) MHz. The absolute frequency was obtained from a recording of the iodine absorption spectrum and comparing it to the tabulated lines.<sup>18</sup>

Tryptamine was purchased from Merck Schuchard (p.A.) and used without further purification. The mixed isotopomers were produced by refluxing tryptamine with a 3-fold excess of DCl (38%) for 1 h. The solution was then neutralized using a solution of NaOD in D<sub>2</sub>O, and washing the precipitation twice with D<sub>2</sub>O. The precipitation was then dried over silica gel and stored under nitrogen. This resulted in a more or less equal amount of the different deuteration grades. The triply deuterated isotopomer could be produced nearly exclusively by co-expanding the tryptamine with D<sub>2</sub>O, kept at 0 °C. Higher water temperatures led to strong signal reduction due to the formation of the water cluster, and lower temperatures resulted in mixed isotopomers. Another explanation for the signal decrease at higher temperatures of the D<sub>2</sub>O sample might be deuterium exchange also in positions of the benzene ring, as has been shown to take place under comparable conditions for 4-hydroxyindole.<sup>19</sup> Nevertheless, the aromatic CH-deuterated isotopomers have generally a quite large shift and are well outside the observed spectral range.

## Computational Methods

**Ab Initio Calculations.** The structures of the conformers of tryptamine in the electronic ground state have been optimized at the MP2/6-311G(d,p) level with the Gaussian 98 program package (revision 11).<sup>20</sup> The SCF convergence criterion used throughout the calculations was an energy change below 10<sup>–8</sup> Hartree, while the convergence criterion for the gradient optimization of the molecular geometry was  $\partial E/\partial r < 1.5 \times 10^{-5}$  Hartree/Bohr and  $\partial E/\partial \phi < 1.5 \times 10^{-5}$  Hartree/degree, respectively. Two conformers with the amino lone pair pointing down to the ring have been shown by Carney et al.<sup>1</sup> to be much higher in energy and have not been further investigated here. Vibrational corrections have been made using the ZPE from B3LYP/6-311G(d,p) calculations. The water cluster is optimized at the MP2/6-311G(d,p) level of theory. The starting geometries for the structure optimizations have been obtained by attaching a water to all seven conformers at four different positions: to the pyrrolic NH group, acting as proton donor, to both amino hydrogen atoms, acting as proton donors, and to the N atom of the amino group, acting as proton acceptor. Thus, 28 different starting geometries have been used. Their relative energies were investigated at the HF/6-311G(d,p) level. The amino group acceptor structures of each conformer have then been further refined at the MP2/6-311G(d,p) level of theory. Basis set superposition errors were corrected using the counterpoise method of Boys and Bernardi,<sup>21</sup> and zero-point energy corrections have been performed with the vibrational frequencies of a B3LYP/6-311G(d,p) normal-mode analysis using analytical gradients.

**Genetic Algorithms.** A fit using genetic algorithms (GA) mimics the concepts of natural reproduction and selection processes. For a detailed description of the GA, the reader is referred to the original literature on evolutionary or genetic algorithms.<sup>22–24</sup>

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(16) Carney, J. R.; Dian, B. C.; Florio, G. M.; Zwier, T. S. *J. Am. Chem. Soc.* **2001**, *123*, 5596–5597.

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(20) Frisch, M. J. et al. *Gaussian 98*, revision a.11; Gaussian, Inc.: Pittsburgh, PA, 2001.

(21) Boys, S. F.; Bernardi, F. *Mol. Phys.* **1970**, *19*, 553.

The molecular parameters are encoded binary, each parameter to be optimized representing a gene. A vector of all genes, which contains all molecular parameters, is called a chromosome. In an initial step, the values of all parameters are set to random values between lower and upper limits, which are chosen by the user. The quality of the solutions then is evaluated by a fitness function. A proper choice of this fitness function is of vital importance for the success of the GA convergence. In refs 25 and 26, the fitness function  $F_{fg}$  has been defined as:

$$F_{fg} = \frac{(\mathbf{f}, \mathbf{g})}{\|\mathbf{f}\| \|\mathbf{g}\|} \quad (1)$$

Here,  $\mathbf{f}$  and  $\mathbf{g}$  are the vector representations of the experimental and calculated spectrum, respectively. The inner product  $(\mathbf{f}, \mathbf{g})$  is defined with the metric  $\mathbf{W}$ , which has the matrix elements  $W_{ij} = w(|j - i|) = w(r)$  as:

$$(\mathbf{f}, \mathbf{g}) = \mathbf{f}^T \mathbf{W} \mathbf{g} \quad (2)$$

and the norm of  $\mathbf{f}$  as  $\|\mathbf{f}\| = \sqrt{(\mathbf{f}, \mathbf{f})}$ ; similar for  $\mathbf{g}$ . For  $w(r)$ , we used a triangle function<sup>25</sup> with a width of the base of  $\Delta w$ :

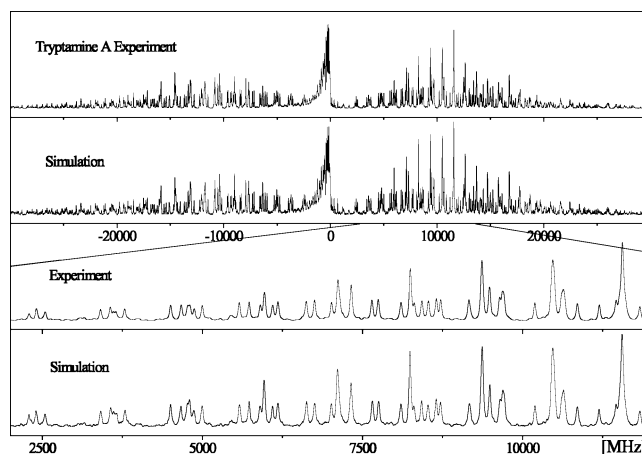
$$w(r) = \begin{cases} 0 - |r| / \left(\frac{1}{2} \Delta w\right) & \text{for } |r| < \frac{1}{2} \Delta w \\ 0 & \text{otherwise} \end{cases} \quad (3)$$

One optimization cycle, including evaluation of the fitness of all solutions, is called a generation. Pairs of chromosomes are selected for reproduction, and their information is combined via a crossover process. Since crossover combines information from the parent generations, it basically explores the error landscape. The value of a small number of bits is changed randomly by a mutation operator. For the simulation of the rovibronic spectra, a rigid asymmetric rotor Hamiltonian was employed.<sup>27</sup>

## Results

**The Tryptamine Monomer.** Figure 1 shows the atomic numbering used for designation of the isotopomers and the clusters used in this publication. The rotationally resolved electronic origin of the *A* conformer of tryptamine at 34915.64  $\text{cm}^{-1}$  is shown in Figure 2 along with a fit based on the genetic algorithms (GA). The technique has been shown before to work reliably even for strongly overlapping bands, where a standard assigned fit would be impossible.<sup>25,26</sup> The origin band is a hybrid with mainly *a*-type character.

Table 1 reports the molecular parameters obtained from the fit and the comparison to previously reported constants of the *A* conformer, either from microwave spectroscopy for the electronic ground state<sup>11</sup> or from LIF spectroscopy for ground and excited states.<sup>6</sup>  $A''$ ,  $B''$ , and  $C''$  designate the rotational constants in the electronic ground state,  $A'$ ,  $B'$ , and  $C'$  are those of the excited state.  $\Delta A$ ,  $\Delta B$ , and  $\Delta C$  are the changes of the rotational constants upon electronic excitation.<sup>8</sup>  $\theta$  and  $\phi$  are the spherical coordinate angles of the transition moment vector in



**Figure 2.** Rovibronic spectrum of the electronic origin of tryptamine *A* at 34915.64  $\text{cm}^{-1}$ . The upper trace shows the experimental spectrum, the following shows the simulation with the best molecular parameters from the GA fit. The following traces present an enlarged portion of the spectrum.

the molecular fixed frame (*a*, *b*, *c*). The  $\mu_a$ ,  $\mu_b$ , and  $\mu_c$  designate the components of the transition dipole moment to the inertial axis of the cluster.<sup>28</sup> They are given for comparison to the respective parameters in ref 6.  $\tau$  (ns) is the excited-state lifetime, calculated from the Lorentzian width. The ground-state rotational constants of the *A* and *B* conformers agree within their uncertainties with the microwave values from Caminati.<sup>11</sup> Deviations are due to the implicitly higher accuracy of the microwave data and the utilization of a different Hamiltonian, including centrifugal distortion in ref 11. The deviations to the ground-state rotational constants from Philips and Levy range between 50 MHz for the *A* rotational constant of the *A* conformer to 170 MHz for the *A* rotational constant of the *E* conformer.<sup>6</sup> Given the small differences between the rotational constants of the conformers, an unambiguous assignment to the respective structures requires the accuracy of nearly fully resolved rovibronic spectra. On the other hand, the differences of the rotational constants upon electronic excitation agree very well with the previously reported values of Philips and Levy.<sup>6</sup> The quite large deviations in the ground-state rotational constants are mainly due to the lower resolution (75 MHz) in the experiments of ref 6. Convolution of our spectra with an additional contribution of about 70 MHz made the assignment quite hard, even for the automated GA technique described above.

Since three rotational constants are not sufficient to give an unambiguous assignment to which conformation band *A* belongs, we recorded the spectra of several deuterated isotopomers. Deuteration with DCI as described in the experimental procedures section in Techniques resulted in a mixture of up to eight different isotopomers. Under these conditions, the highest deuteration grade which can be achieved is the triply deuterated  $\text{d}_3$ . If all deuteration grades are formed, the spectrum of each conformer consists of the undeuterated, three different singly deuterated, three different doubly deuterated, and one triply deuterated isotopomer. With the atomic numbering given in Figure 1, these eight isotopomers are tryptamine, [1b-D]-tryptamine- $\text{d}_1$ , [10a-D]tryptamine- $\text{d}_1$ , [10b-D]tryptamine- $\text{d}_1$ , [1b-

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(28) The components of the transition dipole moment along the inertial axis are defined by:  $\mu_a = \mu \sin \phi \cos \theta$ ,  $\mu_b = \mu \sin \phi \sin \theta$ , and  $\mu_c = \mu \cos \phi$ .

**Table 1.** Molecular Parameters for the Conformers A–F of Tryptamine Determined from GA Fits, as Described in the Text

	A band			B band			C band		D band		E band		F band	
	this work	ref 11	ref 6	this work	ref 11	ref 6	this work	ref 6	this work	ref 6	this work	ref 6	this work	ref 6
$A''$ (MHz)	1731.02	1730.197	1783.8	1710.25	1709.438	1777.8	1594.16		1767.74	1933.6	1761.40	1930.7	1605.11	1636.9
$B''$ (MHz)	682.04	681.86	674.5	682.22	681.87	665.5	755.84		617.78	611.6	614.75	608.6	737.84	722.5
$C''$ (MHz)	551.56	551.48	551.6	551.10	550.84	548.6	561.39		477.00	473.6	475.58	473.6	561.51	584.6
$\theta$ ( $^\circ$ )	71.92			72.25			76.85		75.03		77.43		80.71	
$\phi$ ( $^\circ$ )	14.24			22.28			18.17		5.54		10.90		13.92	
$\mu_A$	0.9234		0.88	0.8812		0.88	0.9317		0.9246	0.85	0.9185	0.85	0.9176	0.77
$\mu_B$	0.2271		0.37	0.3611		0.37	0.2634		0.0087	0.32	0.0341	0.32	0.0564	0.42
$\mu_C$	0.3093		-0.29	0.3050		-0.29	0.2502		0.0667	-0.42	0.0474	-0.42	0.0261	-0.47
$\Delta_{\text{Lor}}$ (MHz)	25.3			29.9			24.3		32.08		25.5		25.2	
$\tau$ (ns)	6.2			5.3			6.5		5.0		6.2		6.3	
$A'$ (MHz)	1724.02		1777.8	1703.62		1783.8	1587.38		1754.07	1918.7	1748.47	1915.7	1592.77	1624.9
$B'$ (MHz)	672.68		665.5	672.92		674.5	743.08		612.34	605.6	609.26	602.6	728.49	716.5
$C'$ (MHz)	544.58		545.6	544.54		554.6	554.20		473.44	470.7	472.16	470.7	555.25	572.6
$\Delta A$ (MHz)	-7.00		-6.0	-6.63		-6.0	-6.78		-13.67	-14.9	-12.9	-15.0	-12.34	-12.0
$\Delta B$ (MHz)	-9.36		-9.0	-9.30		-9.0	-12.76		-5.44	-6.0	-5.5	-6.0	-9.35	-6.0
$\Delta C$ (MHz)	-6.98		-6.0	-6.56		-6.0	-7.19		-3.56	-3.0	-3.4	-3.0	-6.26	-12.0

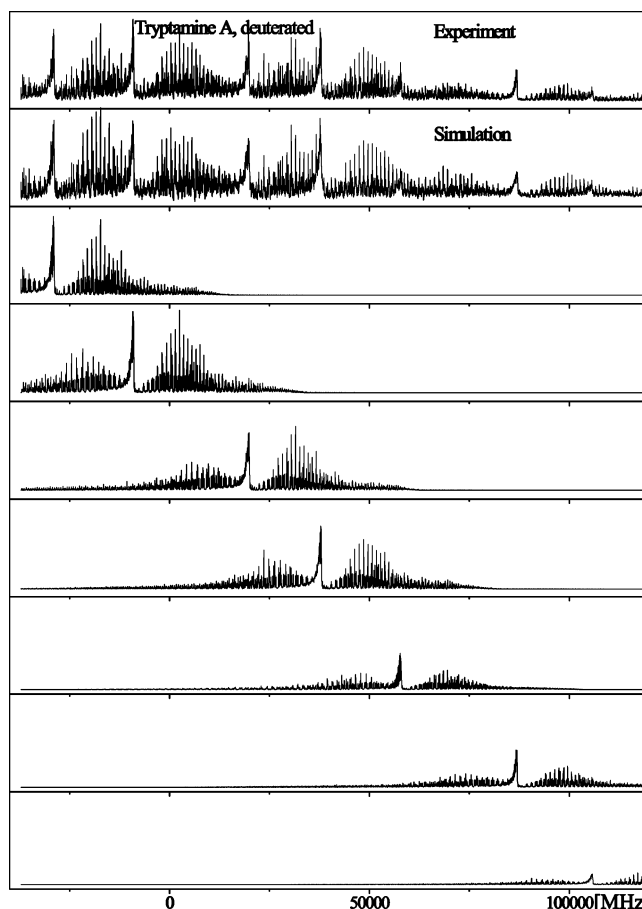
D][10a-D]tryptamine- $d_2$ , [1b-D][10b-D]tryptamine- $d_2$ , [10a-D]-[10b-D]tryptamine- $d_2$ , and [1b-D][10a-D][10b-D]tryptamine- $d_3$ . For the A conformer, we were only able to observe seven out of the eight possible isotopomers. Using the mixed deuteration grades, a serious problem arises for the assignment of single rovibronic lines, due to strong overlap of the different isotopomeric origins. Using the GA, it is possible to automatically fit several bands simultaneously, as we have shown for the overlapping origins of phenol–nitrogen clusters<sup>29</sup> and differently deuterated azaindoles.<sup>30</sup> Figure 3 shows the experimental spectrum of the seven isotopomers of the A conformer together with the fit of all bands and the individual results for each origin band.

To verify the correctness of the rotational constants derived from the spectrum of Figure 3, we selectively produced the triply deuterated tryptamine as described in the experimental procedures section of Techniques. The fit to this single spectrum reproduced the values obtained from the overall fit of all isotopomers. The resulting inertial parameters of all isotopomers are given in Table 2 and will be used in this section for the determination of the exact conformation of each conformer. Since seven different isotopomers contribute a total of 21 rotational constants, sufficient information for an unambiguous assignment is present.

A very good agreement between simulation and experiment is also observed for the electronic origin of the B conformer at 34895.91  $\text{cm}^{-1}$  given in Figure 4. The resulting rotational constants are compiled in Table 1.

For the B conformer, all eight possible isotopomers (vide infra) could be observed. As in the case of the A conformer, the origins overlap strongly due to similar zero-point energies in the ground and excited states of the isotopomers. The spectra are shown in Figure 5; the resulting rotational constants of all isotopomers are given in Table 2. Again, like for conformer A, the results for the rotational constants were cross-checked against the triply deuterated B conformer, produced selectively by the method described above.

The spectra of the undeuterated and triply deuterated C, D, E, and F conformers are shown in the Supporting Information. Here, we will report only the molecular constants that were

**Figure 3.** Rovibronic spectra of the electronic origins of seven isotopomers of the A conformer of tryptamine.

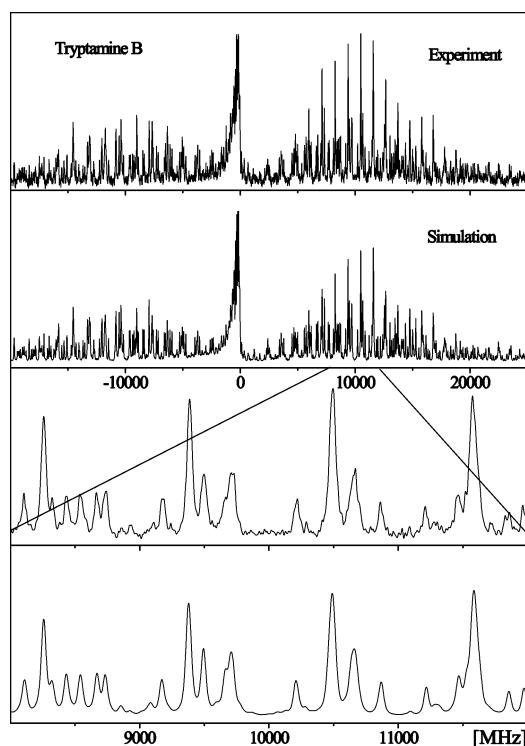
obtained from the GA assigned spectra. The electronic origins of the C (34879.22  $\text{cm}^{-1}$ ) and D conformers (34884.26  $\text{cm}^{-1}$ ) are spectrally very close, so that the mixed deuterated isotopomers would overlap even between the two different conformers. For this reason, we took only the undeuterated and triply deuterated spectra. The electronic origins of the spectra of the  $d_3$ -C (34885.80  $\text{cm}^{-1}$ ) and  $d_3$ -D conformers (34886.32  $\text{cm}^{-1}$ ) are even closer and overlap considerably. Also, here, the GA made it possible to fit both subspectra independently. Philips and Levy<sup>6</sup> and Carney et al.<sup>1</sup> reported the existence of two different origins of the C conformer, namely, C(1) and C(2). The two C conformers were identified by Philips and Levy

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(30) Schmitt, M.; Ratzer, C.; Kleinermanns, K.; Meerts, W. L. *Mol. Phys.* **2004**, *102*, 1605–1614.

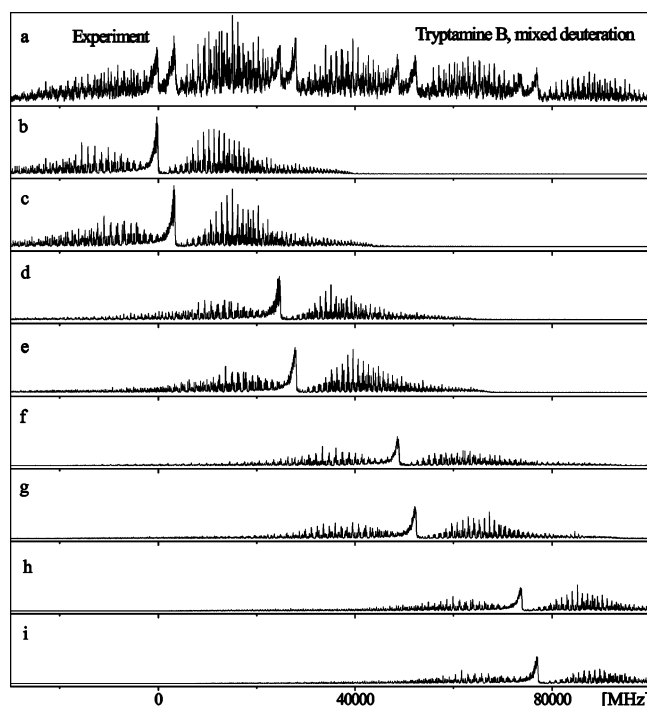
**Table 2.** Rotational Constants for the Isotopomers of the Tryptamine Conformers A–F. Conformers with an Asterisk Had Larger Uncertainties in the Inertial Parameters and were Excluded from the Structural Fits (Rotational Constants Are Given in MHz, and the Origin Frequencies in  $\text{cm}^{-1}$ )

conformer	isotopomer	$A''$	$B''$	$C''$	$A'$	$B'$	$C'$	$\nu_0$
A	$\text{h}_3$	1731.02	682.04	551.56	1724.02	672.68	544.58	34915.64
	[1a-D]	1683.25	682.41	546.52	1675.83	672.75	539.66	34917.20
	[10a-D]	1709.03	667.03	543.53	1702.37	658.08	536.82	34916.30
	[10b-D]	1712.32	675.26	548.85	1706.28	665.69	541.82	34917.27
	[1a-D][10a-D]	1685.30	671.65	542.79	1681.36	662.71	535.49	34918.84
	[1a-D][10b-D]*	1676.44	671.58	538.31	1673.41	662.32	527.94	34917.87
	$\text{d}_3$	1646.11	659.05	534.89	1640.28	649.8	528.27	34919.47
B	$\text{h}_3$	1710.25	682.22	551.10	1703.62	672.92	544.54	34895.91
	[1a-D]	1661.92	681.38	545.19	1655.52	671.68	538.85	34897.66
	[10a-D]	1701.67	667.02	541.27	1695.50	657.87	534.75	34894.89
	[10b-D]	1694.79	674.03	547.37	1688.44	664.74	540.73	34896.85
	[1a-D][10a-D]*	1657.24	673.39	541.89	1651.83	664.06	535.37	34898.49
	[1a-D][10b-D]*	1640.31	678.05	559.93	1631.19	675.62	556.19	34897.55
	[10a-D][10b-D]	1689.51	661.71	537.75	1683.13	652.48	531.26	34896.74
$\text{d}_3$	1641.98	659.18	533.12	1636.75	650.06	526.69	34898.38	
C	$\text{h}_3$	1594.16	755.84	561.39	1587.38	743.08	554.20	34879.22
	$\text{d}_3$	1509.11	737.12	545.22	1503.43	724.67	538.28	34885.80
D	$\text{h}_3$	1767.74	617.78	477.00	1754.07	612.34	473.44	34884.26
	$\text{d}_3$	1648.46	584.20	454.74	1635.78	579.25	451.61	34886.32
E	$\text{h}_3$	1761.40	614.75	475.58	1748.47	609.26	472.16	34868.34
	$\text{d}_3$	1650.34	557.33	429.34	1630.52	542.65	418.75	34869.98
F	$\text{h}_3$	1605.11	737.84	561.51	1592.77	728.49	555.25	34831.95
	$\text{d}_3$	1522.25	725.63	546.97	1511.10	716.32	540.71	34838.31



**Figure 4.** Rovibronic spectrum of the electronic origin of tryptamine *B* at  $34895.91 \text{ cm}^{-1}$ . The upper trace shows the experimental spectrum, the following shows the simulation with the best molecular parameters from the GA fit. The following traces present an enlarged portion of the spectrum.

through their different Q-branches in the rotationally resolved LIF spectrum, approximately  $0.6 \text{ cm}^{-1}$  apart. This finding was confirmed by Carney et al.<sup>1</sup> via different resonant ion dip infrared (RIDIR) spectra taken through two vibronic bands that were shown to belong to the *C* spectrum by UV–UV hole-burning. We carefully scanned the respective region of the *C* conformer, but we were able to identify only one band, absorbing in this range in contrast to the findings of Philips



**Figure 5.** Rovibronic spectra of the electronic origins of the fully protonated and seven deuterated isotopomers of the *B* conformer of tryptamine. Trace *a* shows the experimental spectrum, and the other traces show the simulations of the individual isotopomers. The electronic origin of the undeuterated tryptamine *B*, shown in trace *c*, is at  $34895.91 \text{ cm}^{-1}$ . Trace *b* represents the isotopomer [10b-D]tryptamine- $\text{d}_1$ , trace *d* [1b-D][10a-D]-tryptamine- $\text{d}_2$ , trace *e* [1b-D]tryptamine- $\text{d}_1$ , trace *f* [1b-D][10b-D]tryptamine- $\text{d}_2$ , trace *g* [10a-D]tryptamine- $\text{d}_1$ , trace *h* [1b-D][10a-D][10b-D]tryptamine- $\text{d}_3$ , and trace *i* the [10a-D][10b-D]tryptamine- $\text{d}_2$  isotopomer.

and Levy<sup>6</sup> and Carney et al.<sup>1</sup> The signal-to-noise ratio in our experiment would have allowed for the detection of a band at least by a factor of 50 smaller than the origin of the *C* conformer at  $34879.22 \text{ cm}^{-1}$ . We changed the expansion conditions over a large range in order to rule out the possibility that different cooling conditions in the molecular beam were responsible for

**Table 3.** Comparison of Rotational Constants of the MP2/6-311G(d,p) Optimized Structures of Seven Conformers of Tryptamine with the Experimentally Determined Rotational Constants

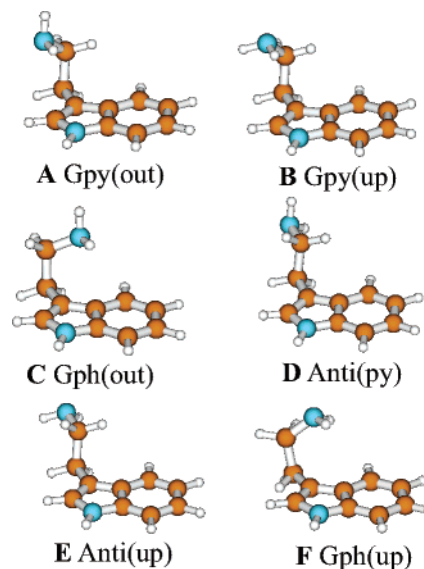
	Gpy(out)	Gpy(up)	anti(py)	Gph(out)	anti(ph)	anti(up)	Gph(up)
$E_{\text{rel.}}$ (kJ/mol)	0.4083	0.5445	6.8644	0	6.8143	5.6123	1.3709
$A''$ (MHz)	1729.9	1711.5	1767.0	1578.9	1756.2	1753.2	1588.7
$B''$ (MHz)	687.4	686.8	614.7	772.0	619.1	616.0	753.5
$C''$ (MHz)	556.6	555.9	476.7	564.8	478.3	476.9	566.9
experiment	<i>A</i>	<i>B</i>	<i>D</i>	<i>C</i>		<i>E</i>	<i>F</i>
$A''$ (MHz)	1731.02	1710.25	1767.74	1594.16		1761.40	1605.11
$B''$ (MHz)	682.04	682.22	617.78	755.84		614.75	737.84
$C''$ (MHz)	551.56	551.10	477.00	561.39		475.58	561.51

the “disappearance” of the second *C* band. Under no experimental conditions, we could find any trace of an additional band with a Q-branch around  $34879.2 \pm 0.6 \text{ cm}^{-1}$ .

The electronic origins of the *E* ( $34868.34 \text{ cm}^{-1}$ ) and *F* ( $34831.95 \text{ cm}^{-1}$ ) conformers are much weaker than the *A* and *B* origins. Therefore, we were only able to record the undeuterated and the triply deuterated conformers. Nevertheless, the six rotational constants for each conformer are sufficient for an unambiguous assignment of the structure, which needs, in principle, only three rotational constants for the three dihedral angles. The parameters from the best fits are given in Table 1. The spectra of the *E* and *F* conformers were taken at considerably lower backing pressures than the other conformers. The optimum expansion conditions for observation of conformers *A* to *D* were 500 mbar of Ar and a temperature of the tryptamine sample container of  $160 \text{ }^\circ\text{C}$ . Optimum conditions for the *E* and *F* conformers were at a backing pressure of 200–250 mbar.

Comparison of the rotational constants of the undeuterated tryptamine conformers with the results of ab initio calculations gives a first clue to the assignment to a specific structure. Table 3 compares the rotational constants of the optimized MP2/6-311G(d,p) structures with the experimentally obtained rotational constants. The best agreement is found by relating band *A* to the Gpy(out) conformer, band *B* to Gpy(up), band *D* to anti-(py), band *C* to Gph(out), band *E* to anti(up), and band *F* to Gph(up). This assignment agrees with the findings of Carney et al. but is still not able to remove their ambiguity in the distinction of the anti(ph) and anti(py) structures. Therefore, the information has to be combined with the rotational constants of the deuterated isotopomers. This will be performed in the following section. Figure 6 shows the six observed conformers.

A comparison of the relative energies of the seven conformers, calculated in this study at MP2/6-311G(d,p), with the B3LYP/aug-ccVTZ results of Carney and Zwier shows important differences. The energies of all anti conformers are quite similar, while the energies of the gauche conformers differ considerably between both methods. For the correlated MP2 method, the Gph(out) conformer becomes the most stable one, while this conformer is only the third most stable one at density functional level. Of course, one would expect the largest differences for the conformers with a potential interaction between the amino group and the aromatic ring. This is the case for all gauche conformers, but not the anti conformers. The relative intensities of the individual tryptamine bands in the low-resolution spectra of refs 6 and 1 seem to favor energetically the Gpy(out) (*A*) and the Gpy(up) (*B*) conformers over the Gph(out) (*C*) conformer. Nevertheless, this comparison of relative intensities relies on the assumption of equal or nearly equal oscillator strengths for all conformers. It is well-known that the



**Figure 6.** Structure of the six tryptamine conformers identified in the rovibronic analysis of the present publication. Gpy represents conformers in which the amino group position is gauche to the pyrrole side of the indole ring. Anti is for a position anti to the indole ring, and Gph for a position gauche to the phenyl side. The orientations of the amino lone pair are designated by “out” and “py”, depending on the direction of the lone pair of the amino group with respect to the rings ( $\pm 60^\circ$ ), or “up” ( $180^\circ$ ). This nomenclature follows the suggestion of Carney and Zwier.<sup>1</sup>

orientation of the transition dipole moment depends strongly on the conformational orientation of a flexible group, attached to a benzene chromophore.<sup>31,32</sup> This interaction takes place both by “through bond” and “through space” interactions.

**Determination of the Monomer Structure Parameters.** The program pKriFit<sup>33</sup> was used to determine the structure of the tryptamine isotopomers and the water cluster in the electronic ground state. We performed a structural fit for the different conformers, in which the different vibrational contributions from the different isotopomers are completely neglected and which is based on the following assumption:

$$I_0^g = I_{\text{rigid}}^g(r_0) \quad (4)$$

In this equation, the three  $I_0^g$  are the (experimentally determined) zero-point averaged moments of inertia with respect to the inertial axes *g*. The function  $I_{\text{rigid}}^g(r_0)$  is calculated from the structural parameters  $r_0$  using rigid-molecule formulas. The resulting structure is called the  $r_0$ -structure.

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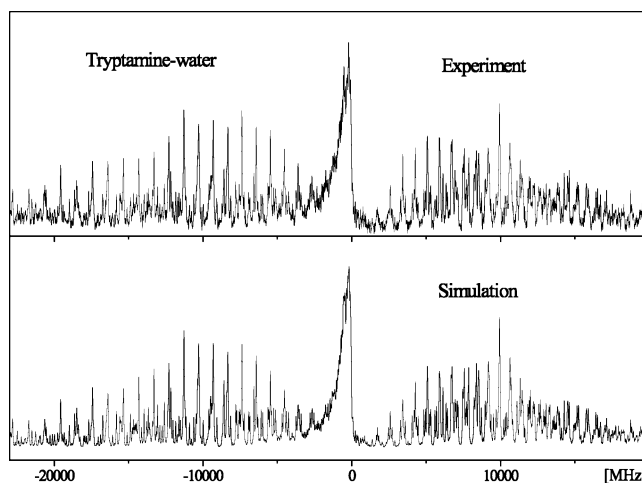
**Table 4.** Results of the Structural Fits of the Tryptamine Conformers for the Electronic Ground State (Dihedral Angles  $\tau_1$  –  $\tau_3$  Are Defined in Figure 1)

	A	B	D	D	C	E	F
	Gpy(out)	Gpy(up)	anti(py)	anti(ph)	Gph(out)	anti(up)	Gph(up)
$\tau_1$	101.9	103.7	104.7	104.6	93.1	107.6	85.5
$\tau_2$	–63.9	–65.3	179.5	182.3	63.5	–11.2	62.8
$\tau_3$	75.1	–59.1	118.8	–147.1	166.6	–102.0	–40.6
$\chi^2$	4	4	6	4	4	10	3

The first step was a simulation of the rotational constants for the different isotopomers, based on the results of the ab initio calculations described above. The assignment of the different isotopomers of the A conformer is very straightforward since the differences between calculated and experimental rotational constants are small. Starting with the known isotopomers,  $h_3$  and  $d_3$ , it was possible to assign all other isotopomers. The assignment of the bands in the order of their appearance in the spectrum is given in Table 2. In all cases, the agreement between the rotational constants of the isotopomers predicted from the ab initio structures is stunning. The next step is the determination of the structural Z-matrix parameters to be fit to the rotational constants. The first choice is, of course, the dihedral angles, which determine the position and orientation of the amino group. Therefore, the three dihedral angles,  $\tau_1$ ,  $\tau_2$ , and  $\tau_3$  (cf. Figure 1 for definition), have been varied to fit the rotational constants. Table 4 presents the results for the best ground-state structure.

**The Tryptamine–Water Cluster.** Low-resolution spectra showed that despite the richness of the potential energy landscape of the tryptamine monomer, only a single band at  $34\,957\text{ cm}^{-1}$  appears upon addition of water,<sup>2</sup> which can be attributed to the binary water cluster. The water molecule might attach to each of the seven conformers that have similar energies in the ab initio calculations. Four attaching positions of the water molecules have been considered for the starting geometries: the pyrrolic NH group, which acts as proton donor with respect to the water molecule, the amino group, which might act with each of its H-atoms as proton donor, and the amino group, which might act as a proton acceptor. Without considering any van der Waals bound structures, there are 28 different geometries possible. Nevertheless, only one shows up in the high-resolution UV spectrum. Figure 7 shows the rotationally resolved spectrum of the electronic origin of tryptamine–water at  $34\,957.11\text{ cm}^{-1}$ . The molecular parameters obtained from the GA fit of this spectrum are given in Table 5 and are compared to the values obtained by Felker<sup>14</sup> and Connell and Felker<sup>10</sup> using rotational coherence spectroscopy. The angle  $\theta$  of  $23^\circ$ , given in ref 14 for the angle of the TDM with the *a*-axis, has been converted into components of the TDM along the inertial axes in Table 5 for better comparison.

Comparison of the experimental rotational constants with rotational constants of Hartree–Fock optimized structures (Table 6) reveals that only the Gpy(out) conformer with the water binding as proton donor to the amino group (Figure 6) can be responsible for the observed band. All other calculated rotational constants are too far off to be considered. In the Hartree–Fock calculations, not all 28 starting geometries converged into an equivalent structure. Clusters in which the H-atom of the amino group that is pointing in direction of the aromatic ring acts as proton donor with respect to the water do not converge at all. Clusters in which the H-atom of the amino group is pointing



**Figure 7.** Rovibronic spectrum of the electronic origin of tryptamine–water at  $34957.11\text{ cm}^{-1}$  along with the simulation using the best parameters given in Table 5.

**Table 5.** Molecular Parameters for the Tryptamine–Water Cluster Determined from GA Fits, as Described in the Text. A, B, and C are the Rotational Constants of the Molecule in the Ground State.  $\Delta A$ ,  $\Delta B$ , and  $\Delta C$  are the Changes of the Rotational Constants upon Electronic Excitation<sup>8</sup> ( $\mu_a$ ,  $\mu_b$ , and  $\mu_c$  Designate the Components of the Transition Dipole Moment to the Inertial Axis of the Cluster, and  $\tau$  (ns) Is the Excited State Life Time)

tryptamine–water	this work	ref 14
$A''$ (MHz)	1465.78	1465
$B''$ (MHz)	483.43	479
$C''$ (MHz)	397.99	379
$\mu_a$	0.8063	0.847
$\mu_b$	0.0221	0.153
$\mu_c$	0.1715	0
$\tau$ (ns)	4.8	
$\Delta A$ (MHz)	–6.82	
$\Delta B$ (MHz)	–4.71	
$\Delta C$ (MHz)	–3.72	

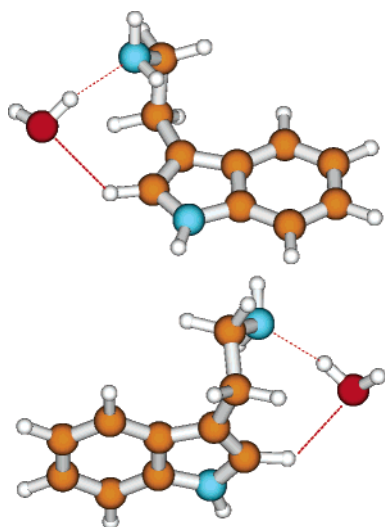
away from the aromatic ring converge for all Gph and Gpy conformers into the respective structure, while for all anti conformers, they converge into the structure with the amino group being proton acceptor. It is intriguing that the calculated energy differences between the conformers complexed with a single water molecule are much larger than those for the respective monomers.

To investigate the physical origin of the structural selection by microsolvation of tryptamine with one water molecule we reoptimized the most stable Hartree–Fock structure for each conformer with Møller–Plesset perturbation theory. The results of the ab initio calculations are summarized in Table 6. The energy differences between the different conformer clusters are much larger than those for the respective monomers using the same method and basis set. If one expresses the energy differences in temperature units, the observed monomer energies differ by less than  $kT$  at room temperature, while for the complexes, the energy differences grow much larger than  $kT$  at room temperature. What is the reason for the pronounced stabilization of the A conformer with respect to all other conformers upon water complexation?

Figure 8 shows the structure of the most stable water cluster. The distance between the O-atom of the water moiety and  $H_{2a}$  at the pyrrole moiety of the indole ring (cf. Figure 1 for atomic numbering of the monomer) is only 238.1 pm. This is already

**Table 6.** HF/6-31G(d,p) Optimized Structures of Different Tryptamine–Water Clusters. The Numbers in Parentheses Give the MP2/6-311G(d,p) Values Where Applicable. The Relative MP2 Energies Contain Corrections of the Basis Set Superposition Error Using the Counterpoise Method of Boys and Bernardi<sup>21</sup> and Zero-Point Energy Corrections

	NH(py)	Gpy(out) NH <sub>2</sub> (a)	NH <sub>2</sub> (d)	NH(py)	Gpy(up) NH <sub>2</sub> (a)	NH <sub>2</sub> (d)
$E_{\text{rel.}}$ (kJ/mol)	12.535	0 (0)	17.140	14.291	11.313 (8.088)	24.325
$A''$ (MHz)	917.0	1469.4 (1483.0)	1160.8	804.1	1163.9 (1079.8)	1399.7
$B''$ (MHz)	548.7	470.8 (488.2)	566.2	591.0	412.9 (490.3)	445.7
$C''$ (MHz)	373.0	387.0 (402.7)	524.4	370.3	356.4 (397.9)	365.4
	NH(py)	anti(py) NH <sub>2</sub> (a)	NH <sub>2</sub> (d)	NH(py)	Gph(out) NH <sub>2</sub> (a)	NH <sub>2</sub> (d)
$E_{\text{rel.}}$ (kJ/mol)	15.294	10.58 (13.228)		14.526	5.457 (4.354)	16.832
$A''$ (MHz)	1035.8	1629.3 (1584.0)		1003.0	1058.7 (1095.1)	1047.1
$B''$ (MHz)	466.1	377.0 (402.2)		538.6	602.4 (617.9)	643.9
$C''$ (MHz)	332.7	316.8 (330.9)		375.8	420.4 (437.2)	523.1
	NH(py)	anti(ph) NH <sub>2</sub> (a)	NH <sub>2</sub> (d)	NH(py)	anti(up) NH <sub>2</sub> (a)	NH <sub>2</sub> (d)
$E_{\text{rel.}}$ (kJ/mol)	15.345	8.149 (12.425)		15.472	12.784 (13.183)	
$A''$ (MHz)	1038.6	1169.1 (1185.7)		1031.7	1342.2 (1231.8)	
$B''$ (MHz)	466.4	509.7 (522.1)		466.4	341.6 (386.9)	
$C''$ (MHz)	333.2	373.1 (381.1)		332.9	304.6 (346.9)	
	NH(py)	Gph(up) NH <sub>2</sub> (a)	NH <sub>2</sub> (d)		experiment	
$E_{\text{rel.}}$ (kJ/mol)	16.035	12.694 (7.099)	23.826			
$A''$ (MHz)	968.2	1231.5 (1247.8)	1065.1		1465.81	
$B''$ (MHz)	542.8	405.5 (430.6)	621.8		483.37	
$C''$ (MHz)	378.1	351.1 (371.0)	520.3		398.02	



**Figure 8.** Structure of the tryptamine–water complex in the electronic ground state obtained from the fit of the water distance and the water orientation to the experimentally determined rotational constants. The lower half gives a back-view of the complex. The fitting procedure is described in detail in the Supporting Information.

a distance that allows for a weak hydrogen bond, thus selectively stabilizing this conformer. What about the other conformers? Clusters of water with conformers in which the amino lone pair is pointing up do not have the possibility to form an additional hydrogen bond. The same holds for all anti structures in which the ethyl amino side chain points away from the indole ring system.

Thus, the only two structures which might be additionally stabilized are Gpy(out) (the *A* conformer) and Gph(out) (the *C* conformer). In case of the *C* conformer cluster, the additional stabilizing interaction takes place between the water O-atom and H<sub>4a</sub> at the benzene moiety of the indole ring. The hydrogen

bond distance is larger (248.4 pm), explaining the lower stability of this cluster relative to the *A* conformer cluster. The stronger bonding interaction in the *A* conformer cluster reflects the increased acidity of the C<sub>2</sub>–H bond compared to that of the C<sub>4</sub>–H bond.

**Determination of the Cluster Structure Parameters.** Since the ab initio calculations guided us in deciding which conformer is present in the water cluster, we determined the structural parameters only for the Gpy(out) geometry with the water molecule attached to the amino group, which acts as acceptor in this cluster. The three rotational constants have been used for a fit of the O<sub>water</sub>–N distance, the O<sub>water</sub>–NC<sub>α</sub> angle, and the O<sub>water</sub>–NC<sub>α</sub>C<sub>β</sub> dihedral angle. The structures of the tryptamine and water moieties have been kept fixed at the respective monomer geometries. A hydrogen bond length of 301.3 pm and a nearly linear hydrogen bond was obtained from the fit. This value is similar to the O<sub>water</sub>–N hydrogen bond lengths of the ammonia–water complex (298.3 pm)<sup>34</sup> and the aniline–water complex (303 pm).<sup>35</sup> The structure shown in Figure 8 is very similar to the structure that was derived by Felker<sup>14</sup> and Connell and Felker<sup>10</sup> based on the rotational constants of the normal isotopomer and the *d*<sub>3</sub>-tryptamine–D<sub>2</sub>O cluster, which were obtained by rotational coherence spectroscopy.

## Conclusions

It is surprising that the microsolvation of tryptamine with a single water molecule freezes out one specific conformer of the possible 27 in tryptamine. While the barriers separating the individual conformers that can be observed in the experiment amount to several times the thermal energy *kT* at room temperature, the energy *difference* between these isotopomers

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is smaller than or of the order of the magnitude of  $kT$ . Thus, if one compares the stabilities of isolated conformational species, nearly all minima on the potential energy surface are accessible thermally, and the respective conformations should all be considered. On the other hand, complexation with a single water molecule already increases the energy differences between the conformers to several times the thermal energy at room temperature. We have traced back the origin of the selective stabilization of one conformer to an additional bonding in the water complex, which can only occur in the *A* conformer.

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**Supporting Information Available:** Spectra of the normal isotopomer and the triply deuterated *C*, *D*, *E*, and *F* conformers of tryptamine, along with a simulation using the best parameters from the GA fits. Cartesian coordinates of the MP2/6-311G-(d,p) optimized structures of the seven tryptamine conformers described in the text. Complete ref 20. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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