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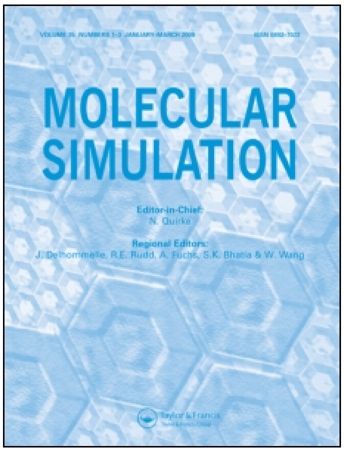

Molecular Simulation

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Structural and electronic features of the ubiquinone and ubiquinol molecules: molecular dynamics and quantum chemical treatments

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Structural and electronic features of the ubiquinone and ubiquinol molecules: molecular dynamics and quantum chemical treatments

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The coenzyme Q (CoQ) molecule plays a critical role in the biochemical generation of energy in the form of adenosine triphosphate. Various types of CoQ can be classified according to their number of isoprenoid units in the tail. In human beings, CoQ10 is produced and is necessary for the basic functioning of cells. CoQ10 exists in two forms, as ubiquinone (UQ) and as ubiquinol (UQH_2), which have different roles in the body. Molecular dynamics (MD) simulations for the analysis of the effects of solvents on the structure of the UQ molecule are presented. Besides, semi-empirical molecular orbital PM3 calculation is applied to obtain structural and electronic properties of both the UQ and the UQH_2 molecules. According to the MD simulation, the UQ molecule seems to be flexible both in vacuum and in water. On the other hand, the molecule stays more rigid in methanol. PM3 calculations show that both molecules are quite hydrophobic. Furthermore, UQ is chemically more reactive than UQH_2, but the latter is kinetically more stable than the former.

Keywords: coenzyme Q10; ubiquinone; ubiquinol; molecular dynamics; PM3

1. Introduction

Coenzyme Q(CoQ) is a lipid-soluble vitamin-like compound composed of quinone with a benzene ring and a hydrophobic tail, which is found mostly in mitochondria of all plant and animal cells. Its primary function in cells is producing energy in the form of adenosine triphosphate, which is needed for muscle contraction–relaxation and other basic cellular functions. The various types of CoQ can be classified according to their number of isoprenoid units in the tail. One form of CoQ in human mitochondria is CoQ10, which has 10 isoprenoid units in the tail. In 1957, Crane et al. [1] discovered CoQ10 and, in 1958, characterised its chemical and physical properties [2]. Its chemical structure (2,3-dimethoxy-5 methyl-6-decaprenyl benzoquinone) was reported by Wolf et al. [3]. It is known that natural production of CoQ10 is reduced in several animal species and in human beings with ageing [4,5]. Preliminary works on both animals and human beings show that decreased levels of CoQ10 are found in patients with mitochondrial disorders, congestive heart failure and other cardiovascular diseases, periodontal diseases, hypertension, neurodegenerative diseases such as Parkinson's disease, Huntington's disease and amyotrophic lateral sclerosis, cancer, diabetes and HIV/AIDS [6–9]. Having said that, it is not yet clear that the deficiency of CoQ10 causes the above-mentioned diseases. However, some clinical studies show that for various patients, additional intake of CoQ10 gives positive results [10–13].

CoQ10 has two forms: ubiquinone (UQ) and ubiquinol (UQH_2). UQ ($C_{59}H_{90}O_4$) is the oxidised form of CoQ10 and has a molecular weight of 864 Da. UQH_2 is the reduced form of CoQ10 and has two more hydrogen atoms ($C_{59}H_{92}O_4$) on the head of the molecule, thus has a molecular weight of 866 Da. UQ is vital for energy production. UQH_2 is an active antioxidant [14,15]. When UQ (oxidised form) is ingested and absorbed in the body, 90–95% of the ingested UQ is converted and stored as UQH_2 (reduced form). Yamamoto and Yamashita [16] investigated the ratio of UQH_2 to UQ as a marker of oxidative stress using high-performance liquid chromatography (HPLC) method. They found that, in human plasma, taken from healthy donors, the ratio of UQH_2 to UQ is 95/5. They also observed in patients with any of the diseases, hepatitis, cirrhosis and hepatoma, a significant decrease in UQH_2. Similar work was carried out by Menke et al. [17]. They developed a HPLC method for the simultaneous detection of UQ and UQH_2 in human plasma. Their study can be of help to explain the function of CoQ10 in the above-mentioned diseases and oxidative damage in neonates and infants. There are many other studies about UQ and UQH_2, for example, Moncelli et al. [18] investigated the kinetics of UQ reduction to UQH_2 and UQH_2 oxidation to UQ in a self-assembled monolayer of dioleoylphosphatidylcholine. Takahashi et al. [19] studied the distribution of UQ and UQH_2 in rat tissues and subcellular functions. More recent experimental works may be found in [20,21].

There have also been simulations of the UQ molecule. Nilsson et al. [22] have done both classical molecular

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dynamics (MD) and Car–Parrinello MD simulations of UQ to investigate the potential surface of rotations and the H-bonds around the UQ. Söderhäll and Laaksonen [23] carried out MD simulations of UQ molecule inside a dipalmitoylphosphatidylcholine lipid bilayer, immersed in water. They investigated the effect of the long tail, attached to the quinine ring and lateral diffusion rate. Miyamoto et al. [24] investigated the 3D structure of CoQ10 inclusion complex with γ-cyclodextrin using chemical analyses, nuclear magnetic resonance, HPLC and differential scanning calorimetry and both molecular mechanics (MM) and MD calculations.

Since UQ and UQH_2 are redox pairs, CoQ10 is converted from UQH_2 to UQ and vice versa according to the body's need. However, with age and diseases, the body's ability to make this conversion gets impaired significantly [http://www.vitafoods.eu.com/page.cfm/action=Seminars/SeminarID=42 (accessed on 21 July 2009); http://blog.nutri.com/tag/ubiquinol-vs-ubiquinone (accessed on 21 July 2009)]. UQ is the more common commercially available form, whereas UQH_2 is comparatively new and more expensive to manufacture [http://www.epic4health.com/idubandubwha.html (accessed on 21 July 2009); http://www.alternativehealthjournal.com/article/ubiquinol_and_ubiquinone_what_s_the_difference_and_why_should_we_care_/2740 (accessed on 21 July 2009)].

The purpose of this study is to gain insight into the structure of UQ in vacuum, water and methanol by MD simulations and to obtain the structural and electronic properties of UQ and UQH_2 using quantum chemical methods. The interesting conformations of the molecules under consideration are shown. The main reason for choosing these molecules is their pharmaceutical importance.

2. Computational details

In this work, the UQ molecule was investigated using both MD simulations and quantum chemical calculations, whereas the UQH_2 molecule was studied only with quantum chemical calculations.

In the MD simulation case, the initial coordinates of UQ were generated with the help of the HyperChem 7.5 program package (Hypercube, Inc., Gainesville, FL, USA). Figure 1 displays the initial structures of the molecules considered. Then, the obtained structure of UQ was converted to GROMACS [25] topology file by the Dundee PRODRG server [26]. All MD simulations were performed using GROMACS software package with the GROMOS9643A1 force field [27]. Water as a solute was modelled as a simple point charge [28]. The UQ molecule was simulated in vacuum, water and methanol separately. All three systems were considered in a cubic box and a constant number of atoms at fixed pressure and temperature (NPT ensemble) was taken into account. In the simulations, 5389 water molecules and 2700 methanol molecules filled the box. The box size was large enough to accommodate the fully extended molecule. The temperature was kept constant at 310 K using Berendsen thermostat [29] with a coupling time constant of 0.1 ps. The pressure was coupled anisotropically using a Berendsen barostat [29] with a reference pressure of 1 bar in all directions, a coupling constant of 0.2 ps and a compressibility of $1.12 \times 10^{-6}\,\mathrm{bar}^{-1}$. The linear constraint solver algorithm [30] was applied to constrain all bond lengths. The long-range electrostatic interactions were computed by the particle mesh Ewald method [31] using Fourier grid spacing of 0.12 nm and a cut-off radius of 1.2 nm. The short range, van der Waals, interactions were computed with a shift scheme using a cut-off radius of 1 nm. The neighbour list was updated at every step. The three systems were minimised using a steepest descent algorithm, and then a leap frog algorithm [32] was used to integrate Newton's equations of motion. The Visual MD software program [33] was used for visualisations.

In the second case, namely, quantum chemical calculations, the UQ and the UQH_2 molecules in the gas phase were pre-optimised by applying the MM method [34] using MM+ force field [35]. Then, the structures which were obtained from MM were entirely optimised using semi-empirical self-consistent field

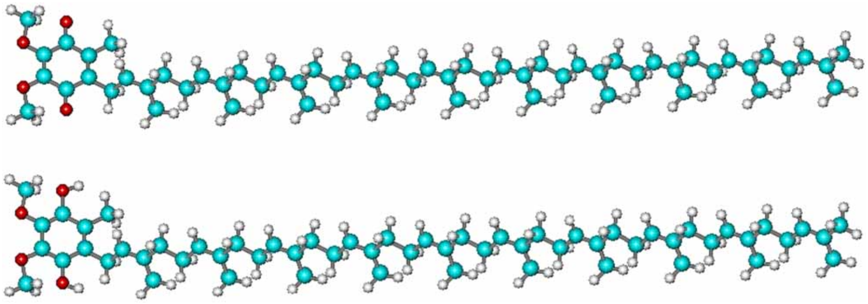

Figure 1. Structures of the UQ ($C_{59}H_{90}O_4$) (upper) and the UQH_2 ($C_{59}H_{92}O_4$) (lower) molecules.

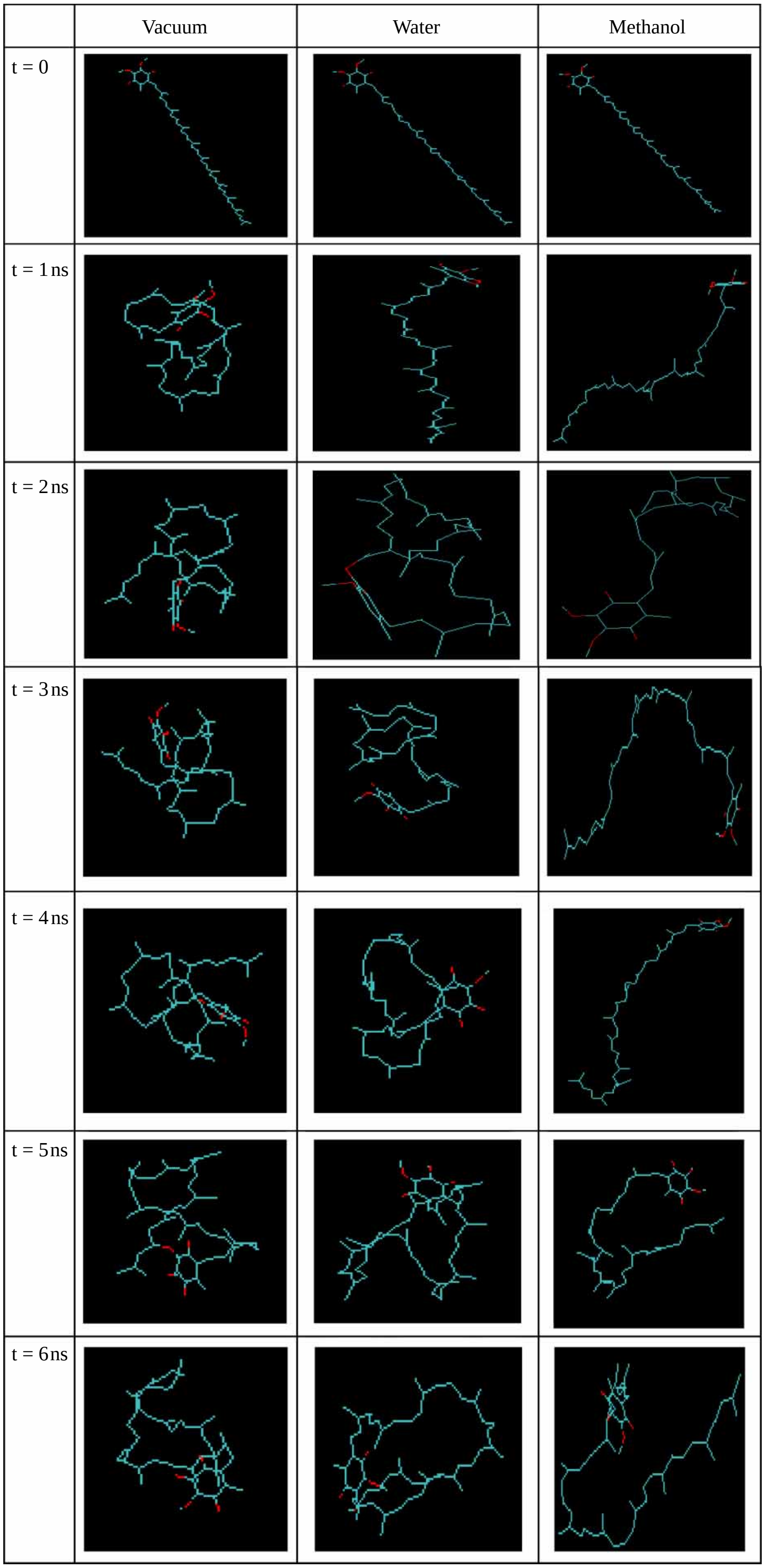

Figure 2. Snapshots of the MD simulations for the UQ molecule in vacuum, water and methanol (solvent molecules in both water and methanol are not shown for clarity).

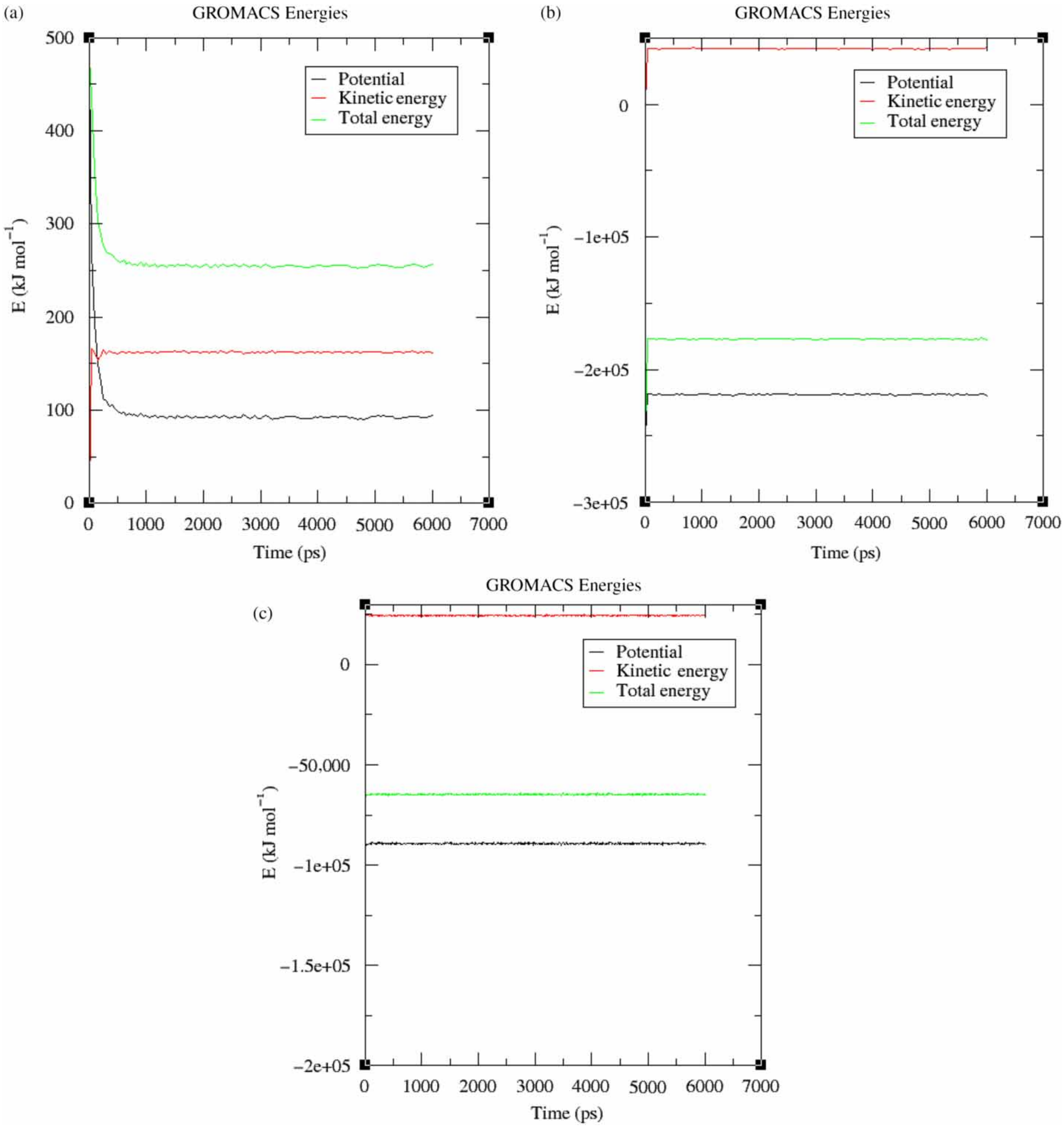

Figure 3. GROMACS energies for the UQ molecule in (a) vacuum (b) water and (c) methanol.

molecular orbital (SCF-MO) method at PM3 level [36] with the restricted Hartree–Fock [37] formalism. Conjugate gradient method (Polak–Ribiere algorithm) [38] was used to optimise geometries and calculate the electronic structure of the molecules. The SCF convergence limit was set to 0.0001 kcal/mol and the criterion of RMS gradient was set to 0.004 kcal/(Å mol) in the calculations. These calculations were performed using HyperChem 7.5 program package (Hypercube, Inc.).

3. Results and discussion

UQ was simulated first in vacuum at 310 K for 6 ns. The same procedure was applied for both water and methanol solvents. A snapshot view for all three cases is displayed in Figure 2. As shown in Figure 2, the geometry of the molecule and its dynamics in water resemble its geometry and dynamics in vacuum. Namely, both in vacuum and water, the molecule seems to be flexible. On the other hand, in methanol, the molecule stays more

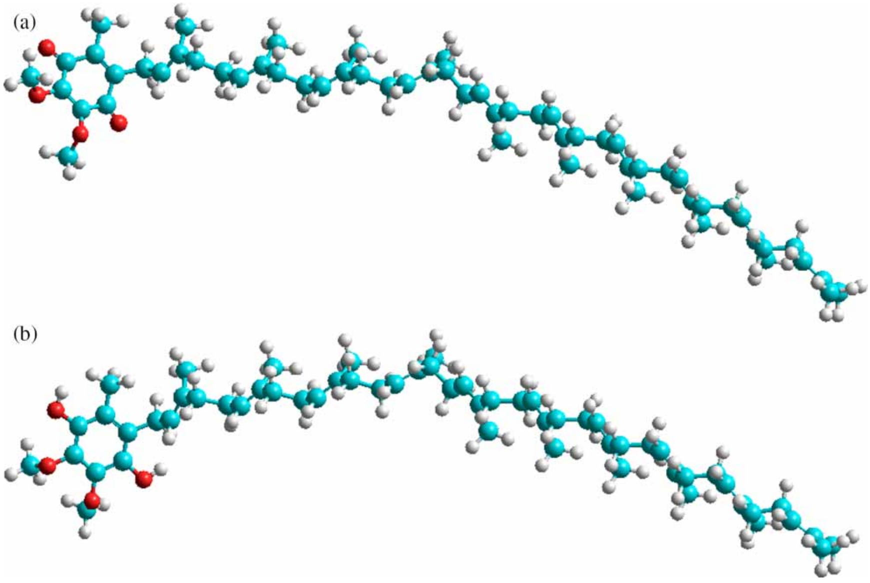

Figure 4. Optimised structure of (a) the UQ and (b) the UQH_2 molecules in the gas phase (PM3 results).

rigid. Since it is lipophilic, it folds to minimise its surface to reduce its interaction with water. As shown in Figure 3, the total energy of the molecule in vacuum is positive with a value of 259.647 kJ/mol. In water and methanol, the total energy is negative with values of −176,909 and − 64737.8 kJ/mol, respectively. This is to be expected since the molecule is interacting with the solute. To be able to calculate the self energy of UQ molecule in the solvent, one should calculate also the pure solvent energy and subtract it from the total energy of the whole system (UQ + solvent).

In Figure 4, the optimised geometries of the UQ and UQH_2 molecules as a result of PM3 calculation are shown. Although the tails of the two molecules are the same, there are some differences on the head groups of the molecules. Bond lengths of the neighbouring atoms in the tails of both of the molecules are the same that is carbon–carbon single bonds (C—C) are 1.5 Å, carbon–carbon double bonds (C═C) are 1.3 Å and carbon–hydrogen bond (C—H) bonds are 1.1 Å. On the other hand, on the head of the molecules, there are slight differences in the bond lengths of the C—C and C═C bonds, which are not that significant. Also, in the UQ molecule, carbon–oxygen double bonds (C═O) are 1.2 Å but in the UQH_2 molecule instead of these bonds, there are oxygen–hydrogen bonds (O—H), which are 1.0 Å. In both molecules, the carbon–oxygen single bonds (C—O) have the same value of 1.4 Å. Distribution of the bond lengths after MD simulations for the UQ molecule in vacuum is shown in Figure 5. Bond length distributions of the UQ molecule in water and methanol are the same as in the vacuum case, therefore they are not shown separately.

In the quantum chemical treatment, the atomic excess charges are calculated through the Mulliken model, the total

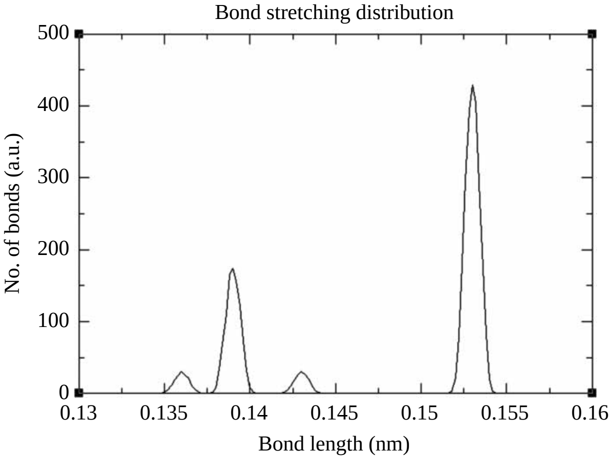

Figure 5. Distribution of the bond lengths (no. of bonds in arbitrary units vs. bond lengths) of the UQ molecule in vacuum (MD result). See text for association of each distribution maxima with the corresponding type of bond.

Table 1. Some of the calculated energy values (in kcal/mol) of the UQ and the UQH_2 molecules (MM results with MM+ force field).

Energy component values	UQ	UQH_2
Bond	3.907	4.160
Angle	17.192	14.483
Dihedral	6.022	7.733
van der Waals	29.914	27.720
Stretch–bend	0.832	0.535
Electrostatic	0.464	2.689
Total energy	58.331	41.850

Table 2. Some of the calculated energy values (in kcal/mol otherwise stated) and dipole moment (in Debye) of the UQ and the UQH_2 molecules (PM3 results).

Quantity	UQ	UQH_2
Total energy	−220,331.389	−221,070.749
Binding energy	−15,169.0176	−15,305.425
Isolated atomic energy	−205,162.371	−205,765.324
Electronic energy	−2,377,465.423	−2,398,346.357
Core–core interaction	2,157,134.035	2,177,275.608
Heat of formation	−159.092	−191.295
HOMO (eV)	−9.315	−8.642
LUMO (eV)	−1.398	−0.064
HOMO–LUMO gap (eV)	7.917	8.578
Dipole moment	2.425	4.827

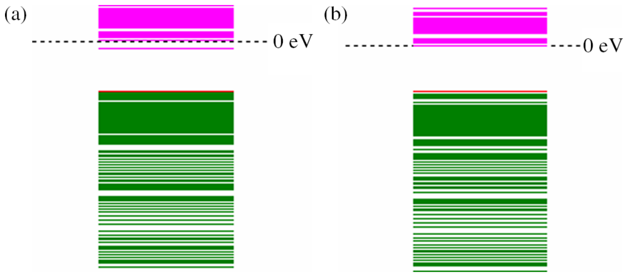

Figure 6. MO eigenvalues of (a) the UQ and (b) the UQH_2 molecules (PM3 results).

charge of each molecule is zero. We note that the atomic charges considered in MD simulations are not exactly the same as in the quantum case. GROMACS considers united atom model, whereas HyperChem provides charge for every atom. These different charge definitions in two different methods of calculations do not affect our results. In the UQ molecule, there are only four positively charged carbon (C) atoms. Two of these with 0.05|*e*| charge are at the outer edge of the molecule and make single bonds with the oxygen (O) atoms. The other two with charges 0.33|*e*| and 0.34|*e*| make double bonds with the O atoms. The charge of the remaining C atoms ranges from −0.03|*e*| to −0.16|*e*|. All the O atoms are always negatively charged with a magnitude of either −0.18|*e*| or −0.27|*e*|. All the hydrogen (H) atoms are positively charged with values in the interval 0.03|*e*|/0.11|*e*|. In the case of the UQH_2 molecule, all the C atoms that make bonds with the O atoms are positively charged with values in between 0.03|*e*| and 0.07|*e*|. The charge of the remaining C atoms ranges from −0.02|*e*| to −0.16|*e*|. All O atoms have a negative charge of −0.18|*e*| or −0.22|*e*|. All H atoms have positive charges in the 0.03|*e*| to 0.20|*e*| interval. There is a large negative charge accumulation on the O atoms.

In Table 1, the values of the energy components obtained by MM with MM+ force field are shown. In both molecules, the largest contribution to the total energy comes from the van der Waals interactions (29.914 kcal/mol for UQ and 27.720 kcal/mol for UQH_2). The electrostatic interactions have the smallest contribution (0464) for UQ, while the stretch–bend interactions (0535) are smallest for UQH_2.

In Table 2, the calculated energy values obtained from the PM3 method are given and the MO eigenvalue spectra are shown in Figure 6. The binding energies of both molecules are nearly the same with a value of −15,169 kcal/mol. Both molecules UQ and UQH_2 are

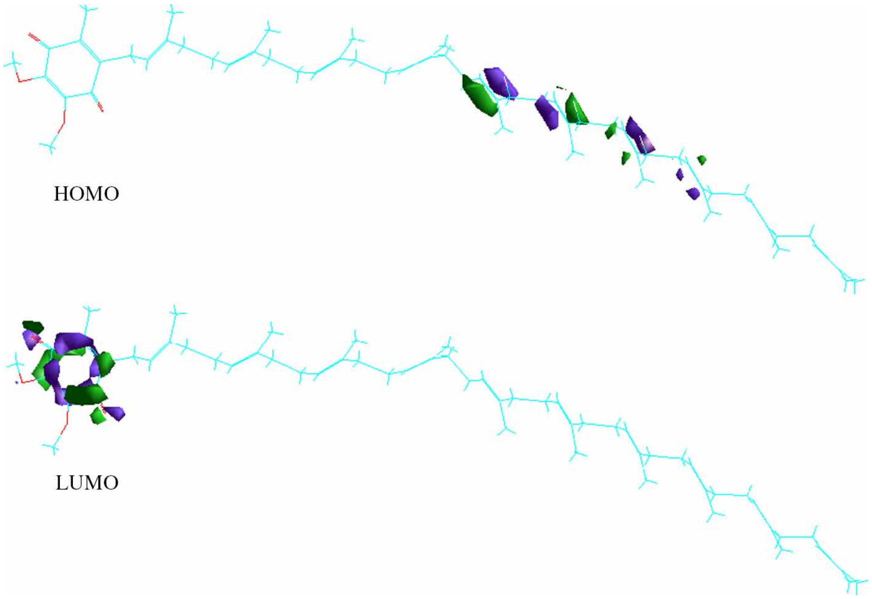

Figure 7. Three-dimensional HOMO and LUMO plots of the UQ molecule (PM3 results).

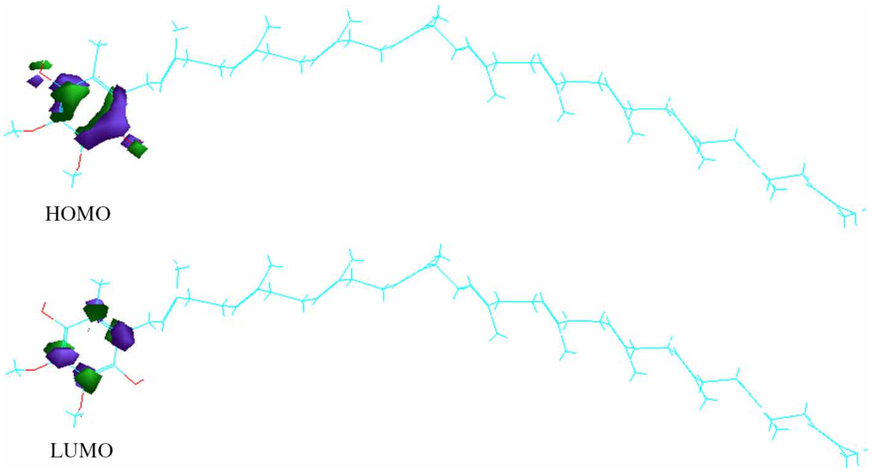

Figure 8. Three-dimensional HOMO and LUMO plots of the UQH_2 molecule (PM3 results).

exothermic with heat of formation of about −159 and −191 kcal/mol, respectively.

The dipole moments of the UQ and UQH_2 molecules are 2.4 and 4.8 Debyes, respectively. With the same method, the dipole moment of water is calculated to be 1.7 Debye, which means that both the molecules are more polar compared to water. Furthermore, the dipole moment of UQH_2 is larger than the dipole moment of UQ, which means that the UQH_2 molecule is more water soluble compared to UQ as is also known [39]. MD simulation predicted the average dipole moment of the UQ molecule to be about 2.5 Debyes in all three cases, namely in vacuum, water and methanol. MD prediction is consistent with the PM3 result.

According to the PM3 calculation, the gap between the highest occupied molecular orbital (HOMO) and lowest unoccupied molecular orbital (LUMO) energies found for UQ is 7.9 eV and for UQH_2 is 8.6 eV. This implies that UQH_2 is kinetically more stable than UQ. Conversely, UQ is chemically more reactive than UQH_2. The present finding is consistent with the recent experimental work on these molecules [40]. Three-dimensional plots of HOMO and LUMO for UQ and UQH_2 are presented in Figures 7 and 8, respectively. In the UQ molecule, the HOMO is mainly localised on the middle part of the tail, while LUMO is mainly localised on the head and the double-bonded oxygen atoms. However, in the UQH_2 molecule, both HOMO and LUMO are localised on the head part only. In Figure 9, 3D electrostatic potential (ESP) plots on UQ and UQH_2 molecules are shown. In both molecules, while negative ESP is mainly localised on the oxygen atoms at the head and on the carbon atoms at the tail, positive ESP is localised on the rest of the molecules. In Figure 10, 3D charge density plots of the UQ and UQH_2 molecules are displayed. Both plots show a uniform distribution.

Additional information can be obtained from log *P*. The calculated log *P* value of the UQ molecule is 14.72,

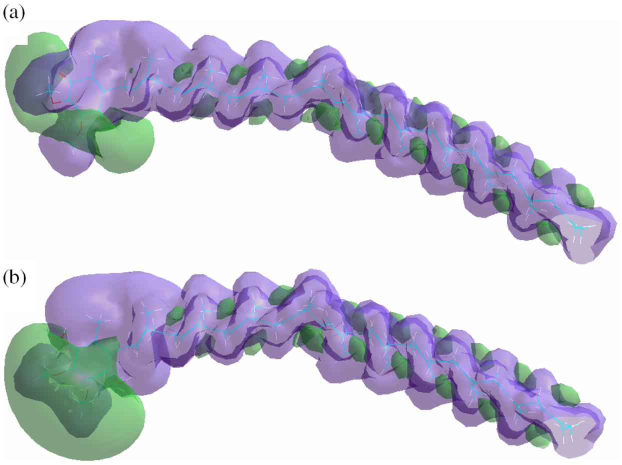

Figure 9. Three-dimensional ESP plots of (a) the UQ and (b) the UQH_2 molecules (PM3 results).

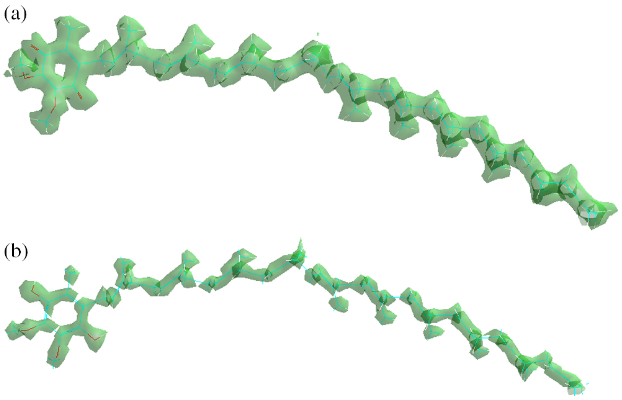

Figure 10. Three-dimensional charge density plots of (a) the UQ and (b) the UQH_2 molecules (PM3 results).

while that of the UQH_2 molecule is 12.26. These values indicate that the molecules considered are quite hydrophobic. HyperChem calculates the $\log P$ values from atomic parameters. Actually, UQ is more hydrophobic than UQH_2 molecule, which means that UQH_2 is slightly more water soluble than UQ. The difference in $\log P$ values of both molecules might be due to the mass difference in their head part, because the two added hydrogen atoms increase the mass of the polar head of the UQH_2 molecule. This analysis confirms the dipole moment calculation.

4. Conclusion

In this study, MD simulations for the analysis of the effects of solvents on the structure of the UQ molecule are presented. Furthermore, semi-empirical MO PM3 calculation is applied to obtain structural and electronic properties of both the UQ and the UQH_2 molecules. The results of the MD simulations show that UQ seems to be flexible both in vacuum and in water and stays more rigid in methanol. The results of the PM3 calculation are compatible with the experiments. Namely, UQ is chemically more reactive than UQH_2, in addition, the simulation suggests that the latter is kinetically more stable than the former. Both molecules are quite hydrophobic.

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