Isolated Monohydrates of a Model Peptide Chain: Effect of a First Water Molecule on the Secondary Structure of a Capped Phenylalanine

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Ⓢ Supporting Information

ABSTRACT: The formation of monohydrates of capped phenylalanine model peptides, CH_3-CO-Phe-NH_2 and CH_3-CO-Phe-NH-CH_3, in a supersonic expansion has been investigated using laser spectroscopy and quantum chemistry methods. Conformational distributions of the monohydrates have been revealed by IR/UV double-resonance spectroscopy and their structures assigned by comparison with DFT-D calculations. A careful analysis of the final hydrate distribution together with a detailed theoretical investigation of the potential energy surface of the monohydrates demonstrates that solvation occurs from the conformational distribution of the isolated peptide monomers. The distribution of the monohydrates appears to be strongly dependent on both the initial monomer conformation (extended or folded backbone) and the solvation site initially occupied by the water molecule. The solvation processes taking place during the cooling can be categorized as follows: (a) solvation without significant structural changes of the peptide, (b) solvation inducing significant distortions of the backbone but retaining the secondary structure, and (c) solvation triggering backbone isomerizations, leading to a modification of the peptide secondary structure. It is observed that solvation by a single water molecule can fold a β-strand into a γ-turn structure (type c) or induce a significant opening of a γ-turn characterized by an elongated C_7 hydrogen bond (type b). These structural changes can be considered as a first step toward the polyproline II condensed-phase structure, illustrating the role played by the very first water molecule in the solvation process.
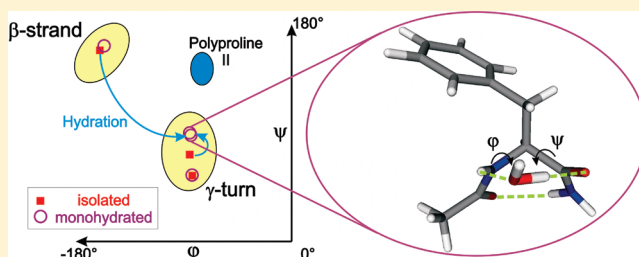
1. INTRODUCTION

Complete understanding of the link between the environment within which a protein resides and its secondary structure is still far from being achieved. From a theoretical point of view, modeling of a solvated protein chain as simple as the alanine dipeptide analogue (Ac-Ala-NH-Me) is still a subject of debate for molecular dynamics studies.[1,2] On such small systems, two-dimensional infrared spectroscopy (2D IR), nuclear magnetic resonance spectroscopy (NMR), vibrational Raman spectroscopy optical activity (VROA), or vibrational circular dichroism (VCD) of peptides in liquids can provide conformational characterization[3−7] as well as a few structural parameters that can be used for benchmarking purposes.[8,9] These approaches, however, suffer in general from an averaging over the whole distribution of conformers present in the medium. Alternatively, gas-phase spectroscopy experiments provide accurate and conformer-selective data but are limited to isolated systems. One approach to address solvation issues and still benefit from the spectral resolution of gas-phase measurements consists of studying mixed solvent/solute molecular clusters, where the number of solvent molecules in the system can be controlled.[10] Such microsolvated solutes (typically with less than 10 solvent molecules) are intermediate systems which can bridge the gap between isolated and fully solvated molecules, as they provide a unique insight into the solvation

process by eventually revealing the role of every single solvent molecule. The effect of a modest number of molecules, which was already suspected from basic *ab initio* calculations,[9] can now be addressed experimentally for a large panel of systems using state-of-the-art spectroscopy coupled to efficient vaporization techniques.[11−13] Infrared/ultraviolet (IR/UV) double-resonance spectroscopy is a popular method which provides single-conformer IR spectra and is thus adapted to flexible systems like peptides. Coupled with the powerful computational arsenal of quantum chemistry, the data provided enable spectroscopists to characterize the conformations adopted by the peptides in the gas phase.[13−15] This approach has proven to be a unique tool in revealing the underlying noncovalent interactions like H-bonds, NH-π bonds, or aromatic—aromatic interactions that control the conformational preferences adopted by short peptides.[16−18]

In this context, gas-phase solvation studies appear quite promising for a complete characterization of microsolvated structures, thus providing a better understanding of solvation processes. Examples can be found in the literature on flexible molecules like tryptamine or 3-indolepropionic acid,[19,20] in which a water bridge is found to modify the conformational

Structure of the Indole−Benzene Dimer Revisited

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ABSTRACT: The structure of the indole−benzene dimer has been investigated using experimental techniques, namely, UV spectroscopy and infrared−ultraviolet (IR/UV) double resonance spectroscopy, combined with quantum chemical calculations such as MP2 and dispersion corrected DFT methods. The red shift of the indole N−H stretch frequency in the dimer provides direct evidence that the experimentally observed indole−benzene dimer is an N−H$\cdots\pi$ bound hydrogen bonded complex. Theoretical investigations suggest that the potential energy surface (PES) of the complex is rather flat along the coordinate describing the tilt angle between the molecular planes of indole and benzene, with several minima of similar energies, namely, parallel displaced (PD), right-angle T-shaped (T), and other intermediate structures which can be categorized as tilted T-shaped (T′) and tilted parallel displaced (PD′) structures. Three different computational methods, namely, RI-MP2, RI-B97-D, and PBE1-DCP, are used to arrive at a new structural assignment after assessing their performance in predicting the structure of the pyrrole dimer, for which accurate experimental data are available. By comparing the computed IR spectra of PD, T, and T′/ PD′ structures with the experimental IR spectrum, the tilted T-shaped (T′) structure was assigned to the indole−benzene dimer. The empirically dispersion-corrected functionals (RI-B97-D and PBE1-DCP) correctly reproduce the experimental IR spectrum whereas the popular post-Hartree−Fock, MP2 method gives disappointing results. These results are also in agreement with the experimental dissociation energy (D_0) reported in the literature. The N−H stretch frequency of the indole−benzene dimer has been found to be a more pertinent parameter for the structural assignment than the dissociation energy (D_0).
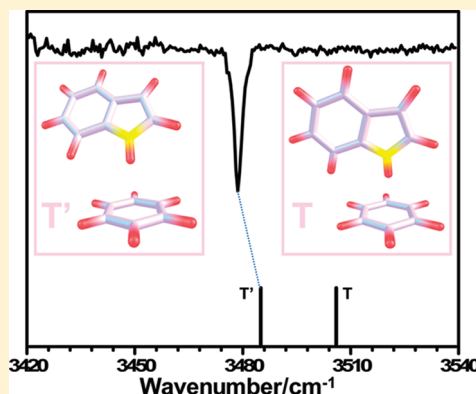
1. INTRODUCTION

Noncovalent interactions between two aromatic (*ar*) systems are ubiquitous in the hydrophobic core of proteins.[1−5] These interactions can be categorized as: (i) polarization, related to the Debye force, which controls the *ar*-X−H$\cdots\pi$ (X = C, N, and O) hydrogen bonding, in which one aromatic system acts as an H-bond donor and the other as an acceptor, and (ii) dispersion (London force), found in the interactions between two aromatic rings like in the benzene dimer.[6−8] For instance, interactions between phenylalanine side chains, which are merely dispersion and quadrupole−induced-dipole interaction, have recently been shown to play a crucial role in the structure and the stability of peptides.[9] The influence of the *ar*-X−H$\cdots\pi$ H-bonds are even more important in controlling the structure and reactivity of biomolecules as these interactions tend to orient both the aromatic systems more specifically than the London forces.[10] As an example, the presence of *ar*-X−H$\cdots\pi$ H-bonds in protein chains play a pivotal role in stabilizing α-helices and β-sheets, which in turn provides them a well-defined shape.[11]

To study such interaction at the molecular level in proteins is still a quite challenging task for both the experimentalists and the theoreticians. However, an alternative approach consists of studying relatively smaller molecular complexes which can be routinely synthesized under gas phase isolated conditions. These simple systems are ideal for modeling the aforementioned interactions and can serve as benchmark systems for quantum chemical methods. A lot of information about the structure, energetics, and the nature of the *ar*-X−H$\cdots\pi$ H-bonded interactions can be extracted by a combined approach of using the state-of-the-art experimental techniques such as IR/UV double resonance spectroscopy and ab initio calculations. In this context, the indole−benzene dimer is one of the simplest intermolecular complexes, which has recently drawn much attention from both spectroscopists and theoreticians to describe the aforementioned interactions at the molecular level.[12−15] The indole−benzene dimer can indeed be considered as a model system for the

Gas-Phase Folding of a Two-Residue Model Peptide Chain: On the Importance of an Interplay between Experiment and Theory

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Abstract: In order to assess the ability of theory to describe properly the dispersive interactions that are ubiquitous in peptide and protein systems, an isolated short peptide chain has been studied using both gas-phase laser spectroscopy and quantum chemistry. The experimentally observed coexistence of an extended form and a folded form in the supersonic expansion was found to result from comparable Gibbs free energies for the two species under the high-temperature conditions ($\leq$320 K) resulting from the laser desorption technique used to vaporize the molecules. These data have been compared to results obtained using a series of quantum chemistry methods, including DFT, DFT-D, and post-Hartree−Fock methods, which give rise to a wide range of relative stabilities predicted for these two forms. The experimental observation was best reproduced by an empirically dispersion-corrected functional (B97-D) and a hybrid functional with a significant Hartree−Fock exchange term (M06-2X). In contrast, the popular post-Hartree−Fock method MP2, which is often used for benchmarking these systems, had to be discarded because of a very large basis-set superposition error. The applicability of the atomic counterpoise correction (ACP) is also discussed. This work also introduces the mandatory theoretical examination of experimental abundances. ΔH(0 K) predictions are clearly not sufficient for discussion of folding, as the conformation inversion temperature is crucial to the conformation determination and requires taking into account thermodynamical corrections (ΔG) in order to computationally isolate the most stable conformation.

Because of the exponential increase in computational power, molecular modeling techniques are now able to address various experimental problems from material sciences to biology. The problem of protein folding remains a difficult one, however, as the complex physics at play require an accurate treatment of noncovalent weak interactions, such as induction and dispersion.[1] In this context, quantum chemistry (QC) methods[2] play a central role, potentially offering access to chemical accuracy for small model peptides and therefore providing useful reference computations for the design of modern tools, such as polarizable force fields,[3] that target large systems like proteins. For such benchmarking purposes, two different strategies are currently applied. On the one hand, ab

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initio post-Hartree−Fock methods are often assumed to be the most suitable because of their high accuracy, but despite their sophistication and their ability to account for dispersion interactions, their limits have been discussed in the literature,[2,4,5] in particular when considering the interaction of electron-rich groups such as phenyl rings with other parts of the molecule. Alternatively, density functional theory (DFT) methods are computationally more efficient, making them more suitable to larger systems, and a wealth of functionals have been recently developed to address the above-mentioned issues and in particular to account for electronic correlation.[6,7] In parallel with these theoretical developments, current gas-phase methods now enable experimentalists to prepare isolated biomolecules and optically characterize the most stable conformers observed.[8−11] By comparison with a library of spectroscopic features or with QC-calculated IR spectra on a selected set of structures, the experimentally observed conformers can be reliably assigned, at least in terms of H-bonding networks and secondary structure. Capitalizing on the state-of-the-art studies in both fields, we have carried out a joint experimental/theoretical investigation of a flexible test molecule aimed at an assessment of emblematic QC techniques. The two-residue Ala-based model peptide chosen, Ac-(Ala)$_2$-O-Bzl (where Ac- and -Bzl stand for *N*-acetyl and benzyl, respectively), is short enough that it can still be tractable theoretically but still contains both a phenyl ring and a flexible chain that can lead to dispersive effects and conformational diversity.

The most stable structures of Ac-(Ala)$_2$-O-Bzl were detected experimentally under isolated conditions using UV and IR/UV spectroscopy. The molecules were vaporized by laser desorption (second harmonic of a Nd:YAG laser) from a pressed powder sample mixed with micrometric graphite powder used as a matrix.[12] Vaporization took place downstream of the nozzle aperture into a pulsed supersonic expansion of a He/Ne mixture or pure Ar (stagnation pressure 5−10 bar). The molecules were efficiently cooled in the jet, eventually leading to conformer-resolved UV features and resolved IR spectra. The near-UV spectrum of Ac-(Ala)$_2$-O-Bzl, as obtained by the mass-resolved resonant two-photon ionization (R2PI) technique (Figure 1a), exhibits two major sets of spectral features (origin band of the $\pi-\pi^*$ transition of the benzyl chromophore), namely, a first series of bands labeled A and a weaker and narrow isolated band labeled B. Double-resonance IR/UV spectroscopy showed that the NH-stretch IR spectra obtained from the A bands were identical and differed from those obtained from band B. This enabled us to assign the UV spectrum to two main conformers, labeled A and B. The IR spectrum of A (Figure 1b) is composed

O−H···O versus O−H···S Hydrogen Bonding. 2. Alcohols and Thiols as Hydrogen Bond Acceptors

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In this paper, the effect of alkyl substitution at the hydrogen bond acceptor and its chain length on the strength and nature of hydrogen bonding is presented. In the present study we combine both experimental and computational methods to investigate the characteristics of O−H···O and O−H···S hydrogen bonding in the complexes of *p*-cresol (*p*-CR) with methanol (MeOH), ethanol (EtOH), methanethiol (MeSH), and ethanethiol (EtSH). The results indicate that, with an increase in the alkyl chain length, both O−H···O hydrogen bonding and O−H···S hydrogen bonding become stronger. Energy decomposition analysis emphasizes the dispersive nature of O−H···S hydrogen bonding. In addition, it revealed that the dispersion energy contribution in O−H···O hydrogen bonding increases with an increase in the alkyl chain length of the hydrogen bond acceptor. In the case of O−H···S hydrogen bonding, however, the dispersion energy contribution decreased from 68% for the H_2S complex to 53% in the case of the MeSH complex; it remained unchanged with a further increase of the alkyl chain length. It was also observed that the red shifts in the OH stretching frequency did not correlate with the proton affinities of the O-centered acceptor vs the S-centered H-bond acceptor, in contrast with the known trend for the conventional H-bonded complexes. The IR/UV double resonance study enabled the assignments of the *anti* and *gauche* conformers of *p*-CR−EtOH and *p*-CR−EtSH.

1. Introduction

In a recent paper the significant difference between O−H···O and O−H···S hydrogen bonding in the complexes of *p*-cresol (*p*-CR) with H_2O/H_2S was illustrated using a variety of experimental and computational methods.[1] It was reported that O−H···S hydrogen bonding is dispersive in nature as opposed to the electrostatic nature of O−H···O hydrogen bonding.[1−3] In this study, the effect of alkyl substitution on the hydrogen bond (HB) acceptor site (O or S atom) on the HB strength as well as on the nature of hydrogen bonding is investigated. This is the second part of the series of OH···SR$_2$ (R = radical) HB investigations that are being carried out in our laboratory.[1,4−6]

Alcohols such as methanol (MeOH) and ethanol (EtOH) were chosen as the O-centered HB acceptors, and thiols such as methanethiol (MeSH) and ethanethiol (EtSH) were chosen as the S-centered HB acceptors. Among the alcohols, the simplest alcohol, methanol, has been extensively characterized by various spectroscopic methods.[7−10] In the case of ethanol, structural characterization[7,11−18] has one more dimension due to the presence of isoenergetic *anti* and *gauche* conformers. Apart from the structural studies of these alcohols, the hydrogen-bonding interaction of these molecules with phenol is well documented in the literature.[19−30] As far as alkanethiols are concerned, the effect of noncovalent interactions of the alkanethiol moiety and its conformational variants in the cysteine residue on protein folding is well recognized.[31,32] There are a few experimental investigations on the structure of ethanethiol.[33,34] Nonresonant two-photon pulsed field ionization photoelectron spectroscopy[33,34] as well as vacuum ultraviolet mass-analyzed threshold ionization spectroscopy[33,34] gave experimental evidence for the existence of *trans* and *gauche* conformers of ethanethiol in jet-cooled conditions. However, a detailed and comparative study of the nature of hydrogen bonding in alcohols and alkanethiols has not been reported to date.

In this study, the nature of OH···O and OH···S hydrogen bonding has been investigated using MeOH, EtOH, and EtSH as the respective HB acceptors. Since MeSH was not commercially available, the experimental results of MeOH could not be compared directly. Therefore, the hydrogen-bonding characteristics of *p*-CR−MeOH and *p*-CR−MeSH were compared using computational methods. The experiments were carried out in the gas phase under supersonic jet conditions. Various computational methods were used to quantify these interactions and substantiate the experimental findings. Experimental techniques such as laser-induced fluorescence (LIF), two-color two-photon ionization (2c-R2PI) time-of-flight mass spectrometry (TOFMS), and fluorescence-detected infrared spectroscopy (FDIRS) and various ab initio computational methods such as density functional theory (DFT), second-order Møller−Plesset (MP2) perturbation theory, atoms-in-molecules (AIM) theory, natural bond orbital (NBO) analysis, and energy decomposition analyses were employed to characterize the HB interactions.

2. Experimental Details

The details of the experimental setup are described elsewhere.[1,35] In brief, *p*-cresol was evaporated at 50−60 °C and coexpanded through a 500 μm pulsed nozzle (General Valve, series 9) into a vacuum chamber using helium as the carrier gas. The molecular beam machine consisted of two 10 in. diameter differentially pumped stainless steel chambers. These two chambers were linearly connected by a skimmer located ∼25

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O−H···O versus O−H···S Hydrogen Bonding. 3. IR−UV Double Resonance Study of Hydrogen Bonded Complexes of *p*-Cresol with Diethyl Ether and Its Sulfur Analog

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In this work the hydrogen bonded complexes of diethyl ether (DEE) and diethyl sulfide (DES) with *p*-cresol (*p*-CR) were investigated. Only one conformer of the *p*-CR·DEE complex and three conformers of the *p*-CR·DES complex were found to be present under the supersonic jet expansion conditions. The conformational assignments were done with the help of IR−UV double resonance studies and ab initio calculations. The red shifts in the OH stretching frequency for the O−H···O and O−H···S hydrogen bonded complexes were quite close to each other. In fact, one of the *p*-CR·DES conformers showed a slightly larger red shift in the OH stretch than that in the *p*-CR·DEE conformer, which suggests that in this case sulfur is not a weak hydrogen bond acceptor as noted previously in case of the *p*-CR·H$_2$O and *p*-CR·H$_2$S complexes (Biswal et al. *J. Phys. Chem. A* **2009,** *113,* 5633). The natural bond orbital analysis also shows that the extent of overlap between sulfur lone pair orbitals (LP) and OH antibonding orbital (σ^*_{OH}) was comparable to the oxygen (LP) and σ^*_{OH} overlap, consistent with the similar magnitudes of the red shifts of OH stretch in the DES and DEE complexes. The computed binding energy of the *p*-CR·DES complex, however, was about 80% of the *p*-CR·DEE complex. The electron densities at the bond critical points indicated that the O−H···S interaction was weaker than the O−H···O interaction in this particular system also. The important finding of this study was that the IR red shifts in the H-bond donor X−H stretching frequency were not quite consistent with the computed binding energies and the atoms-in-molecules analysis contrary to the general understanding. Energy decomposition analysis suggests that O−H···S hydrogen bonding interaction is dispersive in nature and the dispersion contribution decreases with the increase in the length of the alkyl chain of the "S" hydrogen bond acceptor.

1. Introduction

The thrust of our recent work has been to characterize a variety of O−H···S hydrogen bonded complexes to investigate the nature of hydrogen bond involving sulfur atoms.[1−3] The aim of these studies was also to compare the O−H···O versus O−H···S hydrogen bonding to bring out the similarities and the differences between these two types of hydrogen bonded complexes. The lack of microscopic data on the O−H···S hydrogen bonding in the literature necessitates investigations of a large number of such systems to make any statements about the overall nature of the O−H···S hydrogen bonding. By systematically choosing the hydrogen bond acceptor or donor moieties (or both), one can get greater insight. As a first step in this direction, our recent studies included *p*-CR complexes with H$_2$S, CH$_3$SH, C$_2$H$_5$SH, and their oxygen counterparts.[2,3] It was found that in the case of the H$_2$S complex the major component of the interaction was dispersive rather than electrostatic. As one of the H atoms in H$_2$S was replaced by an alkyl group, the dispersion contribution decreased.[1,3] In another series the hydrogen bonded complexes of indole and 3-methyl indole with H$_2$S and dimethyl sulfide have been reported.[4,5]

The current study deals with the hydrogen bonded complexes of *p*-cresol (*p*-CR) with diethyl ether (DEE) and diethyl sulfide (DES). DEE was chosen as the "O" hydrogen bond (HB) acceptor and DES as the "S" HB acceptor. The aim of this study was to explore the effect of the alkyl substitution and its chain length on the ability of sulfur as the HB acceptor and compare it with that of the oxygen. DEE is one of the important dipolar aprotic solvents, used as a medium in various chemical reactions. Apart from this, the structural characterization of DEE and DES has gained a lot of attention in the research community.[6−18] The structural aspects of these molecules are interesting because of the presence of two flexible ethyl chains that give rise to multiple conformers of these molecules. In almost all the cases, the microwave spectroscopy has been employed to elucidate the structure of the conformers. Another important and interesting aspect of these molecules is the intermolecular HB interaction, which probably has got less attention. There are a couple of reports in the literature, where 1:1 complex of DEE with HB donor molecules have been characterized by employing experimental and computational methods.[19,20] Abe et al.[19] used fluorescence spectroscopy to study the hydrogen bonding in the phenol·DEE complex whereas Lam et al.[20] investigated the mechanism of hydrogen bonded complex formation between protonated alcohol and DEE by employing VUV laser ionization techniques and computational methods.

In this study, the nature of OH···O and OH···S hydrogen bonding was investigated using *p*-CR as the HB donor and DEE and DES as the respective HB acceptors. Different conformers of the complexes formed in the jet were assigned to appropriate structures. The experimental techniques such as the laser induced

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O−H···O versus O−H···S Hydrogen Bonding I: Experimental and Computational Studies on the *p*-Cresol·H₂O and *p*-Cresol·H₂S Complexes

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The weak hydrogen bonding ability of sulfur-containing hydrides makes it difficult to study their complexes and has not been characterized experimentally so far. In this work, the hydrogen-bonded complexes of H₂S and H₂O with *p*-cresol (*p*-CR) were studied using a variety of techniques such as two-color resonant two-photon ionization (2c-R2PI) spectroscopy, single vibronic level fluorescence (SVLF) spectroscopy, resonance ion dip infrared spectroscopy (RIDIRS), and fluorescence dip infrared spectroscopy (FDIRS), with an aim of comparing the nature and strength of their respective hydrogen bonding abilities. The intermolecular stretch (σ) and the shift in the O−H stretching frequency of *p*-CR in the complex were taken as the measures of the O−H···O and O−H···S hydrogen bonding strength. The experiments were complemented by the *ab initio* calculations, atoms in molecules (AIM), natural bond orbital (NBO), and energy decomposition analyses carried out at different levels of theory. The experimental data indicates that in the *p*-CR·H₂S complex, the phenolic OH group acts as a hydrogen bond donor, and sulfur as the acceptor. Further, it indicates that the *p*-CR·H₂S complex was about half as strong as the *p*-CR·H₂O complex. The AIM and NBO analyses corroborate the experimental findings. The energy decomposition analyses for the O−H···S hydrogen bond in the *p*-CR·H₂S complex reveal that the dispersion interaction energy has the largest contribution to the total interaction energy, which is significantly higher than that in the case of the *p*-CR·H₂O complex.

1. Introduction

Noncovalent interactions such as van der Waals and hydrogen bonding have been a thrust area of research in recent years. With the advances in the experimental techniques and computational resources, a variety of different hydrogen bonding interactions have been reported in the literature in recent times.[1] It is the most common and yet an important type of interaction which is encountered in many chemical and biological processes. It plays a vital role in defining the crystal packing of many organic and organometallic molecules, in regulating 3D structure and controlling the functions of biological molecules, as well as modulating the reactivity of different groups within a molecule. Owing to its importance, a lot of effort has been put into understanding its nature, and by now, the hydrogen bonding between X−H···Y, where X and Y are two electronegative atoms, is fairly well understood. In the classical electrostatic model, significant charge transfer occurs from the acceptor Y to the donor or, more precisely, from the lone pair orbital on Y to the σ*₍X−H₎ antibonding orbital, resulting in weakening of the X−H bond with concomitant elongation[2] of the XH bond length. This elongation of the X−H bond manifests in a decrease in the X−H stretching frequency, and such a frequency red shift with respect to that of the free monomer has been regularly used as a fingerprint of hydrogen-bonded complex.

Sulfur is the least electronegative element compared to N, O, and F (2.58 for S, 3.04 for N, 3.44 for O, 3.98 for F on the Pauling scale).[3] Further, due to the very small difference in the electronegativity of H and S (Δ ∼ 0.38 on the Pauling scale)

and poorer match between the hard proton (hard acid) and soft sulfur (soft base), intrinsically, it is not a good hydrogen bond (HB) acceptor. Sulfur also happens to be a biologically abundant element (amino acids, disulfide bridges, etc.), and the existence of the X−H···S (X = N, O) HB is well established from the crystallographic data on proteins and organic molecules.[4−15] Despite this, the experimental investigations have been very scant on the X−H···S hydrogen-bonded systems. A large number of computational studies have been devoted, however, to investigate either the H−S···π or S−H···π interaction in the case of H₂S and aromatic hydrocarbon complexes.[15−25] The authors' first report on the experimental observation of O−H···S HB in simple model compounds of two naturally occurring amino acids, tyrosine and methionine (*p*-CResol was taken for tyrosine and dimethyl sulfide (DMS) for methionine),[26] indicated that the O−H stretch red shift in these systems was almost the same as that for the O−H···O HB in the case of the *p*-cresol-(H₂O)₁ complex. However, it was felt that this comparison would not be appropriate as the sulfur bound to two methyl groups in DMS would not be the same HB acceptor as that in the case of H₂S.

The historic Pauling definition of HB states that "for the X−H···Y hydrogen bond, both X and Y atoms should be electronegative, the X···Y distance should be shorter than the corresponding sum of van der Waals radii, and this interaction is mostly electrostatic in nature".[27] Although the electrostatic origin accounts for the major part of the HB strength, there are other interactions which could also contribute to the strength of HBs. Very recently, Desiraju claimed that "the hydrogen bond is not a simple interaction but a complex conglomerate of at least four component interaction types, electrostatic (acid/base), polarization (hard/soft), van der Waals (dispersion/repulsion), and covalency (charge transfer)".[28] The relative extent of each

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Nature of the N−H···S Hydrogen Bond

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The N−H···S hydrogen-bonded complexes of the model compounds of tryptophan (indole and 3-methylindole) and methionine (dimethyl sulfide, Me_2S) have been characterized by a combination of experimental techniques like resonant two-photon ionization (R2PI), resonant ion dip infrared spectroscopy (RIDIRS), and fluorescence dip infrared spectroscopy (FDIRS) and computational methods like ab initio electronic structure calculations, atoms-in-molecules (AIM), natural bond orbital (NBO), and energy decomposition analyses. The results are compared with the N−H···O ($M \cdot H_2O$; M = indole, 3-methyl indole) σ-type and N−H···Φ (M·benzene) π-type hydrogen-bonded complexes. It was shown that the S_1-S_0 band origin red shifts in the N−H···S hydrogen-bonded complexes correlated well with the polarizability of the acceptor rather than their proton affinity, contrary to the trend observed in most X−H···Y (X, Y = O, N, halogens, etc.) hydrogen-bonded systems. The red shift in the N−H stretching frequency in the N−H···S HB clusters (Me_2S as HB acceptor) was found to be 1.8 times greater than that for the N−H···O hydrogen-bonded complexes (H_2O as HB acceptor), although the binding energies for the two complexes were comparable. The energy decomposition analyses for all of the N−H···S hydrogen-bonded complexes showed that the correlation (or dispersion) energy has significant contribution to the total binding energy. It is pointed out that the binding energy of the N−H···S complex was also comparable to that of the indole·benzene complex, which is completely dominated by the dispersion interaction. Atoms-in-molcules (AIM) and natural bond orbital (NBO) analyses indicated a nontrivial electrostatic component in the hydrogen-bonding interaction. Greater dispersion contribution to the stabilization energy as well as greater red shifts in the N−H stretch relative to those of N−H···O hydrogen-bonded complexes makes the indole·dimethylsulfide complex unique in regard to the simultaneous influence of both the dispersion and electrostatic forces. For the sake of comparison, it is pointed out that the red shifts in the O−H stretch for O−H···S and O−H···O hydrogen-bonded complexes were almost the same in the case of *para*-cresol·Me_2S and *para*-cresol·H_2O complexes (*J. Chem. Phys.* **2008**, *128*, 184311. and *J. Phys. Chem. A* **2009**, *113*, 5633−5643). This suggests that the strength of the N−H···S hydrogen bonding is stronger than the N−H···O hydrogen bonding. The N−H···S hydrogen bonding was observed for the first time using jet-cooled conditions, and the most interesting feature of this study is that N−H···S "σ-type" hydrogen bonding behaves more like C−H···Φ or N−H···Φ "π-type" hydrogen bonding in regard to the dispersion domination in the total interaction energy.

1. Introduction

Although the concept of the hydrogen bond is almost a century old,[1] it is still evolving because of the novel experimental findings and high-level computational results.[2] This is the single most important noncovalent interaction, which plays a crucial role in governing the physical and chemical properties of the solvents, controls solute−solvent interactions, and most importantly provides a specific shape, stability, and functionality to the biomolecules like proteins and DNA. The commonly observed hydrogen bonds involve the first row elements such as N, O, and F, and these are most extensively studied and well characterized. The nature of the interaction in these cases is electrostatic in origin, which is responsible for their directionality. The hydrogen-bonding interactions involving the second row elements such as P, S, and Cl are not any less abundant.[3] However, investigations of these are very sparse due to various reasons, namely, they are less electronegative compared to the first row elements, and there is poorer match between the hard

proton (hard acid) and soft bases like P, S, and so forth. It would be very interesting to look at the properties, origin, and strength of X−H···Y hydrogen bonds involving the X and/or Y atoms belonging to the second row elements. As a first step in this direction, we have investigated the X−H···S HBs, where X is O or N. Sulfur is the choice replacement for Y as almost all living systems contain several important sulfur-containing molecules, including two amino acids, methionine and cysteine.

Our first report on the O−H···S HB in the model compounds of tyrosine and methionine[4] followed by the comprehensive study of O−H···O versus O−H···S HB in the *p*-cresol−H_2O/H_2S complexes revealed that the O−H···S HB is relatively weaker and predominantly dispersive in nature.[5] In this work, we have investigated the N−H···S type HB in the model compounds of tryptophan and methionine. The existence of N−H···S HB is evident from the crystal structure data for β-lactam antibiotics such as pencillins,[6] the active site of proteins like cytochrome-P450 and nitric oxide synthase,[7−9] the iron−sulfur proteins,[10−13] as well as in the organic crystals.[14−18] However, the microscopic data on the N−H···S HB is nonexistent in the literature. Owing to the importance of the N−H···S HB in the

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Sulfur, Not Too Far Behind O, N, and C: SH···π Hydrogen Bond

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We report hydrogen-bonded complexes of H_2S with indole and 3-methyl indole stabilized by the S−H···π interaction. It is interesting to discover that although sulfur and its hydrides are known as poor hydrogen-bond donor/acceptors, sulfur is not too far behind oxygen, nitrogen, and carbon in regard to forming the π-type hydrogen bonds. This report also extends the scope of our earlier studies from σ-type hydrogen-bonded complexes of sulfur (O−H···S and N−H···S σ-type hydrogen-bonded complexes) to π-type hydrogen-bonded complexes of sulfur (S−H···π π-type hydrogen-bonded complexes). The experiments were carried out using the supersonic jet expansion technique, and the complexes were probed using laser-induced spectroscopy such as laser-induced fluorescence (LIF), resonant two-photon inonization (R2PI), and fluorescence dip infrared spectroscopy (FDIRS). The FDIR spectroscopy revealed that while there was no shift in the N−H stretch, the S−H stretch was red shifted by about 21 cm^{-1}. For the H_2O complexes of indole and 3-methylindole, however, there was a significant red shift in the N−H stretch. These observations suggest that H_2O forms a NH···O type complex, whereas H_2S prefers to form a SH···π type complex. The experimental results were complemented by ab initio calculations and energy decomposition analysis. The binding energies for both the σ-type and π-type hydrogen-bonded M·L complexes (M = indole and 3-methylindole; L = H_2O and H_2S) were calculated by extrapolating MP2 interaction energies to the complete basis set limit. The calculated M·H_2S (σ-type) interaction energy (2.74 kcal/mol) was considerably smaller than that of the M·H_2S π-type hydrogen-bonded complex (4.89 kcal/mol), which is exactly opposite of the trend found for the M·H_2O complexes. This is consistent with the experimental observations. Comparison of the S−H···π interaction with the other type of X−H···π (X = C, N, and O) shows that the S−H···π interaction is the strongest among them. In all of the π-type HB complexes, the dispersion energy component has significant contribution to the total binding energy.

1. Introduction

The 90s saw quite a few interesting results in regard to the hydrogen-bonding interactions involving a hydrogen atom covalently bonded to some atom and aromatic π-electron density.[1−10] These were termed as π-type hydrogen bonds. The conventional definition of a X−H···Y hydrogen bond had already been expanded[11] to include Y as an "electron-rich atom or group of atoms" rather than just another "electronegative atom". A few celebrated examples of the π-type hydrogen bonds include benzene·H_2O,[1−5,10,12−16] benzene·CH_3OH,[14,17] benzene·NH_3,[6,7,16,18−22] benzene·$CHCl_3$,[9,23−25] benzene·hydrogen halide,[8,26,27] and benzene dimer complexes.[28−42] In each case, it was shown that one of the XH bonds of the hydrogen-bond-donating moiety points toward the aromatic ring and the XH stretching frequency, except in the case of the C−H···Y interaction, which exhibits a red shift that is a hallmark characteristic of a hydrogen bond. Further, these hydrogen bonds are much weaker than the conventional X−H···Y σ-type hydrogen bonds. The benzene·water and benzene·ammonia complexes were shown to be very floppy, with the barrier height for the hindered rotation around the C_2 and C_3 axis of H_2O and NH_3, respectively, being very low.[3,6,7,22,43]

In this work, we present experimental evidence of the S−H···π interaction in indole·H_2S and 3-methylindole·H_2S

complexes. Experimental techniques like LIF and FDIR spectroscopy and ab intio calculations were used to show that H_2S preferentially forms a π-type HB, although the possibility of forming a N−H···S σ-type hydrogen-bonded complex existed in these systems. The importance of S−H···π as well as S···π interaction is evident from the structures of the proteins and biomolecules.[44−49] There have been a few reports in the literature where some efforts have been made to characterize the S−H···π hydrogen bonds computationally.[46,50−54] However, the experimental investigations of the S−H···π HB under isolated jet-cooled conditions have been very sparse. Only one report on S−H···π interaction exists where the interaction between H_2S and benzene was addressed using FT-microwave rotational spectroscopy.[43] The data indicated that H_2S was located on the C_6 axis of the C_6H_6 with the center of mass (C_6H_6)−S distance of 3.818 Å. The angle between the C_6 axis of C_6H_6 and the C_{2v} axis of H_2S was determined to be 28.5° in the complex.

We have recently published a detailed comparative study of hydrogen-bonding interactions between *p*-cresol and the H_2S/H_2O system.[55] It was shown that both H_2O and H_2S form O−H···O/S σ-type hydrogen-bonded complexes. The O−H···S hydrogen bond was found to be weaker than the O−H···O HB and had a major contribution from the dispersion energy component compared to that in the O−H···O interaction. The results presented here are in stark contrast with those reported in the case of *p*-cresol complexes. It is well established that H_2O forms a σ-type HB with indole (IND) and 3-methylindole (3-MI).[56−59] It has also been reported that H_2O forms a π-type

Effect of pyridyl nitrogen on the conformational landscape of 7-azaserotonin: A computational study

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ABSTRACT

The conformational topology of gaseous neutral 7-azaserotonin has been investigated by employing systematic *ab initio* calculations. The whole conformational landscape has been explored by varying four dihedral angles which define the position of ethyl amine side chain and phenolic OH group with respect to the 7-azaindole plane. A total of 22 local minima have been located by geometry optimization of 216 possible trial structures at the B3LYP/6-31+G* level of theory. With the exception of a few conformers, in most cases the OH-*syn* conformers were more stable than their OH-*anti* counterparts. Vibrational frequency analysis for all 22 conformers computed at B3LYP/6-31+G* shows some interesting features in the pyrrole and pyridine C—H stretches. In some of the conformers the presence of intramolecular blue shifted H-bonding is confirmed using the atoms in molecules (AIM) analysis. The AIM analysis explains the differences in the relative energy order of various conformers compared to that observed in the case of serotonin. It also explains the behavior of the pyrrole and pyridine C—H stretches observed for some of the conformers. The conformational distribution of 7-azaserotonin at various temperatures is computed based on simple thermodynamic principle. At lower temperature of about 100 K only six conformers were significantly populated according to their electronic energies while at higher temperature of about 400 K the populations were determined by their vibrational partition functions.

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1. Introduction

The biological functions of flexible bio-molecules like neurotransmitters intimately depend on the conformation that the molecules can adopt. There have been a lot of experimental and theoretical studies on multiconformer biomolecular systems in gas phase [1–5]. Among all the neurotransmitters serotonin has been studied extensively whose flexible ethylamine chain has attracted the most for the quantum chemical investigations. Depending on the orientation of the ethylamine chain it can adopt a number of conformations. Serotonin plays a vital role in biological processes that control the states like depression, anxiety, and sexuality. It is also involved in controlling appetite, behavior, emotions, sleep, and body temperature [6].

The stability of different conformers of serotonin is determined by the interaction of ethylamine chain with aromatic π-electron density [4,5]. The interest in the conformational studies on these large flexible biomolecules has been enhanced by the growing accuracy of quantum mechanical calculations. A great number of theoretical papers treating the conformational landscapes of serotonin and tryptamine have been published [4,5,7–11] both of which have an ethylamine side chain attached to an indole moiety.

We are interested in 7-azaserotonin (Fig. 1) which has 7-azaindole moiety instead. It has been shown that indole and 7-azaindole have different physical and photophysical properties and the difference is due to the presence of electron withdrawing pyridyl nitrogen in 7-azaindole [12–14]. The presence of the potent H-bond acceptor pyridyl nitrogen in 7-azaserotonin makes it biologically interesting, like 7-azaindole and its analogs [15]. It is also evident from the QSAR and photophysical study on 7-azamelatonin (which has similar structure as that of 7-azaserotonin) that it is a potential probe for receptor recognition [16,17]. As far as the authors are aware there is no such QSAR study on 7-azaserotonin, but the additional H-bond acceptor site in 7-azaserotonin compared to serotonin may enhance the ability of binding 7-azaserotonin to receptor site, so that the 7-azaserotonin may act as a potential agonist or antagonist of serotonin receptor.

The purpose of current study is to explore the effect of pyridyl nitrogen in the ring on the conformational landscape of 7-azaserotonin. Moreover, three recent reports, one on the synthesis and photophysical study of 7-azaserotonin in condensed phase [18] and the other two on the conformational study of jet-cooled serotonin [3,5] encouraged us to investigate this molecule in gas phase by quantum chemical methods. We hope this study will compliment theoreticians to design appropriate force field method for 7-azaserotonin-receptor interaction and spectroscopists to assign the experimental spectra.

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Experimental evidence of O–H—S hydrogen bonding in supersonic jet

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Experimental evidence is presented for the O–H—S hydrogen bonding in the complexes of simple model compounds of methionine (dimethyl sulphide) and tyrosine (phenol, *p*-cresol, and 2-naphthol). The complexes were formed in the supersonic jet and were detected using resonantly enhanced multiphoton ionization spectroscopy. In all the complexes, the band origins for the S_1-S_0 electronic transition were redshifted relative to that of their respective monomers. The resonant ion depletion IR spectra of all the complexes show redshifts of $123-140$ cm^{-1} in the O–H stretching frequency, indicating that the OH group acts as the hydrogen bond donor and sulfur as an acceptor. The density functional theory calculations also predict the stable structures in support of this and predict the redshifted O–H stretching frequency in the complex. The atoms-in-molecules and natural bond orbital calculations confirm the O–H—S hydrogen bonding interaction. The significant finding of this study is that the magnitudes of redshifts in the O–H stretch in the O–H—S hydrogen bonded complexes reported here are comparable to those reported for the O–H—O hydrogen bonded complexes where H_2O acts as the H-bond acceptor, which suggests that the OH–S interaction is perhaps as strong as the OH–O interaction. To the best of our knowledge, this is the first such report on the O–H—S hydrogen bonded complexes. © *2008 American Institute of Physics.*
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I. INTRODUCTION

In recent years, hydrogen bonding has been the center of attention for a large number of experimentalists and theoreticians due to its ubiquitous presence and its role in governing the properties of solvents, solute-solvent interactions, crystal structures, and more importantly its role and potential in controlling the stability and activity of biological systems.[1] In most of the cases, these three center two electron bonds are formed due to the interaction between the protic hydrogen and the proximal electron rich atom such as O, N, F, or Cl, although a lot of examples of other types of H bonding[2] including the X–H—S hydrogen bonding exist. Sulfur is not a good acceptor for hydrogen bonding as it is the least electronegative compared to N, O, and F (2.58 for S, 3.04 for N, 3.44 for O, and 3.98 for F on Pauling scale).[3] In addition, owing to the small difference in the electronegativity of H and S ($\Delta \sim 0.38$ on Pauling scale) and poorer match between the hard proton (hard acid) and soft sulfur (soft base), the S–H interaction falls in the regime of weak hydrogen bond.[2,4]

Despite the fact that sulfur is a biologically abundant element (amino acids, disulfide bridges, etc.) and is a well established constituent of the therapeutic agents (penicillins, thionucleosides, etc.) and agrochemicals, not much experimental investigations have been done on the X–H—S hydrogen bonding interactions, where X=N or O atom.[5] The abundance of the X–H—S interactions is evident from the crystallographic data on proteins and organic molecules,[6] where both inter- and intramolecular S–H hydrogen bonding and nonhydrogen bonding interactions prevail. Following the crystal structure data, a large number of computational studies have been carried out to identify the nature, directionality, and energetics of the S–H hydrogen bond.[7] On the experimental side, several articles have been published on the Fourier transform infrared studies of both the intermolecular and intramolecular hydrogen bonded complexes between sulfur [especially S of dimethyl sulfide (Me_2S) in the intermolecular cases) and various proton donors such as H_2O, HF, HCl, HNO_2, HNO_3, and CF_3CCH in isolated argon or nitrogen matrices.[8] However, the investigations on these interactions under isolated jet-cooled conditions have been very sparse. Among the few reported data, Arunan *et al.*[9] looked at the rotational spectra of weakly bonded benzene-H_2S complex under the jet-cooled conditions and in another communication Xu *et al.*[10] reported the rotational spectra of jet-cooled thiodiglycol, where they observed the intramolecular hydrogen bonding between O–H and S. To the best of our knowledge, no experimental evidence has been reported on the intermolecular O–H—S hydrogen bonding in gas phase. The structure and energetics of these interactions can be well understood when studied under isolated conditions.

In this work, we report the intermolecular O–H—S hydrogen bonding in the model compounds of two amino acids, tyrosine (Tyr) and methionine (Met). Me_2S has been taken as a simple model for the Met side chain while phenol (PH), *para*-cresol (*p*-CR), and 2-naphthol (s-2NP) have been chosen as the models for the Tyr side chain[11] to mimic the Tyr-OH–S-Met side chain interaction in proteins.

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Lifetime measurements of SO$_2$ below the Clement's *A*-band

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High resolution laser induced fluorescence spectrum of jet-cooled SO$_2$ is recorded toward the blue side of the Clement's *A*-Band in the region of 314–319 nm. Time resolved fluorescence measurements have been carried out for all the prominent peaks in this region. Most of the peaks exhibited double exponential decay profiles. Some of the rovibronic bands exhibited quantum beats with strong quantum beats observed at 315.261 and 315.271 nm. This is the first observation of quantum beats in SO$_2$ in the absence of any external magnetic or electric fields. The decay profiles of the beating rovibronic bands were fitted using a four-level model by least-squares fitting method. The fitting shows that all the measured bands were double exponential with a similar first lifetime of ~ 3 μs and a varying second lifetime of the order of 1 μs–100 ns with a beating frequency of ~ 1 MHz. These quantum beats, in the absence of any external field, indicate rotational level mixing between the $\tilde{A}\ ^1A_2$ and the $\tilde{B}\ ^1B_1$ vibronic states which are near resonant due to the high density of states of these two states. © *2008 American Institute of Physics*. [DOI: 10.1063/1.2929829]

INTRODUCTION

The spectroscopy of SO$_2$ has been studied for over 75 years.[1] The first UV absorption measurements were reported in the early 1930s.[1,2] It was in 1935 when Clements[3] made the first detailed analysis of the UV spectrum which extends from 390 to 260 nm (25 640–38 460 cm^{-1}) and gave the letter names to the peaks. The first fluorescence spectrum along with lifetime measurements was reported 30 years later by Greenough and Duncan.[4] They also reported anomalously long lifetimes for the observed fluorescence. In a landmark paper, Douglas[5] proposed that these anomalous radiative lifetimes are due to mixing of levels, particularly with those close lying electronic states to which optical transitions are forbidden. Hamada and Merer,[6] based on their own data and the analysis of earlier rotationally resolved spectra, concluded that the Clement's bands are combination of the $\tilde{A}\ ^1A_2$ and $\tilde{B}\ ^1B_1$ states with some contribution from the $\tilde{a}\ ^3B_1$ excited state. The rotational analysis of the Clements' bands indicates that the upper level has a $\tilde{A}\ ^1A_2$ character. Although $^1A_2 \rightarrow {}^1A_1$ transition is dipole forbidden, either due to the Herzberg–Teller coupling or due to the vibronic coupling through the antisymmetric stretch, the transitions become allowed. Time resolved low pressure cell lifetime measurements between 262 and 322 nm reported by Bruce and MacDonald[7] and Su *et al.*[8] showed that the lifetimes had a short and a long component. Later, rotationally resolved measurements of the *E*-band by Holtermann *et al.*[9] yielded only a single lifetime of 14 μs. However, the lifetime measurements done by Watanabe and co-workers[10] on

the rotationally cooled *E*-band, where they used a seeded supersonic beam for their experiments, showed a biexponential decay with lifetimes of 5 and 27 μs. In another publication,[11] Watanabe *et al.* reported that the *E*-band $^1B_1$ $(\nu_1, \nu_2, \nu_3 = 1, 2, 0; J', K_a', K_c' = 1, 1, 0) \rightarrow {}^1A_1$ transition (304.2056 nm, 32 872.51 cm^{-1}) showed weak beats, without application of an external field, with an approximate beating time of 10 μs, while the other lines showed a dual lifetime.
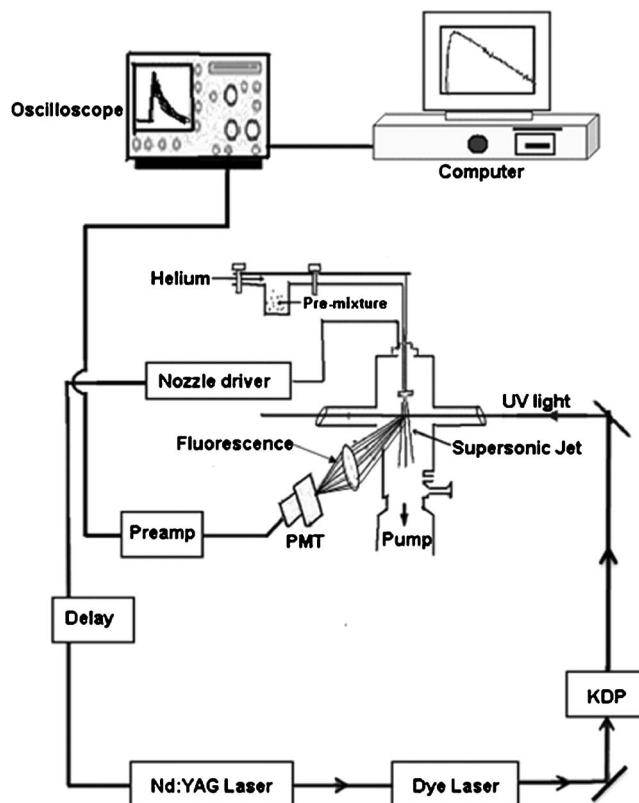

FIG. 1. Schematic of the experimental setup to measure the lifetime of SO$_2$.

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