Scientific report

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Curcumin has been shown to exhibit antioxidant, anti-inflammatory, antiviral, antibacterial, antifungal and anticancer activities and thus has a potential against various malignant diseases, diabetes, allergies, arthritis, Alzheimer's disease, and other chronic illnesses [1-3].In order to improve its systematic applicability, the broad spectrum of applications brings very important questions concerning the solubility and stability of curcumin, its optimum dose, pharmacokinetics, mechanism of action of curcumin for a given disease, bioavailability profile, and intricacies of prevention and cure of an identified disease [1].

Curcumin is a tautomeric compound existing as 2 tautomeric forms 1EK, 1KK. It is naturally that, the tautomerism influences the activity of the compound.

The aim of the current project was to investigate in details the spectral behavior of 1EK and 1KK forms of curcumin in water environment by using abilities of the quantum mechanics and especially the QM/FQ/MM models developed by C.Cappelliand V.Barone [2, 3] Therefore, we employ an integrated QM/MM method, which includes a fluctuating charge (FQ) approach [4] to the MM polarization, to calculate the absorption spectra of curcumin in aqueous solution. The simulation of spectroscopic properties by means of quantum mechanical (QM) methods has been demonstrated to yield accurate results and to be a powerful methodology to predict the spectra of various chemical systems. Most of the experimental measurements in the field of spectroscopy are carried out in solution. For this reason it is crucial to include the environmental effects also in the theoretical description.All of the QM/FQ calculations were performed using a locally modified version of Gaussian 09 quantum chemistry suite of programs, employing the M06-2X functional, which has been previously shown to perform better than other functionals in the description of curcumin tautomerism[5]. The def2-TZVP basis set has been used.Set of atomic charges for the curcumin molecule were calculated by applying the Merz-Kollman procedurewhere the atomic charges are fitted to reproduce the molecular electrostatic potential at a number of points around the molecule. Dispersion and repulsion terms were modeled according to the General Amber Force Field (GAFF) [6].Classical MD simulations were performed with the GROMACS 4.6.5 software [7]. A single curcumin molecule was solvated in a cubic box with a side length of 41.61 Å containing 2366 water molecules modeled using the TIP3P parameter set. The carbonyl oxygens were bonded with dummy atoms in order to recover

the directional behaviour of the lone electron pairs, according to the framework reported by M. Macchiagodena et al. [8]. Electrostatic interactions were taken into account by means of the Particle Mesh Ewald method [9] using a cutoff radius of 12 Å in real space; a cutoff radius of 12 Å was also chosen for the van der Waals interactions. A short (20 ps) simulation was performed at 298.15 K for thermalization purposes. Then a 10 ns trajectory was obtained using the velocity-rescale method [10] with a coupling constant of 0.1 ps, saving coordinates every 0.5 ps. A total of 200 snapshots with a constant stride of 45 ps were extracted for each tautomer and used in further FQ calculations. We then performed a TD-DFT calculation on every snapshot, treating curcumin at the M06-2X/def2-TZVP level of theory and the solvent molecules using the FQ polarizable embedding scheme. The FQ calculations were executed using the SPC parameters of Rick et al. [11]. We extracted the excitation energies and spectroscopic intensities pertaining to the first 3 excited states from each snapshot and then plotted the resulting UV spectra after convoluting each peak using Lorentzian functions with full-width at half-maximum (FWHM) of 0.56 eV.

The results, that have been obtained, for the spectral behavior of curcumin in water solution are quite similar as the experimental ones According to the experimental data, the keto-keto tautomer (1KK) of curcumin has absorption maximum at 355nm. The simulation of spectroscopic properties by means of quantum mechanical (QM) methods shows absorption maximum for 1KK at 329nm. For the enol-keto tautomer (EK), the difference between experimental and theoretical data is only 3nm (430nm according to the experimental data and 433nm as a result of the theoretical approach)

Due to our work, the follow conclusion can be drawn:

- Adding of dummy atoms in order to recover the directional behaviour of the lone electron pairs in the molecule of curcumin, does not leads to improvement of the results.
- QM/FQ/MM model can be successfully used for description of the specific solvent effects in the tautomeric systems.

The results from this project will be summarized as a scientific publication.

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