Description of the specific solvent effect in the tautomeric systems, QM/MM modeling

Curcumin, derived from Curcuma longa plant 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 the light of these promising propertiesseveral questions need to be answered in order to improve its systematic applicability. These pertain to 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, potentially existing as three main tautomeric forms, enol-keto(EK), keto-keto (KK), enol-enol form (EE) and it is naturally that the tautomerism influences its activities [4].

There is substantial number of theoretical studies and experimental data[4-16], showing the strong predominance of the enol–keto form (EK) in solution. However under some structural and environment conditions the diketo form (KK) could be observed as well.[17.18].

One of the important factors for tautomeric systems is the influence of the solvent. Using UV-Vis spectroscopy, which is the only method that can register tautomers as individual species, has been proven by us that the addition of water to organic solvents leads to stabilization of the diketo tautomeric form (KK) [19]. We have done quantitative analysis, based on chemometric analysis of the absorption spectra of curcumin in water/ethanol binary solvent mixtures, which has provided the molar fractions of the tautomers and hence the Gibb's free energies in ethanol and water. The enol–keto form is only presented in ethanol, while in pure water the diketo tautomer is dominating.

Quite often the interaction tautomer-solvent is very specific and it is complicated to be described using conventional methods of the Quantum chemistry.

The group ofProf. Chiara Cappelliis internationally recognized in the Computational Modeling of Complex Systems.Recently, they have developed new method (QM/MM)that can be used for description of the effect of the water and the effect of the ethanol on the position of the tautomeric equilibrium. Our expectations are this method to be very useful in the solvent effect description in other tautomeric system in future.

In the frame of the project the following tasks will be performed:

1) Calculation of energetics and UV-Vis spectra of the three forms of curcumin (EK, KK, EE) in water and ethanol by exploiting implicit solvation models rooted in the Polarizable Continuum Model (PCM). Vibrionic effects will also be considered in the simulation of spectral data.

2) Extraction and plotting of PCM data (populations/spectra), and comparison with experimental findings.

3) Starting from optimized PCM EK, KK and EE structures, Molecular Dynamics (MD) simulations in explicit water will be performed, after suitable parametrization of the intramolecular force-field. Both

fixed-geometry and flexible geometry simulations will be performed. From the obtained trajectories, a set or representative snapshots will be extracted.

4) Calculation of vertical excitation energies on the snapshots (few hundreds) extracted from the MD, by exploiting the fully polarizable QM/FQ/PCM approach using fluctuating charges (FQ). Averaging of the data for the single snapshots and extraction of the averaged spectrum.

5) Plotting of the QM/FQ/PCM UV-Vis spectra in explicit water and comparison with PCM data and then with experiments. Possibly, a refinement on EK,KK and EE statistical weights will be proposed.

6) Steps 3-5 will be possibly be repeated for explicit ethanol solvent. In case the timing does not permit to complete such steps, this part of the work will be performed after the end of the stay.

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