A comprehensive theoretical study of the hydrogen bonding interactions and microscopic solvation structures of a pyridyl-urea-based hydrogelator in aqueous solution

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ABSTRACT

The solvent effects, intermolecular hydrogen-bonding interactions, and supramolecular structures of N,N′-bis(4-pyridyl) urea, a hydrogelator, in aqueous solution were studied through density functional theory (DFT) calculations and molecular dynamics (MD) simulations. DFT calculations show that N,N′-bis(4-pyridyl) urea is polarized from gas phase to highly polar aqueous solution. Correspondingly, the magnitude of the dipole moments of N,N′-bis(4-pyridyl) urea is enhanced as the polarity of the medium increases, which suggests that significant intermolecular interactions may exist in its aqueous solution. Both DFT calculations and MD simulations demonstrate that explicit O⋯H—O, N⋯H—O, and N—H⋯O hydrogen-bonding interactions coexist in aqueous solution and are evenly distributed around N,N′-bis(4-pyridyl) urea, which explains why N,N′-bis(4-pyridyl) urea is a hydrogelator. The hydrogen-bond strength trend is N—H⋯O > N⋯H—O > O⋯H—O for N,N′-bis(4-pyridyl) urea⋯H_2O dimers. The natural bond orbital analysis shows that the intermolecular $n_Y \rightarrow \sigma^*_{X-H}$ orbital interaction dominates the X—H⋯Y hydrogen-bonding interactions in N,N′-bis(4-pyridyl) urea⋯H_2O dimers. In addition, the hydrogen-bonded supramolecular clusters (solute + solvent molecules) are also obtained from MD simulations and DFT optimizations. The hydrogen-bond lengths and angles from DFT optimizations are in good agreement with the values from the experimentally obtained crystal structures of N,N′-bis(4-pyridyl) urea with ethylene glycol and water molecules, whereas MD simulations displayed the wider structural variety characteristic of more realistic solutions.

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1. Introduction

Supramolecular gelators based on intermolecular interactions have attracted extensive experimental interest due to their broad applications in pharmaceutical chemistry, biomedicine, biochemistry, photochemistry, and electrochemistry [1–10]. Supramolecular gels of low-molecular-weight gelators (LMWGs) are assembled through highly specific non-covalent forces, such as electrostatic, hydrogen-bonding, dipole–dipole, and π–π stacking interactions. LMWGs capable of gelling pure water or aqueous solvents are called hydrogelators [2]. To the best of our knowledge, N,N′-bis(4-pyridyl) urea is the lowest-molecular-weight nonpolymeric urea-based hydrogelator. The single-crystal structure of N,N′-bis(4-pyridyl) urea interacting with its gelling solvents, water

and ethylene glycol, through hydrogen bonds was first obtained by the Amitava Das and Parthasarathi Dastidar workgroup [11]. This crystal structure is crucial for understanding and further modulating the structures of self-assembled supramolecular hydrogels through intermolecular interactions between N,N′-bis(4-pyridyl) urea and solvent molecules. However, theoretical investigations of the species and strengths of intermolecular hydrogen-bonding interactions as well as the microscopic solvation structures of N,N′-bis(4-pyridyl) urea in solutions are rarely explored. Herein, we investigate why N,N′-bis(4-pyridyl) urea can act as a hydrogelator and identify the solute–solvent intermolecular interactions and microscopic solution configurations of N,N′-bis(4-pyridyl) urea in aqueous solution.

Because N,N′-bis(4-pyridyl) urea is a hydrogelator, it should exhibit significant solute–solvent intermolecular interactions with water molecules in aqueous solution. As noted, N,N′-bis(4-pyridyl) urea has a carbonyl group, an amine group, and pyridine nitrogen atoms, which can form three types of hydrogen-bonding

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interactions with water molecules: (a) O···H—O, (b) N···H—O, and (c) N—H···O interactions. These interactions have been observed in the experimental crystal structures of hydrogen-bonded complexes of N,N′-bis(4-pyridyl) urea with its gelling solvents, water and ethylene glycol [11]. Additionally, O···H—O, N···H—O, and N—H···O hydrogen bonds also exist in the crystal structures of similar urea-based compounds, N-(2,4-dimethylphenl)-N′-(3-pyridyl)urea and N,N′-bis(3-pyridyl)urea with water molecules [12,13]. Hydrogen bonds are intermediate-range intermolecular interactions between electron-deficient hydrogens and regions of high electron density and play a key role in chemistry, physics, and biology [14–21]. Hydrogen bonds are usually of the X—H···Y type, where X and Y are electronegative elements (e.g., O or N) and Y possesses one or more lone electron pairs, which form the bridge. The formation of a hydrogen-bonded complex generally involves charge transfer from the proton acceptor (Y) to the proton donor (H—X). To achieve the aforementioned goals of this study, we performed quantum chemistry calculations and molecular dynamics (MD) simulations to investigate the structural and electronic characteristics of the hydrogen-bonded supramolecular structures of N,N′-bis(4-pyridyl) urea, a hydrogelator, with water molecules.

The three solvent models, the continuum dielectric model [22–26], discrete solvation model [27–29], and a combination [30–33], implemented at different theoretical levels have distinct strengths and weaknesses for treating the local and bulk solvent effects. In the continuum dielectric model, the solvent is characterized by a continuous dielectric constant (ε), reducing the computational cost in quantum mechanical calculations. However, the simultaneously anisotropic characters of the solvent medium and the local intermolecular interactions are neglected. In contrast, the explicit solvent model takes the specific short-range intermolecular interactions into consideration by including the geometrical structures of individual solvent molecules. Unfortunately, the computational cost increases exponentially with the system size. The compromise strategy is the combined discrete/continuum solvation model, in which both specific and bulk effects are considered. In this work, the integral equation formalism (IEF) [34,35] version of the polarized continuum model (PCM) [25,26,36] was adopted to investigate the solvation effects on the molecular geometries and electronic structures of N,N′-bis(4-pyridyl) urea through density functional theory (DFT) calculations. Water, which is highly polar ($\varepsilon = 78.39$), was selected as a gelling solvent. Force field (FF)-based MD simulations with hundreds of discrete solvent molecules were also employed to investigate the microscopic solvation structures and the short-range solute–solvent intermolecular interactions. In addition, the supramolecular clusters of the solute with one or more solvent molecules were optimized and then applied to analyze the electronic characteristics of intermolecular hydrogen-bonding interactions within the PCM framework through DFT calculations.

The DFT/PCM calculations of the isolated solute show that the molecular structure of N,N′-bis(4-pyridyl) urea is polarized to some extent from gas phase to highly polar aqueous solution. Correspondingly, the gelling capability of N,N′-bis(4-pyridyl) urea with water solvents increases in aqueous solution. The MD simulations and DFT/PCM results also demonstrate that the explicit intermolecular hydrogen-bonding interactions dominate the solute–solvent supramolecular clusters. The structural and electronic features of microscopic solvation structures in aqueous solution are characterized by intermolecular distance, hydrogen-bond angle, solvent coordination number, three-dimensional space distribution function, intermolecular orbital interaction, and charge transfer. The theoretical results will be significant for designing novel gelator molecules from the viewpoint of supramolecular architectures.

2. Computational details

2.1. Choice of DFT functionals and basis sets

In quantum chemistry calculations, density functional theory (DFT) is extensively applied to characterize hydrogen-bonding interactions. Several popular density functionals, such as B3LYP [37], B3P86 [38], PBE [39], PW91 [40], and M06-2X [41], have been found to provide reasonable structures and stabilization energies for some hydrogen-bonded complexes, including organic small molecules, π-conjugated compounds, and biological systems [42–45].

To test the influence of functionals and basis sets, the O···H—O, N···H—O, and N—H···O interaction energies in N,N′-bis(4-pyridyl) urea···H$_2$O dimers were calculated using B3LYP, B3P86, PBE, PW91, M06-2X, and MP2 methods with 6-31+G** and 6-311++G** basis sets. The interaction energies correspond to the energy difference between the isolated molecules. The basis set superposition error (BSSE) [46] was corrected by the counterpoise method [47]. Fig. 1 shows that the B3LYP functional better describes the interaction energies of N,N′-bis(4-pyridyl) urea···H$_2$O dimers than the other DFT methods using the MP2 interaction energies as the benchmark. The hydrogen-bond strengths are in the order of N—H···O > N···H—O > O···H—O for N,N′-bis(4-pyridyl) urea···H$_2$O dimers. In addition, Fig. 1 shows that the influence of the basis set is very small. Thus, the B3LYP functional with a 6-31+G** basis set was chosen to calculate the geometries and interaction energies of solute–solvent hydrogen-bonded complexes.

2.2. Electronic structures: DFT/PCM calculations

To illustrate the influence of solvents on the electronic structures of N,N′-bis(4-pyridyl) urea, the geometries of the isolated
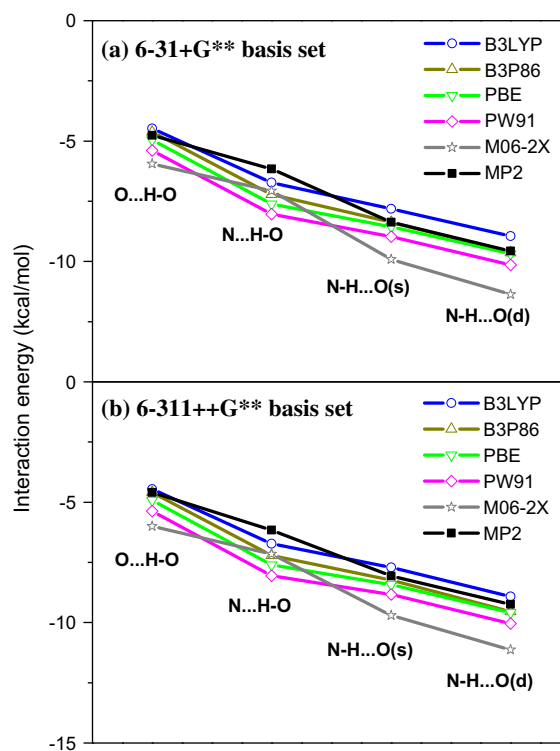

Fig. 1. The interaction energies of N,N′-bis(4-pyridyl) urea···H$_2$O dimers evaluated using B3LYP, B3P86, PBE, PW91, M06-2X, and MP2 methods at the 6-31+G** and 6-311++G** levels. The geometry structures were obtained after optimization at the PCM-B3LYP/6-31+G** level. N—H···O (s) and N—H···O (d) represent the N—H···O single and double hydrogen bonds, respectively.