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Interaction of caffeine dimers with water molecules

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ABSTRACT

Stability of caffeine dimers in the presence of surrounding water molecules was investigated by performing ab initio calculations at B3LYP/CBSB7 level of theory. Dimers were constructed by placing geometry optimized monomers at different relative orientations. These dimers were then fully geometry optimized at the same level of theory. Dimer–water interaction was modeled in two ways. Dimers were geometry optimized in aqueous medium using polarizable conductor calculation model. The energy, enthalpy and Gibbs energy of dimer formation was then calculated. It was found that the thermodynamic parameters are much deviated from experimental values. Caffeine dimer water interactions were also modeled by placing water molecules around the dimer at locations where hydrogen bonds could form. In this manner, the number of water molecules was increased up to six. It was observed that the water molecules form hydrogen bonds with both the caffeine molecules. The caffeine–caffeine inter-plane distance increased from 3.6 Å for isolated caffeine dimers (gas phase) up to 3.9 Å for dimer water clusters. Formation energy change (ΔE) of caffeine dimers, depending on their relative orientation in gas phase, ranged from −5.2 to −6.0 kcal mol^{-1}. The average energy change, enthalpy change and Gibbs energy change for dimer formation in gas phase are −5.9, −3.9 and 8.4 kcal mol^{-1} respectively. Average formation energy change decreased to −13.7 kcal mol^{-1} for dimer–water clusters. The average standard Gibbs energy change of dimer–water cluster formation is positive and observed to be 14.9 kcal mol^{-1}. Compared to formation energy changes, relatively large fluctuations were observed with Gibbs energy changes.

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1. Introduction

Caffeine (1,3,7-trimethylxanthine) is a widely consumed stimulant and is a common ingredient of many natural and artificial beverages. Human intake of caffeine is mainly in the form of water based drinks and the absorption into the body occurs from aqueous solutions. It is known that caffeine molecules form dimers or higher order aggregates in aqueous media [1–12]. Many experimental as well as theoretical investigations have been carried out in order to understand the formation of caffeine dimers and higher order clusters. A molecular dynamic study simulating caffeine in aqueous medium as well as in a cluster of water molecules has been conducted by Falk et al. [1]. This study reported that caffeine dimers exist in different orientations with comparable energies. They have found that the most probable configuration is a parallel stacked one. An experimental and theoretical study by Callahan et al. [2] revealed that caffeine and other xanthine derivatives (7-methylxanthine and theobromine) form dimers in gas phase. Their calculations based on density functional theory (B3LYP/6-311+G(2d,p)) together with IR and UV spectral data have shown that the in-plane dimer structures are the lowest in energy for 7-methylxanthine. In the case of theobromine, a stacked structure has been found to be the lowest in energy. However, they have not carried out density functional theory calculations for theophylline and caffeine. Poltev et al. [3] have optimized caffeine molecules in gas phase at MP2/6-31G(d,p) level of theory. The optimized structures have been used in a molecular mechanics calculation to investigate the dimer formation. They have estimated caffeine–caffeine interaction in dimers to be −11.1 to −11.8 kcal mol^{-1}. However, these values are about three times larger than the experimental enthalpy changes of formation (−3.4 kcal mol^{-1}) reported by Gill et al. [6]. Formation of caffeine dimers has been observed in face to face and face to back configurations where caffeine molecules are rotated at different angles relative to each other [3]. These structures represent minima on the potential energy surface within an energy window of ~1 kcal mol^{-1}. Molecular dynamics simulations have also been employed to investigate the stability of caffeine aggregates in water and water–urea mixed solvent systems [5]. Calculations have revealed that caffeine form stable dimers and higher order aggregates in aqueous media.

To the best of our knowledge there have been no reports of complete ab initio investigations on caffeine dimer–water interactions and influence of surrounding water molecules on the stability

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of dimers. Therefore, in the present study we have investigated the stability of caffeine dimers in the presence of surrounding water molecules in order to investigate their stability in aqueous medium. This was done by placing water molecules near the optimized caffeine dimers, followed by full geometry optimizations. Results are compared with geometry optimizations of caffeine dimers in aqueous phase employing the polarizable conductor calculation model (CPCM). Our study reveals that the formation of caffeine dimers is energetically favorable in aqueous medium. Water molecules around caffeine dimers strongly interact and keep them in a stacked fashion. Dimer formation is entropically unfavorable as reflected in positive free energy changes associated with the process.

We have employed density functional method B3LYP in our calculations. Density functional methods are known to produce very accurate results with minimum computational cost. Studies on caffeine have been conducted using density functional methods [2,8]. These methods have been applied successfully to describe stacking interactions of molecules of biological interest [13]. Complete basis methods are known to produce accurate energies and other thermodynamic parameters. They have been extensively tested for various types of molecules [14]. Therefore, we have employed density functional theory combined with a complete basis set in our calculations.

2. Methods

2.1. Caffeine dimers

Geometry of caffeine molecule was optimized at B3LYP/CBSB7 level of theory as employed in Gaussian 03 [15]. Caffeine dimers were formed by stacking two geometry optimized caffeine molecules at different relative orientations. In each case, the whole system was fully geometry optimized at the same level of theory. The initial inter-plane distance of dimers was kept at the experimentally reported value in the solid state i.e. 3.4 Å. Dimers at these initial orientations were then subjected to full geometry optimizations. Formation energy changes for caffeine dimers were calculated according to the scheme, ΔE (dimer) = E (dimer) − 2E (monomer). Where, ΔE (dimer) = formation energy change of dimer, E (dimer) = energy of dimer, E (monomer) = energy of monomer. Respective enthalpy and free energy changes were also calculated using the same scheme.

2.2. CPCM calculations

Aqueous phase calculations were performed using SCRF = CPCM solvation model in B3LYP/CBSB7 calculations. The gas phase optimized dimer structures were reoptimized in the aqueous medium. The energy, enthalpy and free energy changes were calculated using the scheme outlined in Section 2.1.

2.3. Caffeine dimer water clusters

Interaction of caffeine dimers with water was modeled by placing a water molecule near the optimized dimer and subjecting the dimer–water cluster to a complete geometry optimization. In this manner, the number of water molecules was increased by placing water molecules, one by one near all the sites available for hydrogen bonding. All such structures were then fully geometry optimized. Frequency calculations were carried out using geometry optimized structures and it was verified that the structures represent true minima of the potential energy surface. In this manner, up to six water molecules were introduced and the stability of the caffeine dimer was investigated. In the cases of dimer water cluster formation, energy changes were calculated using

$$\Delta E(\text{dimer} + n\ \text{water}) = E(\text{Dimer} + n\ \text{water}) - 2E(\text{monomer}) - nE(\text{water})$$

where ΔE (dimer + n water) = formation energy change of dimer-n water cluster, E (Dimer + n water) = energy of the dimer + n water cluster, E (monomer) = energy of caffeine monomer, nE (water) = energy of the water cluster with n-water molecules. The same scheme with respective enthalpies or Gibbs energies in place of energies was used in the calculation of enthalpy or Gibbs energy changes of formation.

3. Results and discussion

3.1. Caffeine dimers in gas phase

We selected four dimer conformations for the present study. They are face to face, face to back, face to face rotated by 180° and face to back rotated by 180°. All the initial configurations were then full geometry optimized. The dimer in face to back configuration optimized to an open structure (Fig. 1A). The initial configurations, face to face and face to back 180° rotated, retained their starting geometry (Fig. 1B and C respectively). These geometries are designated as ma3 and mp2 respectively by Poltev et al. [3]. Face to face 180° rotated structure was optimized to a face to face rotated structure where the benzene rings are overlapped and rotated with respect to each other by ~120°. This structure is shown in Fig. 1D (designated as ma2 by Poltev et al.).

It can be seen that the caffeine molecules in the dimer structures are oriented in such a way that the hydrogen bonding and pi-stacking are maximized. The above three stacked structures having different relative orientations have been identified as minima on the potential energy surface [3]. The formation energies of the structures A, B, C and D are −5.2, −5.3, −6.5, −6.6 kcal mol^{-1} respectively. Their Gibbs energy change of formation are 5.5, 10.2, 8.5 and 9.3 kcal mol^{-1} respectively. The positive free energy changes of formation of stacked structures indicate that the entropy is decreased during the formation of dimers. It can be noted that the formation of the open structure (Fig. 1A) is associated with the smallest positive free energy change and least negative formation energy change. Further, it could be observed that this structure is devoid of pi-stacking and has the least number of oxygen–hydrogen interactions. The average inter-plane distance of stacked structure in gas phase was found to be 3.6 Å. This is in close agreement with the average inter-plane distance (3.4 Å) reported by Poltev et al. in their molecular dynamics study on caffeine dimers.

The caffeine molecules in the face–face structure (Structure B, Fig. 1) are oriented in such a way that C=O oxygens on 6-membered ring of one caffeine molecule can interact with the —CH_3 hydrogens on the other caffeine molecule. These interactions play a vital role in keeping the two caffeine molecules together. The average H···O distance was observed to be 2.7 Å and the dimer has four such interactions. The inter-planer distance of this dimer was found to be 3.6 Å. The face–back-180° rotated structure is shown in Fig. 1 C. In this dimer structure, the two caffeine molecules are shifted with respect to each other in such a way that only the six membered rings are overlapped. There are four interactions between C=O oxygen and CH_3 hydrogens between the two caffeine molecules, at an average O···H distance of 2.6 Å. The inter-planner distance of this structure is 3.6 Å. The face–face-180° rotated initial geometry of caffeine dimers were optimized to the dimer structure shown in Fig. 1D. It can be seen that the two caffeine molecules are shifted and rotated with respect to each other in such a way that six membered rings are overlapped and O···H interactions are

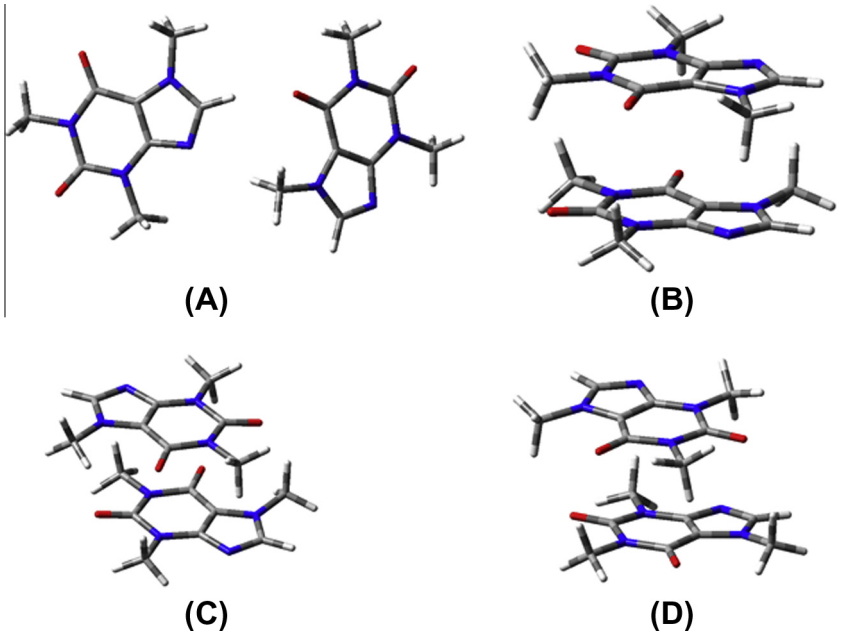

Fig. 1. Caffeine dimer structures obtained after geometry optimization Initial orientations (A) face–back, (B) face–face, (C) face–back 180°, and (D) face–face 180°.

maximized. This dimer structure consists of four O···H interactions between C=O oxygens and CH_3 hydrogens where the average O···H distance is 2.6 Å and the inter-planner distance is 3.6 Å. It is important to note that the inter-plane distance of the caffeine dimers is the same irrespective of the relative shift or the rotation of caffeine molecules. The average energy change, enthalpy change and formation free energy change of dimers are -5.9 kcal mol^{-1}, -3.9 kcal mol^{-1} and 8.4 kcal mol^{-1} respectively. The enthalpy change of dimer formation is in close agreement with experimental self-association enthalpy changes (-3.4 kcal mol^{-1} [6], -5.0 kcal mol^{-1} in [9] taken from [16]). However, the Gibbs energy change of self-association vary widely. The aggregate formation Gibbs energy change of 5.8 kcal mol^{-1} has been reported by Sanjeewa and Weerasinghe [5]. Experimental values reported for self-association Gibbs energy changes at 25 °C are -1.5 kcal mol^{-1} [6] and -1.45 kcal mol^{-1} in [9] taken from [16].

3.2. Caffeine dimers in aqueous phase

All the gas phase optimized stable dimer structures retained their geometry when re optimized in aqueous phase employing the solvation model SCRF = CPCM. The inter-planer distance of dimers in aqueous phase ranged from 3.7 to 3.8 Å. The slight increment in the inter-plane distance indicates that the pi-stacking and O···H interactions are somewhat shielded by the dielectric medium. The average dimer formation energy change and enthalpy change in aqueous phase are -0.8 kcal mol^{-1} and 0.6 kcal mol^{-1}. The face–back initial orientation of the dimer (which resulted an open dimer when optimized in gas phase) could not be optimized in the aqueous phase. The observation of small formation energy changes and positive enthalpy change may be taken as an indication of the inadequacy of continuous dielectric model in appreciating caffeine–caffeine–water interactions. SCRF = CPCM calculations resulted an average standard Gibbs energy change of formation of 12.0 kcal mol^{-1} for dimers.

3.3. Caffeine dimer water clusters in gas phase

In order to further examine the caffeine–caffeine–water interactions, water molecules were placed near caffeine dimers (face to face (ma3), face to back, face to face rotated by180° and face to back rotated by 180°) at positions where hydrogen bonds could be formed. It was found that energetically most favorable places for water molecules are the places near C=O oxygens of caffeine. Then the caffeine dimer and water system was subjected to geometry optimization. It was verified that the optimized structures represented true minima on the potential energy surface by doing frequency calculations. Energy changes of formation of dimer–water clusters as a function of the number of water molecules around the dimer are shown in Fig. 3. We restricted the calculations to a maximum of 6 water molecules due to the difficulty of getting the geometry of the clusters optimized without imaginary frequencies. Missing data in Figs. 3 and 4 are the ones optimized with imaginary frequencies or ones that could not be geometry optimized.

It can be clearly seen from Fig. 3 that the formation energy change for $2\text{Caf} + n\text{H}_2\text{O}_{\text{cluster}} \rightarrow \text{Caf}_2{\cdot}n\text{H}_2\text{O}$ is negative. Further, it can be observed that for all the dimers, the formation energy change varied in the same way regardless of the relative orientation of caffeine molecules in the dimer (Fig. 3). It is interesting to see that the face to back structure, which optimized to an open structure (Fig. 1A) in the absence of water molecules optimized to a stacked form (Fig. 2A) when there are surrounding water molecules. In this structure, the caffeine molecules are slightly shifted with respect to each other and at an inter-plane distance of 3.9 Å. The free energy change of formation of this dimer became more and more positive with the addition of water molecules. This trend continued up to five water molecules and then changed (Fig. 4). The average caffeine–caffeine inter-plane distance in the dimers at face–face and face–back-180° orientations is 3.9 Å. The initial orientation face–face 180° produced a caffeine dimer with slightly inclined (~10°) caffeine molecules (Fig. 2D). The inter-planer distance of this dimer is slightly higher than the others.

The inter-plane distances of dimers in dimer–water clusters is slightly higher than the inter-plane distances derived from molecular mechanics simulations (3.3–3.6 Å [1] and 3.4 Å [3]) for gas phase dimers. The average energy change and enthalpy change of the formation of a dimer–water cluster containing four water molecules were observed to be -13.7 kcal mol^{-1} and -9.9 kcal mol^{-1}. The average Gibbs energy change of formation is 14.9 kcal mol^{-1}

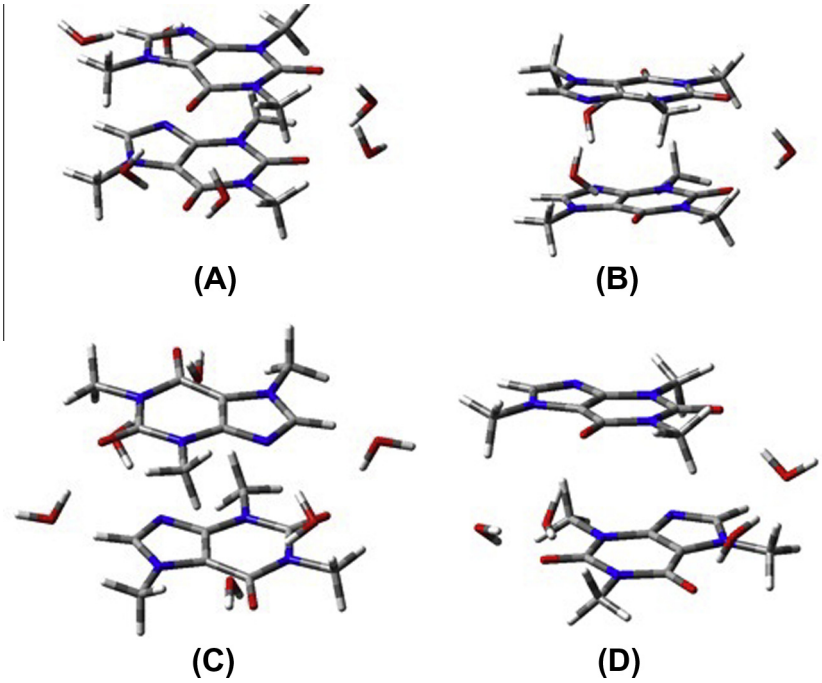

Fig. 2. Caffeine dimers interacting with water molecules. Initial orientations (A) face–back, (B) face–face, (C) face–back 180°, and (D) face–face 180°.

and is comparable to the value obtained using SCRF = CPCM solvation model. However, the energy and the enthalpy changes of dimer formation obtained using SCRF = CPCM solvation model are significantly different from the values obtained using caffeine dimer water clusters.

It can be seen that the formation free energy change of dimer water clusters initially increased and then decreased with the addition of water molecules (Fig. 3). Compared to the formation energy change, formation Gibbs energy change fluctuated significantly (Fig. 4). We also tested the stability of clusters by inserting water molecules between the caffeine molecules in dimers. It was observed that these water molecules always moved out during geometry optimization. This indicates that there are no local minima on the potential energy surface where water molecules exist between caffeine molecules in dimers. It can be seen that the caffeine molecules in initial face–face structure and face–face 180° structure are slightly rotated relative to each other. The planes of caffeine molecules in these dimers are slightly inclined. Compared to those, face–back structures retained their initial orientations well.

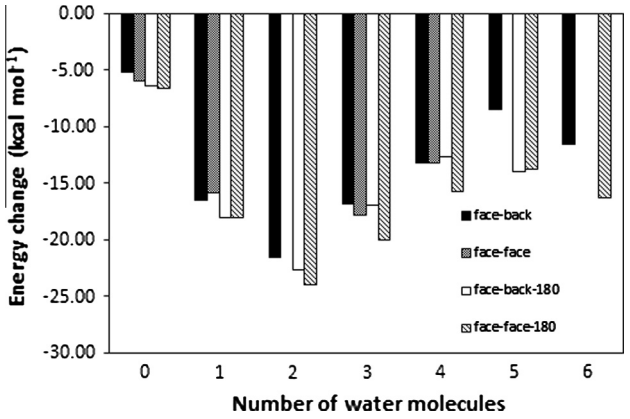

Fig. 3. Formation energy change of caffeine dimer–water clusters.

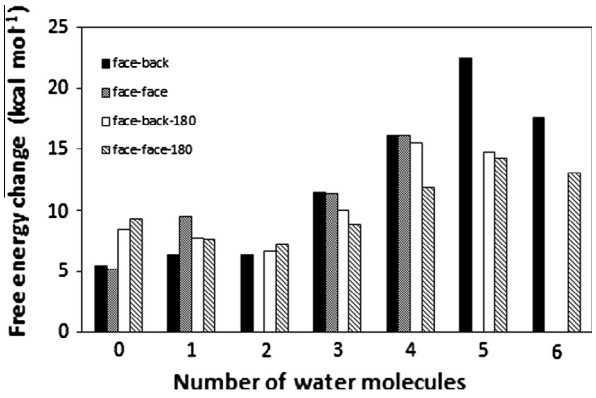

Fig. 4. Formation Gibbs energy change of caffeine dimer–water clusters.

3.4. Disturbance of water–water interactions

In an aqueous medium, formation of a caffeine–dimer disturbs the uniform distribution of water–water interactions. It was attempted to appreciate this by assuming that the water molecules are arranged in a cluster prior to the formation of caffeine dimer–water cluster. In the calculation of energy changes, this was taken into account by including the energy of a water cluster containing *n*-water molecules, rather than including the energies of n-isolated water molecules. Results show that this process is characteristic with a negative energy change and a positive free energy change (Figs. 3 and 4). It can be seen that both, the formation energy change and formation free energy change begin to level off as the number of water molecules is increased. Therefore, the energy and free energy changes are more representative of those in an aqueous medium at higher numbers of water molecules.

4. Conclusions

This study presents an investigation of the stability of caffeine dimers in aqueous medium. Calculations have been conducted

using at B3LYP/CBSB7level of theory. The stability of caffeine dimers in gas phase, in aqueous medium and in water clusters have been studied. The predicted average enthalpy change for dimer formation in gas phase is -3.9 kcal mol^{-1}. Dimer formation in the aqueous phase was investigated using the solvation model CPCM. However, the values predicted by theory are much deviated from experiment. This may be due to the over-screening of pi-stacking by the dielectric medium. Calculations using caffeine dimer–water clusters revealed that ccaffeine dimers are stabilized by surrounding water molecules through interactions like hydrogen bonding. The average inter-plane distance increased from its gas phase value 3.6–3.9 Å in the clusters. Water molecules interact with caffeine molecules and also act as bridges between the caffeine molecules. Interaction with water molecules affect the inter-plane angle especially when the overlap of purine rings is minimal. The face–back initial orientation, which optimized to a non stacked structure in the absence of surrounding water molecules remained as a stacked dimer when clustered with surrounding water molecules.

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