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A computational study of the structure, aromaticity and enthalpy of formation of UVA filter 4-*tert*-butyl-4′-methoxydibenzoylmethane

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ABSTRACT

In this study we have performed a density functional theory (DFT) study of the molecular structure and energetics of the enol and keto tautomers of UVA filter 4-*tert*-butyl-4′-methoxydibenzoylmethane (BMDBM) and for comparison and validation purposes a similar study has been carried out for the parent molecule: dibenzoylmethane (DBM). The molecular structure of the enol and keto tautomers were obtained at the B3LYP/6-311++G(d,p) level. The enol forms were found to have a strong intramolecular resonance assisted hydrogen bond that accounts for the greater energetic stability of the enol relative to the keto form. The aromatic character of the six-membered enol rings has been analyzed by calculation of Nucleus Independent Chemical Shifts (NICS). The standard molar enthalpy of formation in the gas phase of BMDBM was derived from appropriately chosen reactions.

1. Introduction

The raising level of awareness regarding the harmful effects of solar radiation has resulted in an increase in the production and consumption of sunscreens. These commercial products contain ultraviolet (UV) filters that absorb, reflect or scatter UV radiation (290–320 nm for UVB and 320–400 nm for UVA) therefore preventing sunburn, photo-aging and ultimately skin diseases such as skin cancer. There are few organic UV-filters that provide protection in the UVA region. Of these 4-*tert*-butyl-4′-methoxydibenzoylmethane (BMDBM) is the most widely used. BMDBM belongs to the dibenzoylmethanes class of UV-filters [1,2]. Dibenzoylmethanes in general are known to exist in two tautomeric forms: the enol and the keto forms. The preference for the enol form is due to the stabilization gained by the formation of an intramolecular hydrogen bond [3–5]. In the case of BMDBM since the enol tautomer is asymmetric it has two isomeric cis-enol tautomers, as shown in Fig. 1, whereas the keto tautomer occurs only in one form. In sunscreen formulations BMDBM exists predominantly in the enol form which absorbs in the UVA wavelength range [6–8].

Despite the practical importance of UVA-filter BMDBM information about the molecular structure and energetic stability of its tautomers is very scarce. This knowledge is of the utmost importance as a starting point for studies aiming the understanding of its activity once applied on human skin such as the one we have recently performed on the excited state properties of the enol and keto tautomers of BMDBM [9]. The loss of UV protection was attributed to the enol → keto phototautomerism, and subsequent photodegradation. Although this process was not energetically favorable in the singlet bright state, photodegradation is possible due to intersystem crossing to the first two triplet states.

In this work we have performed density functional theory (DFT) calculations with the B3LYP density functional and the 6-31G(d) and 6-311++G(d,p) basis sets to obtain the gas-phase molecular structure and energetic stability of all tautomers of BMDBM. A QTAIM analysis was performed for some selected bonds of the enols tautomers and allowed the explanation of some structural features including the existence of a resonance assisted hydrogen bond (RAHB). The aromatic character of the six-membered enol rings was evaluated from Nucleus Independent Chemical Shifts (NICS) calculations. Using isodesmic or almost isodesmic reactions the standard molar enthalpy of formation in the gas phase of BMDBM, at $T = 298.15$ K, was derived. For comparison and validation purposes a similar study has been performed for the parent

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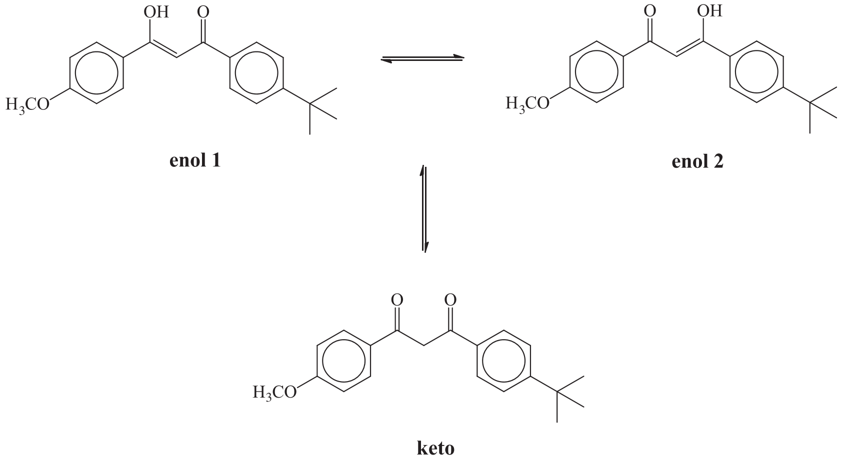

Fig. 1. Tautomeric structures of 4-*tert*-butyl-4′-methoxydibenzoylmethane (BMDBM).

molecule dibenzoylmethane (DBM). DBM has been extensively studied both experimentally and computationally. The crystal structure of different polymorphs of the enol form of DBM has been determined either by X-ray diffraction or neutron diffraction methods [10–15]. Experimental structural crystal data for the keto form is precluded due to the predominance of the enol tautomer. Hansen et al. [16] investigated both experimentally and theoretically (at the DFT/B3LYP/6-31G(d) level) the vibrational transitions in DBM enol. Tayyari et al. [17] used DFT with the B3LYP functional and different basis sets (up to 6-11++G(d,p)) to obtain the molecular structure and the IR and Raman spectra of DBM (only the enol form was considered) making a comparison with those of benzoylacetone and acetylacetone. The authors estimate a slightly stronger intramolecular hydrogen bond in DBM. Recently Belova et al. [18] investigated the tautomeric and structural properties of DBM by gas-phase electron diffraction and quantum chemical calculations (B3LYP and MP2 methods with the 6-31G(d,p) and cc-pVTZ basis sets). Experimental data reveal a strong predominance, 100(5)%, of the enol form in the gas-phase at $T = 300$ K, in agreement with quantum chemical calculations except for the MP2/6-31G(d,p) which predicts preference of the keto form. The authors have argued that this method systematically fails in predicting the tautomeric equilibria of β-diketones [18,19].

2. Computational details

The geometries of all molecules were fully optimized using density functional theory (DFT) with the B3LYP three-parameter hybrid functional proposed by Becke [20] and the 6-31G(d) basis set. The B3LYP functional comprises an exchange–correlation functional that mixes the nonlocal Fock exchange with the gradient-corrected form of Becke [21] and adds the correlation functional proposed by Lee et al. [22]. The obtained optimum structures were re-optimized using the more extended 6-311++G(d,p) basis set in order to get more reliable molecular structures and energies. The stationary points found at each level of theory were characterized as true minima through construction and diagonalization of the Hessian matrix. This procedure provides also the vibrational frequencies needed to obtain the thermal energetic corrections to enthalpy at $T = 298.15$ K. The use of the more accurate Gn methods [23] to obtain enthalpy values for the molecules under study was prevented by their high number of atoms.

To find the most stable conformation of the keto tautomer of DBM and BMDBM the $C_{10}—C_1—C_2—C_3$ (see Fig. 2 for the numbering of the atoms) dihedral angle was scanned by 360°, increasing by a step of 30°. In each point of the calculated potential energy surface (PES) the $C_{10}—C_1—C_2—C_3$ dihedral angle was held fixed while all remaining geometric parameters were fully optimized at the B3LYP/6-31G(d) level. The obtained PES contains two minima and the geometry of the lower energy one was fully optimized with no constraints as described above.

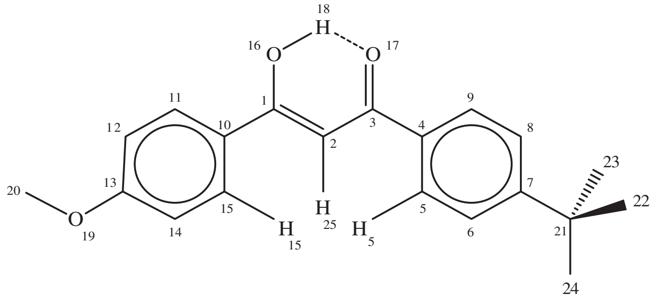

Fig. 2. Atom numbering scheme for the enol tautomers of dibenzoylmethane (DBM) and 4-*tert*-butyl-4′-methoxydibenzoylmethane (BMDBM). In the case of BMDBM the scheme refers to enol 1. For enol 2 the same atom numbering was used but the O—H bond is $O_{17}—H_{18}$ and the intramolecular O···H interaction is $O_{16}\cdots H_{18}$.

To find the most stable conformation of the enol and keto forms of BMDBM the $C_{20}—O_{19}—C_{13}—C_{12}$ and $C_6—C_7—C_{21}—C_{24}$ dihedral angles which define, respectively, the orientation of the methoxyl and *tert*-butyl groups were also scanned by 360°, increasing by a step of 30°. In each point of the PESs the dihedral angles were held fixed while all remaining geometric parameters were fully optimized at the B3LYP/6-31G(d) level.

The calculations of local topological properties of the electron charge density at the bond critical points, as well as the display of the molecular graphs were performed with the AIM2000 software [24], with the electron density obtained at the B3LYP/6-311++G(d,p) level of theory.

In order to characterize the aromatic or antiaromatic character of the six-membered enolic rings of DBM and BMDBM we have conducted calculations of the Nucleus Independent Chemical Shifts (NICS) [25]. Traditionally the NICS values are calculated at the geometric center of the rings and also, in order to account for the fact that the (aromatic) ring planes are nodal planes of the π-electron system, at a point 1.0 Å above it [26,27]. Another important component of the chemical shielding tensor to analyze is the out-of-plane component (conventionally along the *Z* direction, thus designated by σ_{ZZ}) which has been argued [28] to better reflect the effects of the π-electron density, thus being presumably a better aromaticity index. The NICS values are conventionally