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Vibrational spectroscopic study of sodium-1,2,4-triazole, an important intermediate compound in the synthesis of several active substances

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ABSTRACT

The molecular properties, geometric parameters, atomic charges, and vibrational spectra of sodium 1,2,4-triazolate were investigated with both experimentally and quantum chemical modeling. During the quantum chemical calculations the possible tautomery and the aqueous environment were considered since the compound is hygroscopic. The polar environment was modeled as an aqueous solvent, and by adding water molecules as structural water. The two kinds of effects were also applied together.

1. Introduction

The parent molecule, 1,2,4-triazole is a very important and interesting molecule. It plays an important role in the production of active drug substances and is also important from scientific aspects. One can find applications of this molecule in both neutral and anion forms.

El-Azhary et al. [1] reported a detailed analysis of the theoretical (at various levels of theory) and experimental data (by IR and Raman spectroscopy) obtained for 1,2,3-triazole, 1,2,4-triazole and their anions. Billes et al. [2] determined the stable tautomeric forms of the molecule and presented a more correct interpretation of its experimental IR and Raman spectra by the aid of Pulay's SQM method. The effects of tautomerism on the IR spectrum of 1,2,4-triazole was discussed by Aziz et al. [3]. Above the theoretical vibrational spectral data obtained at the DFT/B3LYB/6-311++G** level of theory, the authors report the effects of the substitution position of the H atom on triazole in its IR spectrum. Wrzosek et al. [4] interpreted the surface enhanced Raman spectra of 1,2,4-triazole, based on DFT calculations applying the B3LYP/aug-cc-pVTZ and B3LYP/aug-cc-pVTZ-PP levels for stable neutral, anion and cation forms of the molecule.

The aim of this work is to elaborate on a model for the simulation of the vibrational spectra of a hygroscopic molecule. For the solution of problems both experimental and theoretical tools were used. The study of the external polar fields on a molecular ion pair is an essential aim of this work.

Our present work is the continuation of our earlier results already presented at a conference in Keszthely (Hungary) [5].

As already mentioned, we already dealt with the vibrational spectroscopy of 1,2,4-triazole in a previous work [2]. However, the structure and properties of its sodium salt raise different problems. We discuss them in the present work.

By searching the scientific literature, only one article was found presenting X-ray structure data of sodium-1,2,4-triazole (STRZ) [6].

STRZ is a very important compound in the pharmaceutical industry; it is an often used as a starting material for the production of several active pharmaceutical ingredients (APIs). These APIs are particularly effective against infections of *Candida albicans*, a diploid fungus. Candidae live under normal conditions in the gastrointestinal tract and build part of the human gut flora and also in women's vagina. However, if the balance of the gut flora is disturbed, or an acute disease act on the human organism, Candidae can predominate over other participants of the gut flora.

Candidae are regarded as the reason for several very painful diseases; the effects of Candidae are called candidiasis [7]. Voriconazole [8], itraconazole [9], and diflucan (fluconazole) [10] are three of the well known anti-*Candida* APIs synthesized on the basis of STRZ (see Fig. 1). A new API, isacuvonazole (see Fig. 1) is just under marketing

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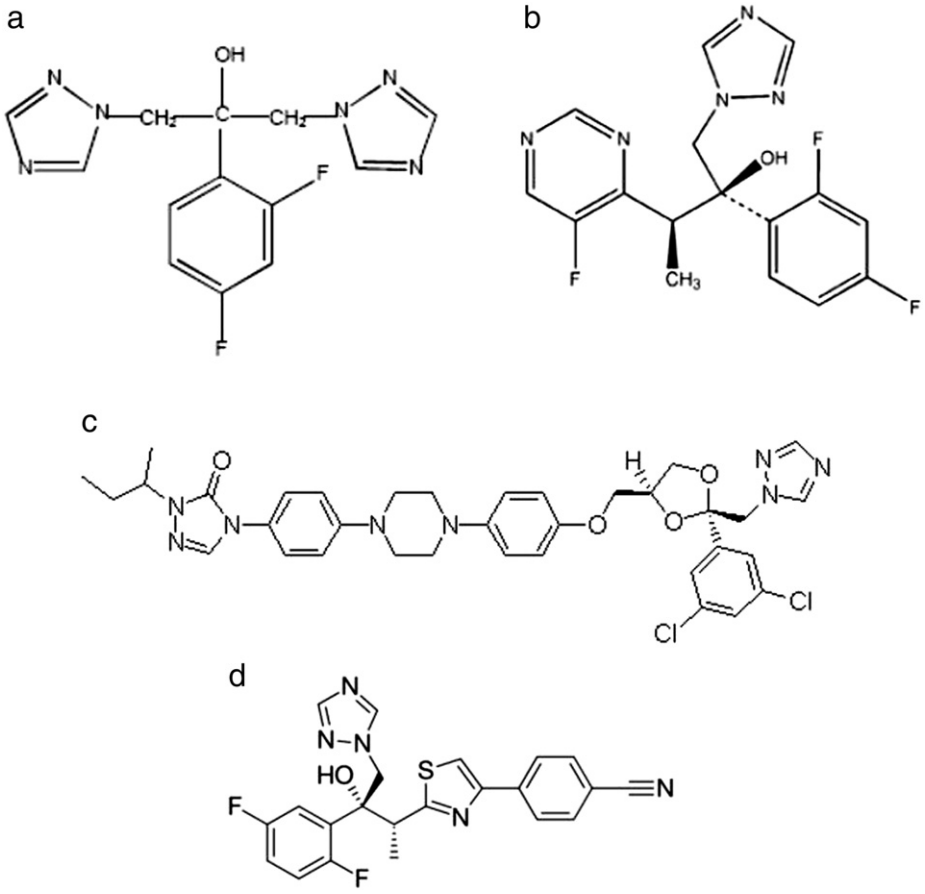

Fig. 1. Anti-*Candida* active pharmaceutical ingredients; a: diflucan, b: voriconazole, c: itraconazole, and d: isacuvonazole.

authorization in Europe and its activity is demonstrated against clinically relevant fungi [11].

STRZ is also applied in the modification of polyvinyl chloride with Na(K) salts of 1,2,4-triazole and 1,2,3-benzotriazole [12], in the modeling of chemical reactions [13]. Some properties of STRZ and its NMR (^{1}H and ^{13}C) data were published in MOLBASE [14].

The synthesis of 1-Na-1,2,4-triazole was published by Kazhemekaite et al. [15]. It is a very simple reaction. 1-Na-1,2,4-triazole is the product of the reaction of 1,2,4-triazole with sodium hydroxide.

In the frame of this article quantum chemical modeling was applied for the calculation of some properties of STRZ. Since the compound is hygroscopic, and tautomerism is possible, we considered also these properties in our calculations (see Subsection 4.4). The experimental vibrational spectra were compared with the calculated ones.

2. Experimental

Infrared spectra of the compound were recorded on a Nicolet Magna FT-IR infrared spectrometer with 2 cm^{-1} resolution, in the 4000–400 cm^{-1} region, in a KBr pellet.

Raman spectra were measured by a Jobin-Yvon LabRAM microprobe using 2 cm^{-1} resolution, in the 4000–100 cm^{-1} region, excited with the 632.8 nm band of a He–Ne laser. The spectra were collected for 20 s at a magnification of 100×; 2 scans were accumulated.

3. Calculations

The Gaussian09 program package was applied for our quantum chemical calculations [16]. The DFT Becke3LYP functional [17] was used with the 6-311++G** basis set. This set contains diffuse functions taking into account the structure of the calculated molecules and molecular ensembles. The molecular geometries were optimized, NBO atomic natural charges [18] were also computed. The second derivative of the molecular energy function to the Cartesian coordinates provided the vibrational force constants and the vibrational frequencies, infrared and Raman intensities and depolarization ratios. Difficulties arose during the second numerical differentiation of the molecular energy functions to the Cartesian coordinates. If it was necessary, the grid was refined using the INT(GRID = ULTRAFINE) and CPHF(GRID = FINE) options. In some cases the convergence was improved by placing an individual sphere around some hydrogen atoms (SphereOnH option, United Atom Topological Model) [19]. These calculations run at the Computer Centre of the Vienna University of Technology.

Potential energy distributions (PED) were also calculated using our home made program [20].

The hygroscopic property of the molecule was modeled with two methods. Either the molecules were surrounded with three structural

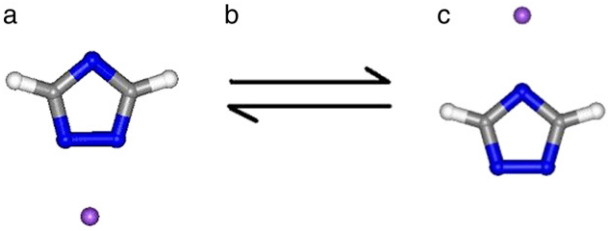

Fig. 2. Tautomeric equilibrium: a: 1STRZ, b: arrows, and c: 4STRZ.