Journal of Molecular Spectroscopy 351 (2018) 62–67

Contents lists available at ScienceDirect

Journal of Molecular Spectroscopy

journal homepage: www.elsevier.com/locate/jms

Conformational dynamics of 1-phenyl-2,2,2-trifluoroethanol by rotational spectroscopy and *ab initio* calculations

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ARTICLE INFO

Article history:
Received 5 June 2018
In revised form 8 July 2018
Accepted 18 July 2018
Available online 19 July 2018

Keywords:
Fluorinated chiral organic alcohol
Conformational analysis
Isotopic substitution
Non-covalent interactions
Chirped pulse FTMW spectroscopy
Ab initio calculations

ABSTRACT

The rotational spectrum of 1-phenyl-2,2,2-trifluoroethanol, a chiral organic alcohol, was investigated using two chirped pulse Fourier transform microwave spectrometers. The molecule is a derivate of 2,2,2-trifluoroethanol, and the phenyl substitution plays a major role in altering the conformational landscape. Three equilibrium minima were identified at the MP2 and B3LYP-D3BJ levels of theory, of which only two exist as stable conformers after applying harmonic zero-point-energy correction. Rotational spectra of the most stable conformer and its eight ^{13}C isotopologues were assigned and the rotational constants obtained were used to refine the *ab initio* structure. The second conformer was not observed experimentally, and subsequent analysis indicates that the conformational conversion barrier was too low to trap this second conformer, even in a helium jet expansion.

1. Introduction

The unique combination of steric and polar effects exhibited by fluorine [1] has resulted in fluorinated organic compounds becoming vital to pharmaceutical, agricultural, and biomedical fields. In particular, this popularity can be attributed to the enhanced metabolic stability resulting from the presence of C—F bonds [1,2], which have greater stability (116 kcal/mol) than C—H bonds (99 kcal/mol) [2]. Additionally, the presence of fluorine often stabilizes neighbouring functional groups, improves bioavailability, and enhances binding affinity in biological systems [1,3]. These effects arise primarily from the high electronegativity of fluorine relative to that of hydrogen. In addition to the above chemical benefits, the low abundance of naturally occurring biological fluorinated compounds has enabled the use of fluorine-18 radiotracers in positron emission tomography [4]. Recent estimates indicate the presence of at least one fluorine atom in 28% of all agrochemicals [3,5] and 20% of leading pharmaceuticals [3], most of which contain difluoro- or trifluoromethyl groups. As such, it is reasonable to infer that more detailed structural characterizations of fluorinated organic compounds would only increase the efficiency with which these pharmaceuticals and agrochemicals are developed and produced.

In this study, the structural and dynamical properties of 1-phenyl-2,2,2-trilfuoroethanol (PhTFE), a chiral fluorinated organic compound, were probed by means of rotational spectroscopy and *ab initio* calculations. PhTFE is structurally related to 2,2,2-trifluoroethanol (TFE) with one of the alkyl hydrogens being substituted with a phenyl group. TFE can take on three conformations: *gauche*+ (g_+), *gauche*− (g_-), and *trans* (t), depending on the dihedral angle τ(CCOH) being +60°, −60°, or 180°, respectively. Only the $g_+/_-$ TFE conformers have been observed in the gas phase by rotational and infrared spectroscopy, and the two forms can interconvert rapidly on the time scale of 170 ps with a tunneling barrier of 763 cm^{-1} [6], while *t*-TFE is predicted to lie on a saddle point or in a shallow minimum which may or may not support a vibrational level [7]. It would be interesting to see if phenyl substitution influences the conformational distribution, what new conformations are generated as a result, and if said conformations shed some light on the existence or absence of *t*-TFEs vibrational level. Furthermore, intermolecular interactions involving TFE have resulted in some unusual, fascinating properties associated with chirality recognition [8–10] and F—F interactions [11]. For example, the TFE dimer exhibits chirality synchronization where the homochiral TFE dimer is strongly preferred over the equivalent heterochiral dimer [8,9]. The most stable TFE trimer contains a monomeric building unit of *t*-TFE, the first observation in the gas phase, which is stabilized by an attractive F—F—F interaction [11]. Thus, another motivation for the study of PhTFE is therefore to pave the road for future rotational spectroscopic studies of its molecular clusters. This would enable one to evaluate the role that aromatic substitution plays in the related molecular recognition events similar to those associated with TFE. In addition, PhTFE is

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https://doi.org/10.1016/j.jms.2018.07.006
0022-2852/

related to polyaromatic hydrocarbons which are of interested to interstellar and microwave spectroscopic community [12].

PhTFE was studied previously in the gas phase using low resolution resonance enhanced two photon ionization (R2PI) spectroscopy, coupled with time of flight (TOF) mass spectrometry [13], with only one conformer being identified experimentally. In the current study, we aim to verify the structure of the observed conformer with high resolution rotational spectroscopy, especially with the investigation of the ^{13}C isotopologues. We further aim to explore the conformational landscape of PhTFE at a higher level of theory than that previously used [13], and to re-evaluate the possible conformers and the interconversion barriers among them.

2. Experimental methods

PhTFE (98% purity) was purchased from Millipore-Sigma and was used without further purification. All eight ^{13}C isotopologues were measured in natural abundance with this sample. Broadband microwave spectra were recorded with two chirped pulse Fourier transform microwave (CP-FTMW) spectrometers with 25 kHz resolution and a frequency accuracy of ~10 kHz. Spectra in the 2–6 GHz region were recorded with a newly completed CP-FTMW spectrometer designed in a fashion similar to that presented by Pate and co-workers [14]. For this instrument, sample injection was accomplished by means of a seeded supersonic expansion with a trace amount of vapor, ca. 0.1 vol-%, generated from racemic liquid PhTFE diluted with helium carrier gas. A 4 μs chirped pulse was generated with a 12 GS/s arbitrary waveform generator and amplified by a 400 W travelling wave tube amplifier capable of amplifying radiation in the 2.5 –7.5 GHz region. The amplified chirped pulse was then broadcasted into a vacuum chamber, which was kept at ca. 10^{-6} Torr without sample, with a 62 cm high gain microwave horn perpendicular to the propagation direction of the pulsed molecular beam. The receiver used to detect the molecular emissions was an identical high gain microwave horn. This was followed by a +56 dBm low-noise amplifier. A 25 GS/s mixed signal digital oscilloscope was used to record the free-induction decay (FID) for digitization, averaging, and conversion into the frequency domain. Oscilloscope saturation was prevented through the use of a 500 ns delay between molecular excitation and the start of the emission recording. In order to maximize the signal-to-noise ratio, the spectrometer ran continuously for approximately 18 h, performing ca. 100,000 experiments. In each experiment, i.e. each gas pulse, six FIDs were collected and averaged. A 10 MHz rubidium atomic frequency standard was used to synchronize the oscilloscope with the arbitrary waveform generator, ensuring that the recorded FIDs are in-phase to each other.

The 7.8–11 GHz region was recorded with an older CP-FTMW spectrometer described before [15,16], the design of which is similar to that developed by the Cooke group [17]. Sample injection was also accomplished by means of a seeded supersonic expansion, under conditions identical to those previously mentioned.

3. Computational methods

Quantum chemistry calculations were completed with the Gaussian 16 suite of programs [18]. Harmonic geometry optimizations, harmonic frequency calculations, and potential energy surface (PES) scans were carried out at the levels of theory of Møller-Plesset second order perturbation theory (MP2) [19] and density functional theory with the B3LYP [20,21] functional, including D3 dispersion corrections [22] with Becke-Johnson damping [23]. The 6-311++G(2d,p) basis set [24] was used for all calculations, at both levels of theory. To search for the possible conformations of PhTFE, we performed two relaxed one-dimensional PES scans related to rotation of the OH group about the C—O bond and rotation of the phenyl ring about the C2—C17 (atom numbering is given in Fig. 1). These scans were performed at the B3LYP-D3BJ and MP2 levels of theory, utilizing 400 and 100 steps respectively. These scans utilized the algorithm developed by Schlegel and co-workers [25–27]. Lastly, quantum theory of atoms-in-molecules (QTAIM) [28] and non-covalent interaction (NCI) [29] analyses were performed in order to rationalize the observed differences in stability among the conformers. The QTAIM analysis was visualized with both Avogadro [30] and MultiWFN [31], while the NCI analysis was visualized with Chimera [32]. Please note that the *R*-PhTFE enantiomer is used for the presentation of the results through the paper.

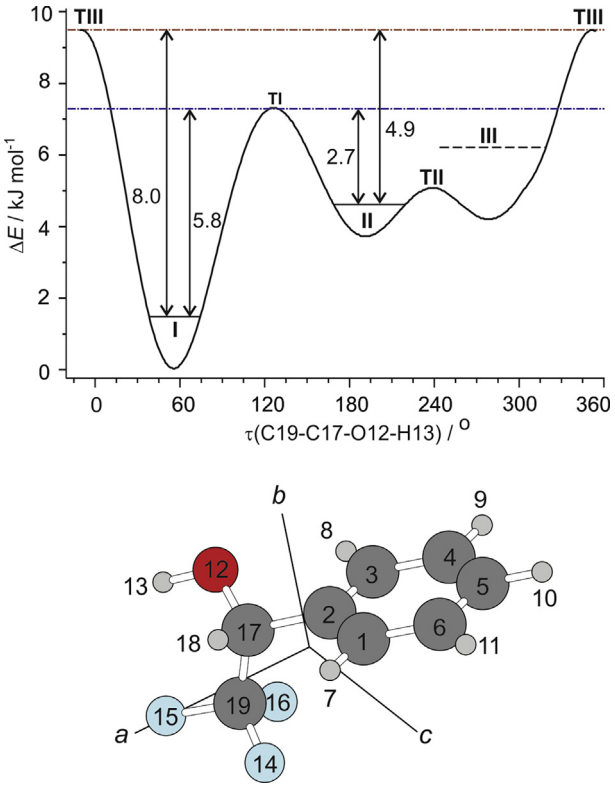

Fig. 1. A 400 step, 0.9°/step, one-dimensional relaxed PES scan of the τ (C19—C17—O12—H13) dihedral angle in PhTFE. The atom numbering is given at the bottom. The scan was performed at the B3LYP-D3BJ/6-311++G(2d,p) level of theory on PhTFE. The ZPEs of each potential well are also shown as solid or dashed lines. See text for discussions. The associated conformational conversion barriers are displayed in kJ mol^{-1}.

4. Results and discussion

The one-dimensional relaxed PES scan along the τ (C19—C17—O12—H13) dihedral angle in PhTFE is shown in Fig. 1, along with the atom numbering. This scan corresponds to the OH rotation scan in TFE which produces the $g_+/_-$ and *t* conformations. Three low energy conformations, **I**, **II**, and **III**, were identified in the scan. The structures for the three minima and the transition states were then optimized, and the resulting spectroscopic constants for the minima are listed in Table 1 at both the MP2 and DFT levels of theory, together with illustrations of the optimized structures.

The harmonic zero-point energy (ZPE) values of each potential well were crudely estimated by taking ½ of the imaginary frequency of the corresponding transition state. Here, **TI** is used for estimating the ZPE of **I**, **TII** for **II**, and **TIII** for **III**, respectively. These ZPE levels thus identified are depicted in Fig. 1 with a solid line if it