Chalcogen substitution: Effect of oxygen-by-sulfur exchange on structural and spectroscopic properties of flavonols

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ABSTRACT

Quantum chemical calculations using density functional theory have revealed that the substitution of the ketone group by a thioketone one doesn't significantly change the structure of 3-hydroxyflavone. Notably, the strong intramolecular hydrogen bond involving the hydroxyl function is preserved if the O atom is substituted by an S atom, but also by Se or Te atoms. However, fundamental modifications are observed in both absorption and emission electronic spectra upon substitution, particularly the non-fluorescent behavior of the flavothione. All these changes were explained by the optimizations of the different excited states carried out by time-dependent DFT method.

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1. Introduction

The substitution of atoms by their heavier counterparts in the periodic table is an interesting way to modulate the properties of some molecules. This has been studied intensively in some families such as alkalies (group 1) or halogens (group 17), but also more recently in other ones such as the crystallogens (group 14) in molecular chemistry [1] or in material sciences [2] and the pnictogens (group 15) in explosives chemistry [3] or in coordination chemistry [4]. Some clear general trends are obtained such as the increasing metallic character down a group, whereas some properties (for instance promotion energies [5]) display a saw-tooth behavior due to the secondary periodicity. The existence of those two different behaviors then requires a comprehensive study of each property as the trends are quite unpredictable.

Chalcogen family (group 16) is formed by oxygen, sulfur, selenium, tellurium, polonium and, incidentally, livermorium. The first four elements are quite common in molecular chemistry and some reagents have been developed to favor their interconversion, for instance the Lawesson's reagent [6] and the Woollins's one [7]. Polonium is less common owing to its more metallic behavior and its radioactive properties. Oxygen is universally encountered in the biological medium. Sulfur is also widespread in biological medium being the eighth most abundant element in the human body [8] owing to its presence in the proteins under the form of two aminoacids (cysteine and methionine). The metabolism of several bacteria also implies sulfur as an oxidant (either on its sulfate [9] or its elemental form [10]) or a reductant [11]. Selenium

is also present in proteins, in the form of two analogues of sulfur amino acids (selenocysteine and selenomethionine), in all biological domains [12]. Some bacteria are also able to reduce selenates [13]. Tellurium is less common and has no particular role in the human organism, but the possible tellurocysteine and telluromethionine have been evidenced [14]. Once again, bacteria can reduce oxidated tellurium [15]. Due to its radioactive properties, polonium does not have any biological role, but sulfate-reducing bacteria are able to interact with this element [16].

The substitution of oxygen by another chalcogen is then a common phenomenon in the environment that is worth studying for the consequences it has on several properties. Structural parameters are always modified, but other properties such as reactivity [17] and photophysics are also altered [18,19]. The difference between oxygen and sulfur has been especially studied [20,21] owing to the omnipresence of these elements. For these studies, many molecular frameworks have been used, but among them, the nucleobases are predominant, especially guanine and uracil [22,23]. Indeed, the increase of the quantum yield from the lowest triplet state, that is attributed to a heavy-atom effect [24], enables its use as a probe in biological tissues.

In this study, we focus on another family of molecules widely present in the vegetable kingdom. Flavonoids are compounds involved in the secondary metabolism of higher vegetables. Their photophysical and complexation properties are widely studied [25]. The numerous hydroxyl functions contained by this compounds forms a hydrogen bond network. In this work, the 3-hydroxyflavone molecule (3HF), that belongs to the subgroup of flavonols, was chosen as a characteristic example of this family: it presents only one intramolecular hydrogen bond. There is a great amount of detailed theoretical and experimental

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information on 3HF that ensures a more comprehensive understanding of the structural, spectroscopic and photophysic features of this compound [26,27]. The H-bonding properties in this family make it a good candidate for an in-depth study of the evolution of its properties upon substitution of the ketone oxygen by sulfur (leading to 3-hydroxyflavothione noted 3HFT). This study involves both electronic spectra measurements and quantum chemistry computations, whose association leads to a good confidence in the proposed interpretations. Moreover, the quantum chemistry tools deepen this study by exploring non-measurable quantities and by extending the oxygen/sulfur series to selenium and tellurium that would have been quite tough to use experimentally. Then, the structure, the intramolecular bonding, the electronic spectra and the excited states properties were studied and are presented below. The structure of 3HF and 3HFT is depicted in Fig. 1. The determination of the dihedral angle (noted θ) between the B ring and the rest of the molecule is an issue often met in the studies concerning flavonoids [28,29]. Its value is obtained by means of X-rays diffraction for compounds in the solid state, whereas it is computed by quantum chemical calculations for molecule in gas-phase or in solution. Molecular planarity is often associated with the presence of a hydroxyl group in position 3 [30,31].

2. Experimental and Theoretical Section

2.1. Spectroscopic Measurements

Just like the 3HF molecule, 3HFT is sparingly soluble in water and all the experiments were carried out in methanol solution. UV–visible spectra were recorded with a double beam Cary 100 (Varian) spectrometer. The Excitation-Emission Matrixes were recorded with a Fluorolog (Horiba) spectrofluorimeter.

2.2. Computational Procedure

All the computations were carried out using the Gaussian 09 program [32]. Energy values were computed using DFT (density functional theory) based methods, namely the B3LYP global hybrid functional [33–36] and, for one check mentioned in the text, the PBE0 functional [37,38]. The 6–311 + G(d,p) basis set [39,40] was used for all atoms except Te; this atom was represented by the AZDP all-electron basis set [41]. The orbitals described in the text are then always Kohn-Sham canonical orbitals.

Optimizations were carried out using the standard algorithms implemented in this software and the nature of the stationary points obtained was checked by subsequent vibrational analysis. The solvent was taken into account in an implicit way, using the PCM model [42] as implemented in Gaussian 09 [43]. Relaxed scans were performed

by step of 1° around the two studied dihedral angles in both positive and negative senses to challenge the reproducibility of the presented conclusions. The results of both senses being indistinguishable, only those in one sense are presented in this article. The calculations of the scans were performed in vacuum to avoid artefacts due to the solvent cavities.

Excited states computations were carried out in the TD-DFT formalism using the same DFA as in the ground state. For vertical excitations, the 40 lowest-energy excited states were computed, that was enough to cover the whole measured spectra, and the solvent, still in the PCM model, was considered in the linear response non equilibrium formalism [44]. For optimizations in the excited states, only 10 excited states were computed to save computation time, the solvent being still computed in the PCM model, but in the linear response equilibrium formalism. This aspect has been challenged around crossing points, but the way to consider the solvent (especially the state for which the solvent is equilibrated at a given geometry) did not change significantly the computed values (changes below 0.02 eV, below both the accuracy of TD-DFT and the variations computed in this study). The nature of the minima was checked by numerical vibrational analysis.

NPA charges were computed using the internal facilities of Gaussian 09 (NBO 3) [45]. Atoms-in-molecules (AIM) computations were carried out using the AIMAll program [46]. The AIM theory is based on the analysis of critical points of charge density in a molecule. A critical point is characterized by a zero value of the gradient of the electronic density.

The bond paths were depicted in a simplified way: a first linear interpolation was processed between an atom of the bond and the bond critical point (BCP) localized with AIMAll, a second one between the same BCP and the second atom of the bond. Then, the value of the density was sampled on both interpolations using 50 regularly spaced points. The representation is normalized to better compare the results in different molecules by placing the two atoms at abscissa 0 and 2 respectively, while the BCP is located at abscissa 1.

3. Results and Discussion

3.1. Ground State Structure of 3HF and 3HFT

The electronic and structural features of 3HF in both ground and first excited states have been extensively studied [47–50] and so the sole purpose of the results reported here is to compare them to those obtained for 3HFT. The most relevant structure parameters of both 3HF and 3HFT calculated with the B3LYP/6–311 + G(d,p)/PCM method are reported in Table 1. 3HF is a flat molecule of C_s symmetry that presents a strong intramolecular H-bond between the H3 atom of the hydroxyl group and the O4 atom (noted X in Fig. 1). This H-bond enables the formation of a tautomer form by proton transfer. The two tautomeric forms are commonly referred to as normal and tautomer forms. The tautomer form has an energy 10.5 kcal mol^{-1} higher than the normal form; therefore, its population is insignificant at room temperature. For 3HFT, a local energy minimum corresponding to a tautomer form is also found 13.6 kcal mol^{-1} above the normal form minimum. In the same way as for 3HF, from a thermodynamic point of view, the ground state of the 3HFT tautomer form is very sparsely populated at room temperature. It seems worthwhile to examine and compare the structural properties of these different forms and to this end the geometrical parameters for all forms are gathered in Table 1. For both 3HF and 3HFT in the ground state, the two states are noted S_0^N and S_0^T, while the transition state lying between S_0^N and S_0^T is noted TS.

In a first step, we will be interested in the comparison of the structure of the normal forms of 3HF and 3HFT. The A and B benzene rings are not significantly affected by the substitution of the oxygen in the 4 position by a sulfur atom. Indeed, comparing the structures of S_0^N(3HF) and S_0^N(3HFT), the mean deviation of the C—C bond lengths of rings A (including C9–C10) and B are 0.20 and 0.05 pm, respectively. The inter-ring bond is also slightly modified by the substitution. The
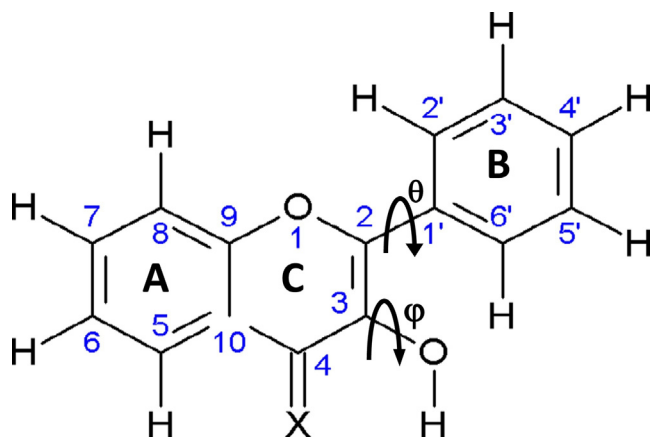

Fig. 1. Structure and atomic numbering used in text for 3-hydroxyflavone (X = O) and 3-hydroxyflavothione (X = S).