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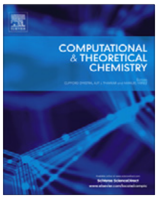

Theoretical structural and vibrational properties of the artificial sweetener sucralose

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ABSTRACT

The structural and vibrational properties of sucralose were predicted by combining the available experimental infrared spectrum in the solid phase and ab initio calculations based on density functional theory (DFT). The highest occupied molecular orbital (HOMO)-lowest unoccupied molecular orbital (LUMO) energy gaps HOMO–LUMO frontier orbitals, Natural Bond Orbital (NBO) and Atoms in Molecules (AIM) theory calculations were employed to study the stability, bond order, possible charge transfer and the topological properties of the glucopyran and glucofuran rings. To perform a complete assignment of the vibrational spectra, the density functional theory (DFT) calculations were combined with Pulay's Scaled Quantum Mechanics Force Field (SQMFF) methodology. The calculations were also used to predict the Raman spectrum of sucralose. A complete assignment of the 120 normal vibrational modes for sucralose was performed. Four strong bands in the infrared spectrum at 1093, 1040, 1025 and 990 cm^{-1} are characteristic of sucralose in the solid phase. In this work, the calculated structural and vibrational properties of sucralose were analysed and compared with those of sucrose. The high stability of sucrose in relation to sucralose was justified by means of NBO and AIM analyses.

1. Introduction

Sucralose is the common name of an artificial sweetener whose chemical names are 1,6-dichloro-1,6-dideoxy-ß-D-fructofuranosyl-4-chloro-4-deoxy-α-Dgalactopyranoside or 4,1′,6′-trichlorogalactosucrose (TGS). This compound can be synthesised through a three-step reaction from sucrose [1]. The crystal and molecular structures of 4,1′,6′-trichloro-4,1′,6′-trideoxysucrose monohydrate (1,6-dichloro-1,6-dideoxy-β-Dfructofuranosyl-4-chloro-4-deoxy-α-Dglucopyranoside monohydrate) were determined by Linden et al. by means of X-ray reflections at 160 K [2]. The conformation of the sucralose is quite different from the conformation of the sugar molecule, particularly with regard to the conformation of the glycosidic linkage, which affects the observed pattern of intramolecular hydrogen bonds. A complex series of intermolecular hydrogen bonds links the sugar and water molecules into an infinite three-dimensional framework [2]. Studies related to the toxicity of sucralose in humans were carried out by Rodero et al. [3], who suggested that various organs can be affected by ingestion of high doses of sucralose because of its diffusion through the placental barrier. The hydrolysis products 4-chloro-4-deoxy-Dgalactose (4-CG) and 1,6-dichloro-1,6-dideoxy-Dfructose (1,6-DCF) are more rapidly absorbed than sucralose; 4-CG is excreted intact in the urine, while 1,6-DCF undergoes reduction during elimination in the urine or rapid conjugation with glutathione. The thermal stability and thermal decomposition of sucralose were studied by Bannach et al. [4], who demonstrated that this compound is thermally stable up to 119 °C and that, above this temperature, the thermal decomposition takes place in three steps, without melting up to 550 °C. Moreover, Bannach et al. [4] determined that the endothermic peaks at 131 °C and 128 °C are due to thermal decomposition with the release of water and hydrogen chloride, while the experimental infrared spectra confirm that the thermal decomposition occurs above 119 °C, which is in disagreement with the literature data. In the study published by Bannach et al. [4], the experimental infrared spectra of sucralose at different temperatures were presented, but the observed bands were not assigned. In another study, a new type of solid dispersion in the form of core-sheath nanofibers using coaxial electrospinning with acyclovir as a model drug and sucralose as a sweetener was successfully prepared by Yu et al. [5]. In that work, the characterisation of the core-sheath nanofibers was performed by obtaining the ATR-FTIR spectra of the components (acyclovir, polyvinylpyrrolidone, sodium dodecyl sulphate, and sucralose) between 4000 and 500 cm^{-1}; however, only two OH stretching bands of sucralose were assigned. Birch

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showed, by means of FTIR spectroscopy of sweeteners in water, that there are substantial differences between the infrared spectra of sucrose and sucralose [6]. Recently, the vibrational spectra of sucrose in the solid phase were completely assigned [7], while the corresponding vibrational spectra of sucralose, so far, remain unassigned. To evaluate the behaviour and action of sucralose on the human species, studies of the structural and vibrational properties of this molecule are necessary and useful. As part of spectroscopic studies of diverse compounds of pharmacological, industrial and chemical interest [8–21], we now consider sucralose. The aim of this paper is to perform a more detailed study on the available experimental infrared and Raman spectra of sucrose. This study combines an approximate normal coordinate analysis with Pulay's Scaled Quantum Mechanics Force Field (SQMFF) methodology [22] to conduct a complete and reliable vibrational analysis of the isolated molecule. For this reason, the optimised geometries of sucralose and the wavenumbers for the normal modes of vibration were calculated using density functional theory (DFT). In this work, a complete assignment of the 120 vibrational normal modes of sucralose and a set of scaled force constants are reported. The bond orders, the possible charge-transfer and topological properties of both glucopyran and glucofuran rings and their stabilisation energies were studied using HOMO and LUMO orbitals, NBO [23] and AIM calculations [24]. The calculated properties of sucralose were analysed and compared with those of sucrose.

2. Computational details

The initial geometrical parameters of the geometric optimisation of the sucralose structure were taken from the X-ray crystal structure reported by Linden et al. for 4,1′,6′-trichloro-4,1′,6′-trideoxysucrose monohydrate [2] using the hybrid B3LYP method [25,26] with the 6-31G* and 6-311++G** basis sets, as implemented in the GAUSSIAN 03 program [27]. The initial structure of sucralose was modelled using the *GaussView* program [28]. In both calculations, the natures of the stationary points reached were checked by calculating the vibrational wavenumbers. The stable theoretical structure of sucralose together with the labelling of the atoms is presented in Fig. 1.

The NBO calculations were carried out using the NBO 3.1 program [29], as implemented in the GAUSSIAN 03 package [27], while the topological analysis was performed using AIM methodology [24] with the AIM200 program [30]. The B3LYP/6-31G* and B3LYP/6-311++G** methods were also used to calculate the harmonic wavenumbers and the valence force fields expressed in Cartesian coordinates. The resulting force fields were transformed to natural internal coordinates using the MOLVIB program [31]. The natural internal coordinates of sucralose were defined as those reported for sucrose [7]; these coordinates are listed in Table S1 (Supporting material). Taking into account the SQMFF procedure [22], the harmonic force fields were evaluated at the same theory level, and the potential energy distribution (PED) components greater than or equal to 10% were subsequently calculated with the resulting SQM.

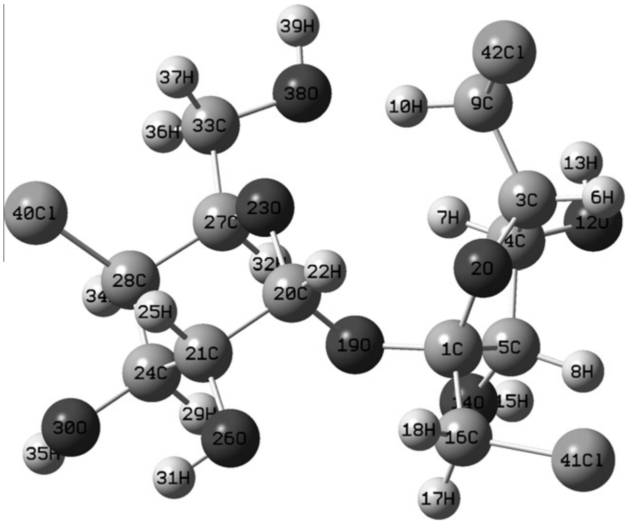

Fig. 1. Molecular structure of sucralose with labelling of atoms.

3. Results and discussion

3.1. Geometry optimisation

The optimised structures of sucralose using both basis sets have C_1 symmetries and two glucopyranosyl and fructofuranosyl rings, as shown in Fig. 1. Table 1 shows a comparison of the calculated geometrical parameters using both calculation levels with the corresponding parameters observed from X-ray diffraction for 4,1′,6′-trichloro-4,1′,6′-trideoxysucrose monohydrate [2] and 2,3,6,3′,4′-penta-O-acetyl-4,1′,6′-trichloro-4,1′,6′-trideoxysucrose [32], presented in terms the root-mean-square deviation (rmsd) values.

The results show that both basis sets reproduce the bond lengths (0.014–0.013 Å) better than the bond angles in relation to those of 4,1′,6′-trichloro-4,1′,6′-trideoxysucrose monohydrate [2] (38.6–27.4°), while a contrary result is obtained when the geometrical parameters of sucralose are compared with the corresponding parameters of 2,3,6,3′,4′-penta-O-acetyl-4,1′,6′-trichloro-4,1′,6′-trideoxysucrose [32]. A water molecule is the only difference with the first compound. When the parameters are compared with the second compound, the rmsd values for the bond lengths vary between 0.017 and 0.016 Å, and the value corresponding to the bond angles obtained using both basis sets is 1.6°. The presence of five acetyl groups and three Cl atoms in 2,3,6,3′,4′-penta-O-acetyl-4,1′,6′-trichloro-4,1′,6′-trideoxysucrose [32] justify those differences in the rmsd values. The significant difference between the calculated bond angles of sucralose and those of the monohydrated compound (rmsd 19.6°) has been explained by Linden et al. [2]; this explanation attributed the difference to the glycosidic C–O bond because this bond, in the hydrated compound, is quite different from the glycosidic C–O bond of sucralose. This difference is mainly a result of rotation about the C1–O19 bond. In sucralose, the calculated C1–O19–C20–C21 dihedral angle is -133°, while in the hydrated compound; the dihedral angle is −178.3°. The epimerisation at C28 apparently alters the most stable packing arrangement, which leads to the twisting of the molecule into the most economical conformation that allows for this packing arrangement [2]. As a result, there is a difference in the intramolecular hydrogen bonds formed by each compound. In sucralose, the two rings are linked by intramolecular O23–H10, O26–H18, O38–H7 and O38–H10 hydrogen bonds, as the AIM results show; this structure is in agreement with the structure determined by Kanters et al. [33]. In the hydrated compound, the glycosidic O19 atom forms a very weak intramolecular hydrogen bond [2]. For sucralose, the calculation predicts, using both approximation levels, that the C1–O19–C20 angle between both rings is slightly less than the experimental value observed in 4,1′,6′-trichloro-4,1′,6′-trideoxysucrose monohydrate [2] but slightly higher than the value observed in 2,3,6,3′,4′-penta-O-acetyl-4,1′,6′-trichloro-4,1′,6′-trideoxysucrose [32], as shown in Table 1. The C3–C9–Cl42 angle is overestimated (112.6°) relative to the experimental value of 109.8° in 4,1′,6′-trichloro-4,1′,6′-trideoxysucrose monohydrate [2].