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Reaction Pathway and Free Energy Barrier for Urea Elimination in Aqueous Solution

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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.

Introduction

Urea, $\text{CO}(\text{NH}_2)_2$, 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 ($\text{CO}(\text{NH}_2)_2 \rightarrow \text{HNCO} + \text{NH}_3$) and

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hydrolysis reaction ($\text{CO}(\text{NH}_2)_2 \rightarrow \text{H}_2\text{NCOOH} + \text{NH}_3$). 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 to 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 Gaussian98 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 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 (Me₄U) [13]. All of the computational results are consistent with available experimental data for Me₄U, suggesting that the computational prediction of the free energy barrier (44.1 kcal/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.

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 $\epsilon = 78.5$ 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 Gaussian03 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 4,768 processors at the Computer Center of the University of Kentucky.

Results and discussion

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 end of the reaction, the net changes are that the N2 atom has lost a proton, the N1 atom has obtained a proton, and the C1-N1 bond has been broken. As seen in Figure 2, the transition-state (TS-b) structure for the water-assisted elimination pathway has a six-membered ring formed from the H2, O1, H1, N1, C1, and N2 atoms. The six-membered ring in TS-b depicted in Figure 2 is expected to be more stable than the four-membered ring in TS-a depicted in Figure 1.

Free energy barriers

The free energy barriers calculated for the two reaction pathways at various QM levels are summarized in Table 1. The energetic data in Table 1 reveal that the calculated free energy barriers are not very sensitive to the size of the basis set used in the QM calculations. There

is essentially no basis set dependence at the MP2 level, and even the free energy barrier obtained from the DFT calculations using the 6-31+G* basis set is close to the MP2 results. By increasing the basis set size from 6-31++G** to 6-311++G(2d,2p), the calculated free energy barriers did not change considerably, suggesting that the 6-311++G(2d,2p) basis set is adequate for the current computational study. Below we will only discuss the energetic data obtained from the use of the 6-311++G(2d,2p) basis set.

As expected, the free energy barrier (25.3 kcal/mol) calculated for the water-assisted elimination pathway is significantly lower than that (39.0 kcal/mol) calculated for the direct elimination pathway. So, the dominant reaction pathway for urea elimination in aqueous solution should be the water-assisted. It is not surprising because it has been known that water-assisted proton transfer generally helps to lower the energy barrier [5,40–44]. The calculated free energy barrier of 25.3 kcal/mol for the dominant reaction pathway of urea elimination in aqueous solution is in good agreement with available experimental kinetic data [14]. As summarized in Table 1, available experimental kinetic data were measured at high temperatures (60 to 100°C), leading to the experimental activation energy of 24.6 to 32.7 kcal/mol. To more appropriately compare the experimental data with the calculated free energy barrier, we also extrapolated the reported experimental rate constant values measured at high temperatures (60 to 100°C) to 298.15 K (25°C) using the reported equations and parameters [14]. The extrapolated rate constant values (6.30×10^{-10} to $8.31 \times 10^{-9} \text{ s}^{-1}$) at 298.15 K were then used to estimate the free energy barrier values (28.5 to 30.0 kcal/mol) according to the classical transition state theory (TST) [45]. Our calculated free energy barrier of 25.3 kcal/mol is not far away from the lower limit (28.5 kcal/mol) of the experimentally derived free energy barrier.

In comparison with the previously reported computational studies, our calculated free energy barrier of 25.3 kcal/mol is significantly lower than that (37 kcal/mol) reported most recently by Alexandrova *et al.* [6], but relatively closer to that (23 kcal/mol) based on the earlier calculations reported by Estiu *et al.* [4]. As mentioned above, the SVPE calculations performed in the present study accurately accounted for the volume polarization effect which was ignored completely in the IPCM calculations by Estiu *et al.* [4]. The two calculated free energy barrier values are reasonably close to each other, suggesting that the volume polarization effect is less important for this particular reaction system compared to the previously studied reaction systems involving ions.

Further, compared to the free energy barrier of 44.1 kcal/mol predicted in our previous computational study [13] for the dominant reaction pathway of urea hydrolysis, the free energy barrier of 25.3 kcal/mol predicted for urea elimination is ~19 kcal/mol lower. The large difference in free energy barrier between the two reactions indicates that urea hydrolysis should be negligible compared to the elimination, which is consistent with the fact that the hydrolysis of urea has never been observed in aqueous solution.

Conclusion

The reaction-coordinate calculations have demonstrated that the direct elimination pathway for urea elimination in aqueous solution has a free energy barrier of 39.0 kcal/mol and the

corresponding water-assisted elimination pathway has a free energy barrier of 25.3 kcal/mol. So, the participation of a water molecule in the reaction coordinate helps to decrease the free energy barrier of urea elimination by ~14 kcal/mol. Thus, the water-assisted elimination pathway is dominant for urea elimination in aqueous solution. 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. Compared to the free energy barrier of 44.1 kcal/mol predicted previously for the dominant reaction pathway of urea hydrolysis, the free energy barrier of 25.3 kcal/mol predicted for urea elimination is ~19 kcal/mol lower, which is consistent with the fact that reported experiments on urea degradation in aqueous solution only observed the elimination reaction.

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Research Highlights

- We revisit the reaction pathways and energy barriers for urea elimination
- We accurately evaluate the free energy barriers in aqueous solution
- The lowest barrier is associated with water-assisted elimination pathway
- The calculated free energy barrier is consistent with experimental data

Figure 1. Geometric parameters and free energy profile for the direct elimination pathway of urea. The geometries were optimized at the B3LYP/6-31+G* level. The relative free energies shown for these geometries include the zero-point and thermal corrections and solvent shifts, in addition to the single-point electronic structure energies calculated at the MP2/6-311++G(2d,2p) level in the gas phase.

Figure 2. Geometric parameters and free energy profile for the water-assisted elimination pathway of urea. The geometries were optimized at the B3LYP/6-31+G* level. The relative free energies shown for these geometries include the zero-point and thermal corrections and solvent shifts, in addition to the single-point electronic structure energies calculated at the MP2/6-311++G(2d,2p) level in the gas phase.

Table 1

Calculated Gibbs free energy barriers (FEB, in kcal/mol) for the direct elimination and water-assisted elimination pathways of urea in aqueous solution at 298.15 K.^a

Theoretical level	Direct elimination	Water-assisted elimination
FEB at B3LYP/6-31+G*	39.5	23.8
FEB at MP2/6-31+G*	40.6	26.5
FEB at MP2/6-31++G**	39.3	25.7
FEB at MP2/6-311++G**	38.3	26.0
FEB at MP2/6-311++G(2d,2p)	39.0	25.3
Expt. activation energy ^b	24.6 to 32.7 kcal/mol	
Rate constant extrapolated to 298.15 K ^c	6.30×10^{-10} to $8.31 \times 10^{-9} \text{ s}^{-1}$	
FEB extrapolated from expt. data ^d	28.5 to 30.0 kcal/mol	

^a All energy calculations were performed by using the geometries optimized in the gas phase at the B3LYP/6-31+G* level. The obtained free energy barriers were based on the single-point energy calculations at various levels, plus the zero-point vibration and thermal corrections calculated at the B3LYP/6-31+G* level and the solvent shifts calculated at the HF/6-31+G* level (using the default 0.001 a.u. contour).

^b Experimental activation energy data (based on kinetic data measured at 60 to 100°C) summarized in ref.[14].

^c Rate constant k at 298.15 K (25°C) was extrapolated from the available kinetic data (ref.[14]) measured at 60 to 100°C; the extrapolation was based on the equation and parameters given in ref.[14]: $\log k = -a \times (1000/T) + b$.

^d Free energy barrier (FEB) estimated from the extrapolated rate constant at 298.15 K (25°C) according to the classical transition state theory (TST) [45].