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The Rotational Spectrum of Tyrosine

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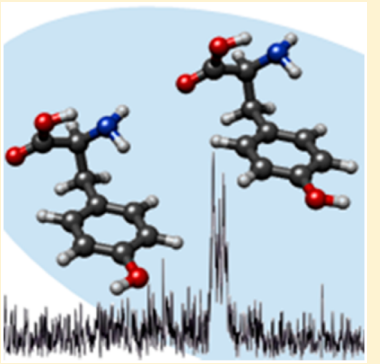
Supporting Information

ABSTRACT: In this work neutral tyrosine has been generated in the gas phase by laser ablation of solid samples, and its most abundant conformers characterized through their rotational spectra. Their identification has been made by comparison between the experimental and *ab initio* values of the rotational and quadrupole coupling constants. Both conformers are stabilized by an O−H•••N hydrogen bond established within the amino acid skeleton chain and an additional weak N−H•••π hydrogen bond. The observed conformers differ in the orientation of the phenolic −OH group.



INTRODUCTION

Proteinogenic amino acids are indispensable agents of biological function since they constitute the building blocks of peptides and proteins. In addition they may have nonprotein functions as neurotransmitters or being precursors of important neurotransmitters or hormones. The function of proteins and their multidimensional structure are highly dependent upon the conformation that their constituent amino acids may adopt. The knowledge of the structure and conformational behavior of those building blocks is thus an important question not only to biochemistry but also for chemistry, since those flexible molecules constitute structural models to study the intermolecular forces that control molecular conformation. The advantage of gas-phase conformational studies lies in the opportunity to obtain the intrinsic properties of the amino acids in isolation, free of the intermolecular interactions which occur in condensed phases where amino acids are bipolar zwitterionic species. Electronic spectroscopy techniques such as high resolution laser-induced fluorescence (LIF) or resonance enhanced multiphoton ionization (REMPI) in combination with supersonic jets have been used to elucidate the structures of gas phase proteogenic amino acids bearing chromophore groups. Hence, these techniques have been applied to tyrosine (Tyr), tryptophan (Trp), and phenylalanine (Phe), which were the subject of a large number of investigations.[1−18] REMPI and LIF experiments on Tyr[12−15] reported up to ten vibronic bands which suggested the presence of a large number of stable conformers. More recently, eight different structures of Tyr were confirmed by using UV−UV and IR−UV hole burning techniques.[16,17] In a last work, using the same experimental approach, Shimozono et al.[18] interpreted the jet cooled electronic spectra on the basis of 12 different conformers.

Microwave spectroscopy is particularly well adapted to the study of multiconformer systems such as amino acids, since it has an inherently high resolution and is exceptionally sensitive to molecular geometry and mass distribution changes and it is not constrained by the need for a chromophore group. However, the vaporization of solid biomolecules imposed serious limitations to study high melting compounds such as amino acids which easily decompose by classical heating methods. Recent developments in laser ablation techniques have allowed us to overcome vaporization problems. In particular, combining Fourier transform microwave spectroscopy with laser ablation techniques in a supersonic expansion (LA-MB-FTMW)[19−21] has provided a new approach to the structural studies of amino acids. Apart from glycine[22,23] and alanine,[24] first studied by classical heating methods, a large number of proteogenic and nonproteogenic aliphatic amino acids[19−21,25−34] have been studied by the above technique. Their applicability to aromatic amino acids was first tested in phenylglycine[35] and latter applied to the studies of Phe[36] and Trp.[37] Significant photofragmentation was detected, and consequently, our experimental setup was modified trying to minimize it. Shorter laser pulses (30 ps length pulse) and shorter wavelengths (Nd:YAG 355 nm) have been recently implemented in our new instrumentation[37,38] in order to minimize photofragmentation processes. In the context of our ongoing investigation of the conformational panorama of amino acids using rotational spectroscopy, we report in this paper the first rotational study of the proteogenic aromatic amino acid tyrosine.

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Table 1. Experimental Spectroscopic Parameters for the Observed Conformers IIa1 and IIa2 of L-Tyrosine

	Experimental		Theory	
Parameter[a]	Rotamer X	Rotamer Y	Conformer IIa1	Conformer IIa2
A	1529.6791(40)[b]	1525.2543(29)	1519.5	1516.4
B	463.94021(32)	465.48173(25)	472.6	474.2
C	425.76168(40)	427.31023(27)	433.2	434.8
Δ_J	0.0507(29)	0.0527(19)		
χ_{aa}	0.709(14)	0.740(15)	0.94	0.96
χ_{bb}	0.236(88)	0.247(92)	−0.29	−0.28
χ_{cc}	−0.945(88)	−0.988(92)	−0.64	−0.67

[a]A, B, and C are the rotational constants; Δ_J is the cuartic centrifugal distortion constant; χ_{aa}, χ_{bb}, and χ_{cc} are the diagonal elements of the ^{14}N nuclear quadrupole coupling tensor. [b]Standard error in parentheses in units of the last digit.

EXPERIMENTAL SECTION

The rotational spectrum of Tyr was observed using a new laser ablation molecular beam Fourier transform microwave (LA-MB-FTMW)[20,21,38] spectrometer operating in the 4−10 GHz frequency range. Solid rods of fine-powdered tyrosine (mp 290−295 °C) were mixed with minimum quantities of a commercial binder to form a cylindrical rod. The samples were then vaporized using the third harmonic (355 nm) of a Nd:YAG picosecond laser (30 ps length pulse) using energies of ∼2 mJ/pulse. The neutral vaporized molecules were seeded in the carrier gas (Ne, 15 bar) and expanded into a Fabry-Pérot resonator. After sending the microwave pulses through the cavity, the emission FID (free induction decay) of the molecules was recorded in the time-domain and Fourier transformed to yield the frequency-domain spectrum. Since the supersonic jet and the microwave resonator axis are collinearly placed, signals appeared split into Doppler doublets. The arithmetic mean of the doublets was taken as the final frequency. The estimated accuracy of the frequency measurements is better than 3 kHz.

RESULTS AND DISCUSSION

Before starting the experimental study, we extended the previous *ab initio* calculations[39] on the low energy conformers of Tyr to predict the rotational and nuclear quadrupole coupling constants as well as electric dipole moment components which are needed for the interpretation of the rotational spectrum. Geometry optimizations were carried out with the Gaussian suite of programs[40] using second-order Møller−Plesset perturbation theory (MP2) in the frozen-core approximation and Pople's 6-311++G(d,p) basis set. This level of theory has proven to give very good results for the rotational parameters at a reasonable computational cost.[19−33] The calculated spectroscopic parameters for the ten lowest-energy conformers of Tyr are shown in Table S1 of the Supporting Information.

All conformers are predicted to be near-prolate asymmetric tops with a nonzero μ_a component of the electric dipole moment. In this way, their R- branch, μ_a-type spectra are expected to show the characteristic patterns consisting of groups of lines separated by approximately $B + C$. Initially, the polarization power was set to optimally polarize the transitions associated with moderate values of μ_a. Hence, we were able to detect two sets of weak μ_a-type R-branch series transitions, attributable to two different rotamers which initially were labeled as X and Y. The subsequent fitting and prediction iterative procedure allows us to observe new μ_a transitions and to extend our measurements to the R-branch μ_b-type spectrum.

All the observed transitions (see Figure S1 and Table S3 and S4 of the Supporting Information) were split into several close hyperfine components showing the characteristic pattern due to a ^{14}N nucleus, which confirms the presence of a single nitrogen atom in the observed species. This hyperfine structure arises from the interaction of the electric quadrupole moment of the ^{14}N ($I = 1$) nucleus with the electric field gradient created at the site of the quadrupolar nucleus by the rest of the electronic and nuclear charges of the molecule. This interaction gives rise to the coupling of the ^{14}N nuclear spin with the overall angular momentum, which results in a characteristic hyperfine structure observable in the rotational spectra. The associated spectroscopic parameters are the quadrupole coupling constants $\chi_{\alpha\beta}$ ($\alpha\beta = a, b, c$). These are the elements of the quadrupole coupling tensor χ, which is related to the electric field gradient tensor q by $\chi = eQq$, where eQ is the electric quadrupole moment. According to this, the spectra were analyzed[41] using the semirigid rotor Hamiltonian of Watson in the A reduction and the I^r representation $H_R^{(A)}$,[42] supplemented with a term to take into account the quadrupole interaction H_Q,[43] namely $H = H_R^{(A)} + H_Q$. The analysis allowed the determination of the rotational constants, the centrifugal distortion constant Δ_J, and the diagonal elements of the quadrupole coupling tensor for both X and Y rotamers (see Table 1).

The comparison of the experimental and predicted rotational parameters in Table 1 shows that the observed rotational constants are in good agreement with those predicted for conformers IIa1 and IIa2 (collected also in Table 1 for comparison). The same conclusion can be reached from the comparison of the values of the ^{14}N quadrupole coupling constants. The experimental values are only in good agreement with those predicted for conformers IIa1 and IIa2. The values of the ^{14}N quadrupole coupling constants are very sensitive to the orientation of the $-NH_2$ group with respect to the principal inertial axis system so that in most cases these constants led to a conclusive assignment of the observed conformers. However, in this case, conformers IIa1 and IIa2 have practically the same values of the ^{14}N quadrupole coupling constants because the rotation of the principal inertial axis system induced by the change in the structure of the phenolic −OH group does not contribute to significant changes in the quadrupole coupling constants. Therefore, it is not possible to carry out an unequivocal assignment of both observed rotamers on the basis of these constants. Fortunately, the change in orientation of the −OH group in conformers IIa1 and IIa2 causes distinctive shifts in the inertial moments which are translated to the rotational constants. Thus, the small shifts in the rotational constants do have the key to discern between both conformers. The changes in the experimental values of the rotational

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constants between rotamers X and Y are $\Delta A = \Delta A_Y - \Delta A_X \approx -4.4$ MHz, $\Delta B \approx 1.5$ MHz and $\Delta C \approx 1.5$ MHz. These values are in good agreement with the differences between the rotational constants of conformers IIa1 and IIa2; $\Delta A = \Delta A_{IIa2} - \Delta A_{IIa1} \approx -3.1$ MHz, $\Delta B \approx 1.6$ MHz, and $\Delta C \approx 1.6$ MHz. This fact allows the identification of rotamers X and Y as the lowest lying energy conformers IIa1 and IIa2, respectively. The small discrepancy found between the experimental and predicted values of quadrupole coupling constants (Table 1) is due to a slight variation in the actual orientation of the amino group with respect to that predicted via ab initio methods. Hence, when the amino group rotated (6° on the dihedral angle ∠HNCC) from the equilibrium value, the predicted and experimental values of the nuclear quadrupole coupling constants are nearly in coincidence (see Table S2).

In the next stage of our investigation, we focused the experimental searches to detect spectral signatures of Ia and IIb conformers, predicted higher in energy. We observed sets of very weak μ_a-type R-branch rotational transitions in the predicted frequency intervals for conformers IIb1 and IIb2, predicted to have high values of the μ_a electric dipole moment component. We were only able to observe a few lines of each set with a non-well-resolved hyperfine structure; no spectroscopic constants could be derived. After performing wide scans with different experimental conditions, no lines attributable to other conformers of Tyr were observed.

The two observed conformers of Tyr shown in Figure 1 are stabilized by an O−H···N hydrogen bond with a COOH trans

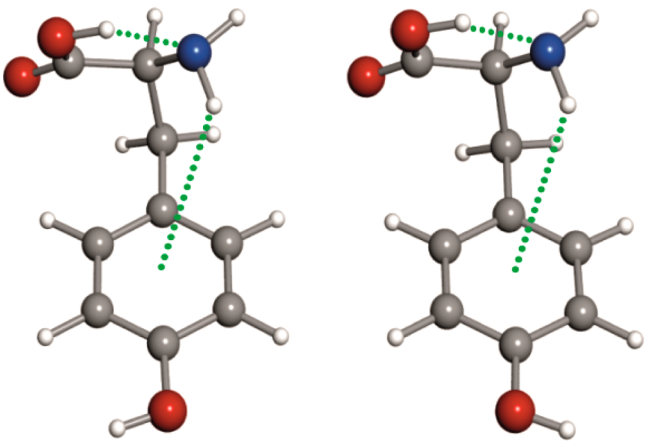

Figure 1. 3D structures of observed conformers (IIa1(left) and IIa2 (right)) of Tyr showing the intramolecular interactions which stabilize both structures.

configuration (type II of the amino acids[20]). Moreover, one of the hydrogen atoms of the amino group is pointing toward the π electron density of the ring, indicating the existence of an N−H···π interaction. The modified orientation of the amino group mentioned above points to the establishment of this N−H···π interaction by decreasing the hydrogen bond distance. Both intramolecular hydrogen bonds form a chain that reinforces their strength through cooperative effects.[44,45] For the overwhelming majority of the α-amino acids studied so far, a type I conformer has been found as global minimum. A few exceptions have been found for which a type II conformer has been found to be the most stable conformer. Those include the imino acids proline,[19,32] and hydroxyproline,[28] asparagine,[34] phenylalanine,[36] tryptophan,[37] and histidine.[38] With the exception of proline and hydroxyproline, the type II O−H··· N hydrogen bond established within the amino acid backbone is reinforced by an additional bond from the amino group to the lateral chain in all cases. In the case of the phenylalanine,[36] tryptophan,[37] and tyrosine, this additional interaction corresponds to a weak N−H···π weak hydrogen bond.

Relative intensity measurements on selected μ_a-type lines of the IIa1 and IIa2 conformers indicate that the relative populations follow the order IIa2 > IIa1, in agreement with the theoretically predicted relative energies. This pair of conformers, which differ only in the OH arrangement, have a predicted energy difference of 132 cm^{-1}. This energy difference could be tentatively explained by the existence of local dipole−local dipole[46] interaction between the amino acid group and the side chain ($-CH_2-C_6H_4-OH$). These dipoles find a more favorable arrangement for conformer IIa2, increasing in this way the relative stability of this conformer.

In conclusion, we have observed two conformers of Tyr through the analysis of its rotational spectrum. These conformers are stabilized by O−H···N and N−H···π hydrogen bond interactions and derive from the most stable forms observed for the related amino acid Phe.[36] The weakness of the spectrum and the low number of observed conformers for Tyr compared with those detected for aliphatic amino acids[30−33] can be attributable to photofragmentation/ionization processes during the laser ablation course. As reported for Phe,[47] ionization processes would favor the presence of only IIa and IIb conformers, with higher ionization energy, in the supersonic jet. We have monitored photofragmentation effects using a time-of-flight mass spectrometer (TOF-MS) coupled with the same laser ablation nozzle used in our LA-MB-FTMW experiment and we found (See Figure S2 of the Supporting Information) a large amount of Tyr fragments, indicating that photofragmentation of Tyr occurs to a large extent in the ablation process. The subsequent depletion of the number density of tyrosine in the supersonic expansion would cause the observation of weaker spectra. Despite the important improvements recently achieved in the observation of nucleoside uridine,[48] the intrinsic effects of photofragmentation associated with the aromatic amino acids make extremely difficult the observation of their complete conformational panorama.

■ ASSOCIATED CONTENT

Supporting Information

Complete ref 40, predicted ab initio molecular properties for the lower-energy conformers of the tyrosine together with MP2/6-311++G(d,p) equilibrium principal axis coordinates, quadrupole coupling constants calculated at the different dihedral angles ∠HNCC for the observed conformers, observed rotational transitions for the two detected conformers, and list of measured transitions and mass spectrum of tyrosine. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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