Reaction pathway and free energy barrier for urea elimination in aqueous solution

Min Yao [a,b,c], Xi Chen [a,b,d,*], Chang-Guo Zhan [a,b,*]

[a] Molecular Modeling and Biopharmaceutical Center, College of Pharmacy, University of Kentucky, 789 South Limestone Street, Lexington, KY 40536, United States
[b] Department of Pharmaceutical Sciences, College of Pharmacy, University of Kentucky, 789 South Limestone Street, Lexington, KY 40536, United States
[c] Key Laboratory of Pesticide and Chemical Biology of Ministry of Education, College of Chemistry, Central China Normal University, Wuhan 430079, PR China
[d] College of Chemistry and Material Science, South-Central University for Nationalities, Wuhan 430074, PR China

ARTICLE INFO

ABSTRACT

To accurately predict the free energy barrier for urea elimination in aqueous solution, we examined the reaction coordinates for the direct and water-assisted elimination pathways, and evaluated the corresponding free energy barriers by using the surface and volume polarization for electrostatics (SVPE) model-based first-principles electronic-structure calculations. Based on the computational results, the water-assisted elimination pathway is dominant for urea elimination in aqueous solution, and the corresponding free energy barrier is 25.3 kcal/mol. The free energy barrier of 25.3 kcal/mol predicted for the dominant reaction pathway of urea elimination in aqueous solution is in good agreement with available experimental kinetic data.

© 2015 Elsevier B.V. All rights reserved.

1. Introduction

Urea, $CO(NH_2)_2$, is a well-known biologically interesting molecule which exists in the bodies of all humans and animals. This compound is a nonvolatile and environmentally benign material used primarily as fertilizer [1,2]. It is nontoxic and reveals essentially no danger to environment, plants, animals, and humans [3]. Urea gradually degrades into ammonia and carbon dioxide in aqueous solution. There have been extensive efforts to understand the mechanism of urea degradation [4–13]. It has been known that urea degradation consists of both elimination reaction ($CO(NH_2)_2 \rightarrow HNCO + NH_3$) and hydrolysis reaction ($CO(NH_2)_2 \rightarrow H_2NCOOH + NH_3$). It is commonly accepted that, in aqueous solution, urea is degraded mainly through elimination, and that non-enzymatic hydrolysis of urea is so slow that it has never been observed experimentally [6]. It has been a challenge for both experimental and computational studies to accurately determine the activation energy or free energy barrier for urea elimination in aqueous solution at room temperature. On the experimental

side, the reported values of the experimental activation energy for urea elimination have a big range (24.6–32.7 kcal/mol) [14], partly because the reaction is too slow to be measured accurately at room temperature. Nevertheless, it has been known that the urea elimination is a first-order reaction with respect to urea within a wide pH range, showing that the rate constant is independent of pH [14]. So, the reaction rate constant may be measured under any pH in aqueous solution.

On the computational side, the earliest computational study by Lee et al. [11] using semi-empirical molecular orbital (SMO) methods (MNDO and AM1) considerably overestimated the free energy barrier for urea elimination. Their calculated energy barrier was as high as ~70 kcal/mol [11]. The free energy barrier (23 kcal/mol) calculated by Estiu et al. [4] was much lower. The calculations by Estiu et al. [4] were carried out at the MP2/6-311++G** level and using an isodensity continuum polarizable model (IPCM) available in the GAUSSIAN 98 program to account for the solvent effects. Most recently, Alexandrova et al. [6] carried out quantum mechanical/molecular mechanical (QM/MM) Monte Carlo (MC) simulations (using a SMO method for the QM part) on urea elimination reaction. Their free energy barrier obtained from the QM/MM MC simulations was 37 kcal/mol. So, the reported computational values of the free energy barrier for urea elimination had a range between 23 kcal/mol and 70 kcal/mol, and the free energy barrier (37 kcal/mol) calculated most recently by Alexandrova et al. [6] was

* Corresponding authors at: Molecular Modeling and Biopharmaceutical Center, College of Pharmacy, University of Kentucky, 789 South Limestone Street, Lexington, KY 40536, United States.
E-mail addresses: ccnuchen@yahoo.com (X. Chen), zhan@uky.edu (C.-G. Zhan).

significantly higher than that (23 kcal/mol) calculated by Estiu et al. [4].

Within the previously reported computational studies, the free energy barrier (23 kcal/mol) obtained from the QM calculations by Estiu et al. [4] at the MP2/6-311++G** level and using the IPCM method was the lowest. It deserves to mention that, within self-consistent reaction field (SCRF) theory, solute-solvent electrostatic interaction includes both surface polarization (which is commonly determined in all of the available SCRF methods) and volume polarization (which is due to the charge penetration of the solute) [15,16]. The IPCM model implemented in the GAUSSIAN program only accounts for surface polarization and completely ignores volume polarization [15,16]. It has been demonstrated that volume polarization significantly affects molecular structures [17–20], properties [21–23] and reactivity [24–27]. Hence, volume polarization must be accounted for in computational determination of solvent effects on the free energy barrier.

In our previous studies, we developed a SCRF model, known as the surface and volume polarization for electrostatics (SVPE) [15,16,21]. The SVPE method is also known as the fully polarizable continuum model (FPCM) [17,19–23,28,29], as it fully accounts for both surface and volume polarization effects in solute-solvent electrostatic interactions [24,30].

Our previous computational studies on hydrolysis reactions of a variety of compounds, including carboxylic acid esters, amides, and phosphate esters, showed that the energy barriers determined by the SVPE-based quantum mechanical (QM) calculations were all reasonably consistent with available experimental activation energies [25,26,28]. The SVPE-based QM approach was also used to examine reaction pathways and free energy profiles for hydrolysis of urea and 1,1,3,3-tetramethylurea (Me$_4$U) [13]. All of the computational results are consistent with available experimental data for Me$_4$U, suggesting that the computational prediction of the free energy barrier (44.1 kcao/mol) for urea hydrolysis is reliable [13]. The same SVPE-based QM approach used to study these hydrolysis reactions was employed, in the present work, to examine the reaction pathway and free energy barrier for urea elimination in aqueous solution. Based on the SVPE-based QM calculations, the predicted free energy barrier (25.3 kcal/mol) for urea elimination in aqueous solution is in good agreement with available experimental kinetic data.

2. Methods

All geometries of the reaction systems, including those of reactants, transition states, and products, were optimized by using density functional theory (DFT) with Becke's three-parameter hybrid exchange functional and the Lee–Yang–Parr correlation functional (B3LYP) [31–33] in combination with the 6-31+G* basis set. Vibrational frequency calculations were carried out to ensure that the geometries are indeed associated with local minimal or saddle points on the potential energy surfaces and to determine the zero-point vibrational and thermal corrections to the Gibbs free energies. Intrinsic reaction coordinate (IRC) calculations were performed to confirm the correct connections between reactants, transition states, and products on the potential energy surfaces.

Previous studies indicated that electron correlation effects are not important in the geometry optimizations and solvent shift calculations, but are important in calculating the relative energies of the geometries [28]. Thus, the geometries optimized at the B3LYP/6-31+G* level were used to perform the second-order Møller-Plesset (MP2) energy calculations with four different basis sets: 6-31+G*, 6-31++G**, 6-311++G**, and 6-311++G(2d,2p). The geometries optimized at the B3LYP/6-31+G* level in the gas phase were also employed to perform SCRF single-point energy

calculations using the SVPE method at the HF/6-31+G* level. Previous computational studies demonstrated that solvent effects have little influence on the geometries of chemical reaction systems and the corresponding energy barriers [34]. Geometrical parameters optimized in the gas phase are quite similar to the ones optimized in the aqueous solution, and the free energy barriers calculated by using the geometries optimized in the gas phase are very close to the corresponding ones calculated by using the geometries optimized in aqueous solution. Hence, all of our energy calculations in the present study were based on the geometries optimized in the gas phase. According to the SVPE procedure [16,21,25], the solute cavity surface is defined as a solute electron-charge isodensity contour determined self-consistently during the SVPE interaction process, and the SVPE results converge to the exact solution of the Poisson's equation with a given numerical tolerance. The converged SVPE results merely rely on the contour value at a given dielectric constant and a certain QM calculation level [16]. Our previous calculations on a variety of chemical reactions showed that the energy barriers determined by the SVPE calculations using both the default 0.001 au and 0.002 au contours were all qualitatively consistent with the corresponding experimental activation energies [25,26,28]. As the SVPE procedure using 0.001 au contour was shown to be reliable for evaluating the bulk solvent effects [17–21,23,26,27,29,35,36], the 0.001 au [16] contour was also used in this study for all of the SVPE calculations. The dielectric constant (ε) used in the SVPE calculations for solvent water is dependent on the temperature (T) [37], with $\varepsilon = 78.5$ at $T = 298.15$ K. The free energies in solution were obtained by adding the gas phase free energies to solvent shifts obtained from the SVPE calculations.

All calculations were carried out by using a local version [38] of the GAUSSIAN 03 program [39] in which the SVPE solvation model was implemented. All of the computations in this study were carried out on a Dell supercomputer cluster with 384 nodes or 4768 processors at the Computer Center of the University of Kentucky.

3. Results and discussion

3.1. Reaction pathways and geometries

According to the reaction-coordinate calculations, urea elimination reaction can occur either through direct elimination pathway (intramolecular elimination pathway) without involving a water molecule in the reaction coordinate or water-assisted elimination pathway (intermolecular elimination pathway) with a water molecule involved in the reaction coordinate. The optimized geometries and their relative Gibbs free energies were depicted in Figures 1 and 2.

As seen in Figure 1, the direct elimination pathway is a 1,3-hydrogen transfer from one amino group of urea to the other amino group which will be released from carbonyl carbon of urea. Specifically, a proton gradually transfers from the N2 atom to the N1 atom. Meanwhile, the C1—N1 bond gradually breaks during the proton transfer process. In the reaction pathway, the transition state (denoted as TS-a in Figure 1) has a four-membered ring formed from the N1, C1, N2, and H1 atoms. A transition-state (TS-a) structure like this with such a four-membered ring is expected to be unstable.

As seen in Figure 2, the water-assisted elimination pathway involves a water molecule which connects the two amino groups through hydrogen bonds in the reactant (RC-b). This water molecule helps to assist the proton transfer between the two amino groups of urea: the oxygen atom of the water molecule gradually transfers a proton to the N1 atom while gradually accepting a proton from the N2 atom. Meanwhile, the C1—N1 bond gradually breaks during the concurrent proton transfer processes. At the