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Conformational stability, spectroscopic and computational studies, HOMO–LUMO, NBO, ESP analysis, thermodynamic parameters of natural bioactive compound with anticancer potential of 2-(hydroxymethyl)anthraquinone

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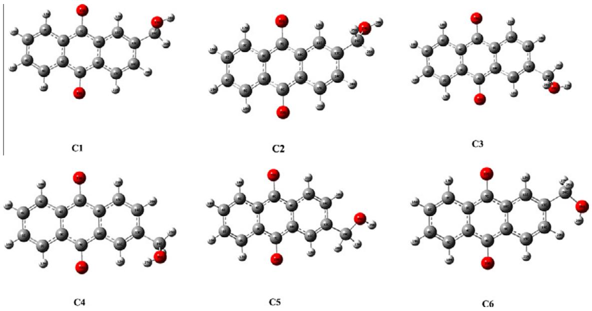
HIGHLIGHTS

- The optimized geometrical parameters of HMA were obtained by HF and B3LYP methods.
- Global minimum energy for six conformers of HMA have been studied.
- HOMO and LUMO analysis have been performed.
- Electrostatic potential surface has been performed.
- Thermodynamic parameter has been performed.

GRAPHICAL ABSTRACT



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ABSTRACT

Natural product drugs play a dominant role in pharmaceutical care. Nature is an attractive source of new therapeutic candidate compounds as a tremendous chemical diversity is found in millions of species of plants, animals, marine organism and micro-organism. A antifungal activity against important opportunist micro-organism and against those involved in superficial mycosis, all from nosocomial origin. The acute *in vitro* cytotoxicity evaluation of each anthraquinone (AQ) isolated from these bioactive extracts, on a mammalian eukaryotic cell line (Vero cells), allowed us to establish the non-cytotoxic concentration range, which was used to evaluate the anti-microbial effect. A comprehensive *ab initio* calculation using the DFT/6-31+G(d) level theory showed that 2-(hydroxymethyl)anthraquinone can exist in four possible conformations, which can interchange through the OH group on the five-membered ring. Density functional theory calculations were used to predict the vibrational frequencies and to help in normal mode, assignments. Furthermore, a natural bond orbital analysis was performed describing each hydrogen bond as donor accepter interaction. The Fourier transform infrared spectra (4000–400 cm^{-1}) and the Fourier transform Raman spectra (3500–100 cm^{-1}) of the HMA in the solid space have been recorded. The calculated HOMO and LUMO energies show that charge transfer occurs within the molecule. The calculated ESP contour map shows the electrophilic and nucleophilic region of the molecule.

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Introduction

Our body is made up of many types of cells. All cancers begin within cells, when cells become old (or) damaged; they die and are replaced with new cells. The role of natural products as a source for remedies has been recognized, since ancient times [1,2]. Natural products have a rich source of compounds that have many applications in the field of medicine. In microbiology, particularly, several plant-derived compounds have been studied with this aim, including alkaloids, flavonoids, tannins, quinines, essential oils and other secondary metabolites [3]. Among them, anthraquinone derivatives (AQ) have aroused special interest since they have demonstrated potential therapeutic uses as antibacterial, antiviral, antifungal agents and other biological activities [3–7]. Within this family of compounds, several AQs have been thoroughly studied in relation to their photosensitizing properties in photodynamic reactions [8,9].

Anthraquinones such as aloe-emodin was able to inhibit cell growth in several tumor cells, including human lung carcinoma [10], hepatoma [11,12], and leukemia cell lines [13]. Aloe-emodin shows a high specificity for neuroectodermal tumor cells [14,15]. One of the important approaches for cancer chemotherapy is to regulate cell-cycle progression. G1/S cell-cycle arrest was found in human hepatoma [12,16], glioma [17], breast [18], lung [11], and colon [19] carcinoma cells upon treatment of rhubarb anthraquinones (emodin [18,19], aloe-emodin [12,17], and rhein [16].

Anthraquinone is in soluble in water, and only slightly soluble in most Organic solvents. This is solubility is misleading in the context of the effectiveness of AQ. AQ is electron-donating, alkyl substituents made up slightly more effective. Anthraquinone is not considered to be a particularly toxic chemical. This can even lead to an explosion hazard. Because of this, protective clothing, including rubber gloves and a dust mask is recommended when handling large amounts of AQ powder. The future for anthraquinone will depend largely on any decisions made by the Food and Drug Administration (FDA). If it is to be used widely, it must be cleared as an indirect food additive.

Experimental details

The compound 2-(hydroxymethyl)anthraquinone (HMA) in the solid form was purchased from the Sigma–Aldrich Chemical Company (US), with a stated purity of greater than 98% and it was used as such without further purification. The FT-Raman spectrum of title molecule has been recorded using the 1064 nm line of a Nd:YAG laser as excitation wavelength in the region 100–3500 cm^{-1} on a BRUKER model IFS 66V spectrometer. The reported wavenumbers are expected to the accurate within $\pm 1\ \text{cm}^{-1}$. The FT-IR spectrum of this compound was recorded in the region 400–4000 cm^{-1} on IFS 66V spectrometer equipped with an MCT detector using KBr beam splitter and globar source. The data were recorded in the co-addition of 200 scans at $\pm 1\ \text{cm}^{-1}$ resolution with 250 mW of power at the sample in both the techniques.

Computational details

Quantum chemical calculation was used to carry out the optimized geometry and vibrational wave numbers with the 2009 version of the Gaussian suite [20] using the HF and B3LYP functional [21,22] supplemented with standard 6-31+G(d) basis set. For the plots of simulated IR and Raman spectra pure Lorentzian band shapes were used with a band width (FWHW) of 10 cm^{-1}. The vibrational modes were assigned by means of visual inspection using GAUSS VIEW program [23], the analysis for the vibrational modes of HMA is presented in some detail in order to better describe the basis for the assignments.

A detailed description of vibrational modes can be given by means of normal coordinate analysis. For this purpose, the full set of 78 standard internal coordinates containing 31 redundancies was defined as given in Table 1. From these, non-redundant set of local symmetry coordinates were constructed by suitable linear combinations of internal coordinates following the recommendation of Pulay et al. [24] and they are presented in Table S1(Supplementary Material).

Natural bond orbital analysis was also performed by the Gaussian 09 W program at the B3LYP level of theory analysis transforms the canonical delocalized Hartee-Fork (HF) molecular orbital's (MO) into localized MOs that are closely tied to chemical bonding concepts. This process involves sequential transformation of non-orthogonal atomic orbital's (AOs) to the sets of natural atomic orbital's (NAOs), natural hybrid orbital's (NHOs) natural bond orbitals. The localized basis sets are completely describes the wave functions in the most economic method, as electron density and other properties that are described by the minimum amount of filled NBOs describe the hypothetical, strictly localized Lewis structure. The interaction between filled and anti-bonding (or Rydberg) orbital's represent the deviation of the molecule from the Lewis structure and be used as the measure of delocalization. This non-covalent bonding anti-bonding charge transfer interactions can be quantitatively described in terms of the second order perturbation interaction energy ($E^{(2)}$) [25–28]. This energy represents the estimate of the off-diagonal NBO Fock matrix elements. It can be deduced from the second-order perturbation approach [29] as follows:

$$E^{(2)} = \Delta E_{ij} = q_i \frac{F^2_{(i,j)}}{\varepsilon_j - \varepsilon_i}$$

where q_i is the ith donor orbital occupancy, ε_j and ε_i the diagonal elements (orbital energies) and $F_{(i,j)}$ the off-diagonal NBO Fock Matrix element.

Results and discussion

Structural descriptions

In order to find the most optimized geometry, the energy calculations were carried out for HMA, using HF/6-31+G(d) and B3LYP/6-31+G(d) methods and basis sets for various possible conformers. The computationally predicted various possible conformers obtained for the title compound are shown in Fig. 1. The total energies obtained for these conformers are listed in Table 2, the structure optimizations have shown that the conformer of Fig. 1(C1) have produced the global minimum energy. The optimized molecular structure with the numbering of atoms of the title compound is shown in Fig. 2. The most optimized structural parameters were also calculated by HF and B3LYP and they are depicted in Table 3. The optimized structural parameters were used to compute the vibrational frequencies of the stable conformer (C1) of HMA at the HF/6-31+G(d) and B3LYP/6-31+G(d) level of calculations.

Potential energy distributions

To check whether the chosen set of symmetric coordinates contribute maximum to the potential energy associated with the molecule, the PED has been carried out. The vibrational problem was set-up in terms of internal and symmetry coordinates. The geometrical parameters of the molecule were allowed to relax and all the calculations converged to an optimized geometry which