

# Density functional theory study on the reaction mechanism of synthesizing 1,3-dimethyl-2-imidazolidinone by urea method

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**Abstract** We report a first-principles density functional theory investigation on tailoring the fundamental reaction mechanism of synthesizing 1,3-dimethyl-2-imidazolidinone (DMI) through the urea method with water serving as both solvent and catalyst. The nucleophilic cyclization reaction is implemented by two ammonia removal steps. One  $-NH$  group of dimethylethylenediamine (DMEDA) first attacks the carbon atom of urea, eliminating one  $-NH_3$  group and forming an intermediate state  $CH_3NHC_2H_4N(CH_3)CONH_2$  ( $IM^I$ ).  $IM^I$  subsequently undergoes the cyclization process through a secondary ammonia removal via similar manner. Without water, the two ammonia removal steps are both slightly exothermic with high activation barriers ( $\sim 50$  kcal mol $^{-1}$ ). As water participated in the reaction, the kinetics of the two steps can be significantly improved, respectively. The role that water plays, beside as solvent, more importantly, is to serve as a proton exchange *bridge*. Due to the spatial configuration, the direct proton migration from the N atoms of ethylenediamine to

urea is difficult to occur. The water *bridge* facilitates the proton migration by shortening the migration distance. As a consequence, the activation barriers are considerably lowered down to  $\sim 30$  kcal mol $^{-1}$ , indicating a strong catalytic effect from water. In contrast, the three possible side reactions of  $IM^I$ , even catalyzed by water, have higher activation barriers due to strong steric inhibitive effect and consequently become difficult to occur at the same condition. The current computational understanding on the prototypical reaction to DMI can be extended to guide developing more efficient routes to synthesize imidazolidinone derivatives through the urea method.

**Keywords** Density functional theory · 2-imidazolidinone · Urea method · Water-catalysed cyclization

## Introduction

2-imidazolidinone is one of the most critical precursors for synthesizing numerous important derivatives such as industrial chemicals, pharmaceutical and bioactive compounds [1–4]. The properties and functionalities of its derivatives are primarily determined by the substitution groups at the two symmetric 1 and 3 N sites. Two routes can be readily envisioned to synthesize the derivatives. The first is to start from 2-imidazolidinone. Several patents and literature [5–7] had proposed that, by reacting 2-imidazolidinone with formaldehyde and formic acid, one can produce 1,3-dimethyl-2-imidazolidinone (DMI) with cuprous chloride serving as catalysts through a nucleophilic substitution process. Generally, due to the chemically equivalent nature of the two N sites, symmetric and simultaneous substitution will occur without preferential selectivity. Consequently, side products separation would become a difficult issue which

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prevents the technique from large scale deployment. As a consequence, asymmetric mono substitution can only be implemented under crucial condition. For example, Stabile et al. [8] reported the synthesis of mono N-arylation of 2-imidazolidinone with various aryl iodides and 2-imidazolidinone. Using *n*-butanol as solvent and CuI as catalyst, a yield of 70 % can be reached. Several studies [9, 10] suggested that by reacting 2-imidazolidinone with *n*-BuLi and propionyl chloride (or methyl iodide) at very strict condition, the asymmetric derivatives 1-propionyl or 1-methyl-2-imidazolidinone can be produced with acceptable yield (>80 %).

The second route is to form the 5-membered ring structure with expected substitution groups directly via a cyclization process between ethylenediamine and urea derivatives [11]. In fact, using ethylenediamine to react with phosgene [12, 13], carbon dioxide [14, 15] or urea [16–18] to produce 2-imidazolidinone have been exceedingly matured in industry. In particular, the non-toxic urea method, which operates at low pressure with a high yield when water serves as solvent [16, 17], has become an economic and applicable choice for entrepreneurs. By selecting appropriate homogeneous catalysts, symmetric derivatives, such as 1,3-diphenyl-2-imidazolidinone [19], and asymmetric derivatives, such as 1-phenyl-3-cyclohexyl-2-imidazolidinone [20], can be obtained with moderate yield. For example, Ni<sub>2</sub> catalyzed cross-coupling reactions of aziridines coupled with isocyanates to form symmetric or asymmetric N-substituted 2-imidazolidinone derivatives have been described [19, 20]. Although numerous methods are available for the preparation of symmetrical and unsymmetrical N-substituted 2-imidazolidinones in moderate yield, until now, due to the chemical equivalence of the two nitrogen atoms in 2-imidazolidinone, producing these asymmetric substituted derivatives are relative more difficult to obtain high yield and purity. In contrast, using unsymmetrical substituted ethylenediamines to undergo direct cyclization reaction is a possible and applicable pathway to achieve high synthesis efficiency. A few examples have been reported so far [21–24]. The intramolecular N-cyclization of N-(2-hydroxyethyl)urea prepared from the reaction of primary 1,2-amino alcohol with phenyl isocyanate leads to N-cyclized 2-imidazolidinone formation in good yield [21]. Primary amine coupled with 2-chloroethyl isocyanate to give the corresponding urea intermediate, which is cyclized and resulted in the formation of mono N-substituted imidazolidinone under acid catalysis conditions [22–24]. Unfortunately, besides synthesizing 2-imidazolidinone itself, the yield for the target products is generally below 80 %. Since the reagents for specific applications are always expensive, developing more rational and efficient routes to synthesize target 2-imidazolidinone derivatives become genuinely important for industrial demand. To this end, it requires a detailed understanding on the

cyclization insight of urea method, which still remains unclear and debatable to date.

In this paper, we investigated the cyclization reaction process of urea with ethylenediamine and its derivatives using first-principle density functional theory to depict the controlling factors that govern the reaction rate and mechanism. By analyzing the Mulliken charge distribution and the transition state of the chemical species throughout the whole process, we identified the key catalytic role that water plays by shortening proton transfer pathway during ammonia removal. Although the simulations are conducted for symmetric derivatives, our method and conclusions could be easily extended to asymmetric systems and should be helpful in guiding realistic chemical engineering processes.

### Computational details

We carried out the first-principles calculations using density functional theory (DFT) under the generalized gradient approximation (GGA) with Perdew-Burke-Ernzerhof (PBE) exchange-correlation functional as implemented in DMol<sup>3</sup> package [25, 26]. A double numerical basis set augmented with polarization functions (DNP) was employed to describe the valence electrons. The core electrons were dealt by the all-electron method. All the geometries were fully optimized without symmetry constraints. Spin-unpolarization scheme was utilized throughout our calculation except for the transition state search and optimization, where open-shell nature may occur. For the transition state calculations, we employed the protocol of complete linear synchronous transit/quadratic synchronous transit (LST/QST) [27], and for the transition state optimization, we utilized a Newton-Raphson search algorithm. Normal-mode analysis was performed to validate the correctness of the located transition states. The SCF and energy convergence threshold was set to be  $1.0 \times 10^{-5}$  Ha and  $2.0 \times 10^{-5}$  Ha, respectively. A continuum solvation method (COSMO) [28] is employed here for an implicit description of the water environment. This dielectric continuum model simulates water by a macroscopic dielectric continuum characterized by a dielectric constant of 78.54, thus neglecting any atomistic nature but including implicitly configurational sampling. The above computational scheme had been widely utilized to study similar systems and had been demonstrated to be capable of providing excellent structural and energetic information [29–32].

### Results and discussion

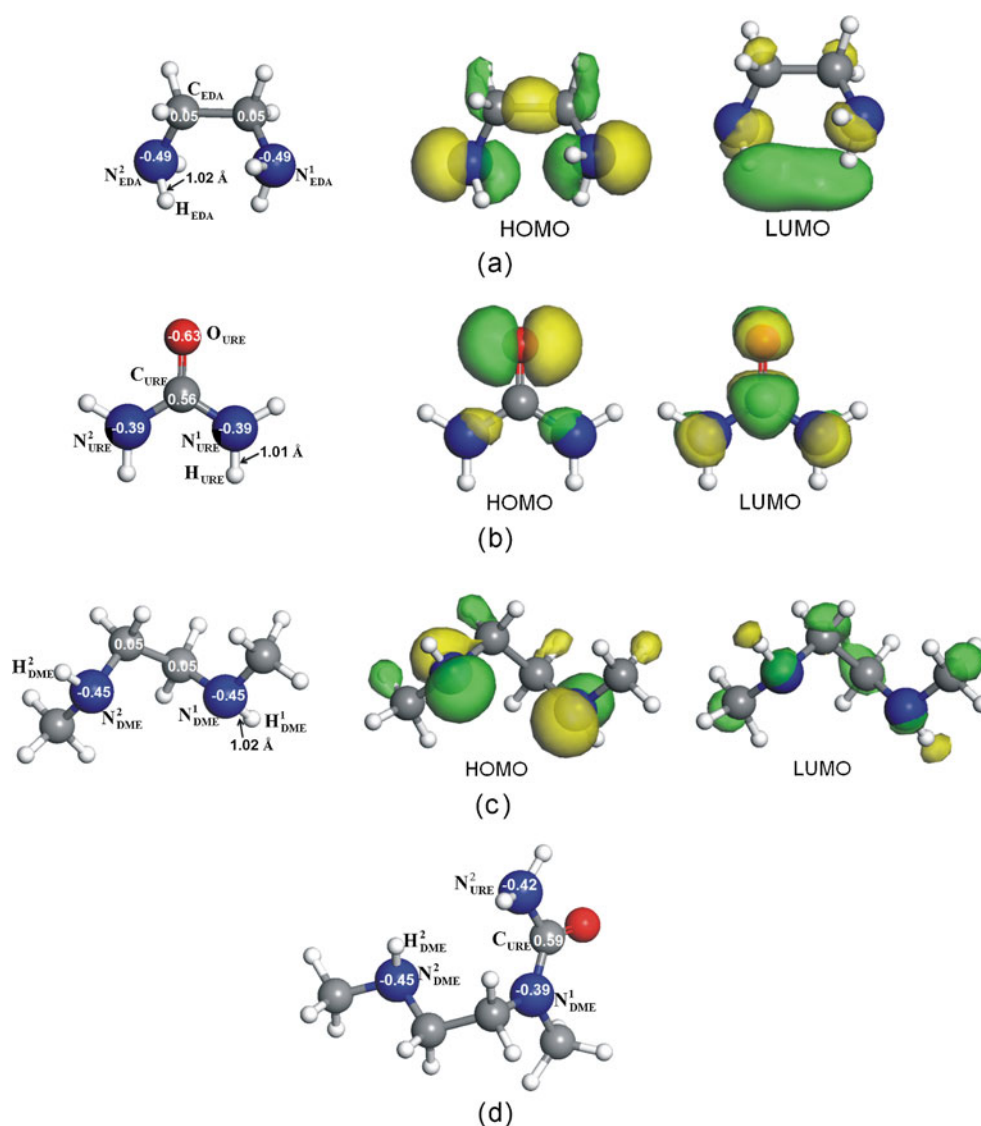
The cyclization between urea and ethylenediamine (EDA) is a typical nucleophilic elimination reaction. Two ammonia molecules are removed upon the formation of

2-imidazolidinone. Isotope experiments by Butler et al. [16] suggested that the removed amine groups originate from urea instead of from EDA. Figures 1a and b display the charge distribution, atomic notations and HOMO, LUMO of EDA and urea, respectively. Apparently, the N atom of EDA ( $N_{\text{EDA}}$ ) is more negative than that of urea ( $N_{\text{URE}}$ ), while the positive charge of  $C_{\text{URE}}$  atom is more abundant than that of the  $C_{\text{EDA}}$  (Fig. 1a and b). It is thus understandable that  $N_{\text{EDA}}$  first attacks  $C_{\text{URE}}$  and forms a new N-C bond. An  $H_{\text{EDA}}$  atom dissociates from the  $N_{\text{EDA}}$  atom and attaches to the  $N_{\text{URE}}$  atom simultaneously which removes an ammonia molecule. Another ammonia removal process follows the same route to implement the cyclization process. It can be anticipated that the electronegativity of the N atoms of EDA and its derivatives play a key role in determining the reaction rate. For the prototypical reaction toward DMI using urea method, similar nucleophilic reaction, including ammonia removal and cyclization

process, is expected to occur between urea and the N, N'-Dimethylethylenediamine (DMEDA, Fig. 1c) precursor. In comparison, the N atoms of DMEDA are less negative than those of EDA. We thus estimate that the reaction rate targeting DMI should be slower than toward 2-imidazolidinone. The interaction of EDA and DMEDA with urea is via the overlap between the HOMO of EDA or DMEDA and the LUMO of urea to form the C-N bond.

As mentioned above, the cyclization process includes two distinguished steps. We first investigated the whole process by calculating the reaction pathways. The calculated energies are listed in Table 1 and the structures of the reactant states, optimized transition states and the final product states are displayed in Fig. 2. Figure 2a shows that one -NH group of DMEDA first approaches the  $C_{\text{URE}}$  atom with a closest  $H_{\text{DME}}-N_{\text{URE}}$  distance of 3.30 Å. This  $H_{\text{DME}}$  atom subsequently migrates to the amine group of urea forming a R-NH<sub>3</sub> transition state, where the  $N_{\text{DME}}-C_{\text{URE}}$

**Fig. 1** Optimized structures and HOMO, LUMO of **a** EDA, **b** Urea, **c** DMEDA and **d** IM<sup>I</sup>. The typical charge distribution and bond parameters are labeled



**Table 1** Reaction barrier ( $E_a$ ) and reaction energy ( $\Delta E_r$ ) of N,N'-dimethyl-ethylenediamine with urea. The data in the parentheses are the energies without solvent effect

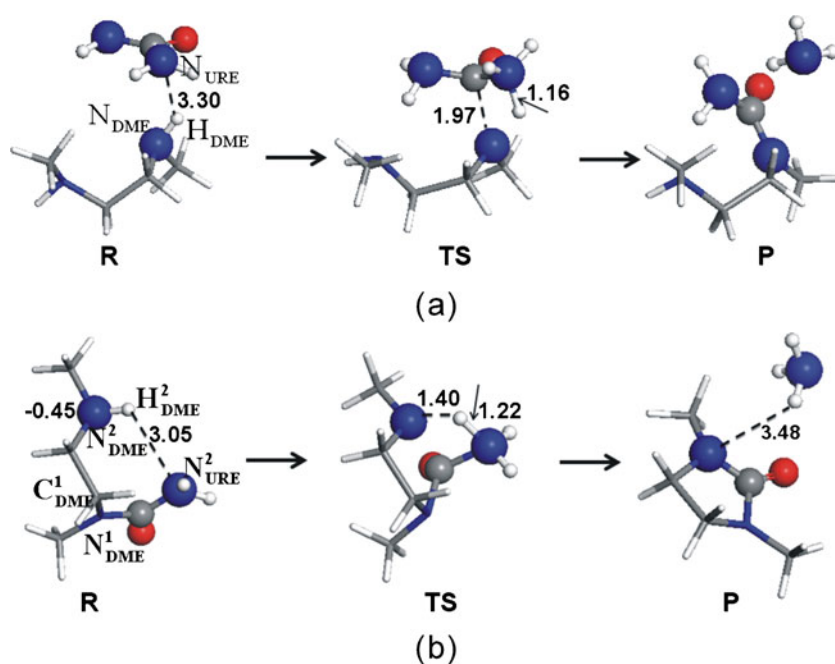
		$E_a/\text{kcal}\cdot\text{mol}^{-1}$	$\Delta E_r/\text{kcal}\cdot\text{mol}^{-1}$
1st $\text{NH}_3$ elimination	No water	50.26(45.28)	-4.05(-10.85)
	water	33.86(48.15)	3.47(1.98)
2nd $\text{NH}_3$ elimination	No water	48.74(41.68)	-3.21(-8.56)
	water	29.81(33.55)	-4.56(-2.75)

distance becomes 1.97 Å. As the  $\text{N}_{\text{DME}}\text{-C}_{\text{URE}}$  forms, the  $\text{C}_{\text{URE}}\text{-N}_{\text{URE}}$  bond dissociates that releases an ammonia molecule and the intermediate state (**IM**<sup>1</sup>,  $\text{CH}_3\text{NHC}_2\text{H}_4\text{N}(\text{CH}_3)\text{CONH}_2$ ) is achieved. The process has a slight exothermic energy of  $-4.05 \text{ kcal mol}^{-1}$ , however, a high activation barrier of  $50.26 \text{ kcal mol}^{-1}$ , suggesting an unfavorable kinetic nature. It is due to the fact that, the electron lone pairs of the N atoms of both DMEDA and urea are repulsive to each other, which prevents the two reactants to approach an appropriate spatial configuration for initializing the reaction. As a consequence, the long  $\text{H}_{\text{DME}}\text{-N}_{\text{URE}}$  distance of the initial state thus inhibits the proton transfer to occur under mild condition. We then considered the situation that an adjacent water serves as catalyst (Fig. 3a). Water first participates in the reaction via hydrogen bonding. The H atom of water ( $\text{H}_{\text{WAT}}$ ) points to the electron lone pair of the  $\text{N}_{\text{URE}}$  atom ( $\text{H}_{\text{WAT}}\text{-N}_{\text{URE}}$  distance is 1.94 Å), and the  $\text{H}_{\text{DME}}$  atom points to the lone-pair of O atom of water ( $\text{O}_{\text{WAT}}$ ) ( $\text{H}_{\text{DME}}\text{-O}_{\text{WAT}}$  distance is 2.19 Å) (Fig. 3a). Such a water-bridging structure should indubitably facilitate the proton

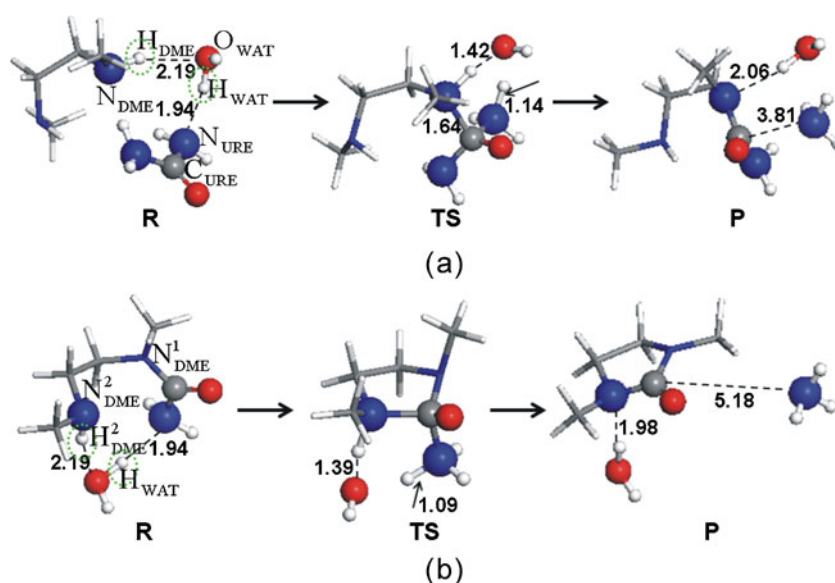
transfer from DMEDA to urea. At the transition state,  $\text{H}_{\text{WAT}}$  attaches the  $\text{N}_{\text{URE}}$  atom that forms ammonia-like configuration;  $\text{H}_{\text{DME}}$  approaches  $\text{O}_{\text{WAT}}$  ( $\text{H}_{\text{DME}}\text{-O}_{\text{WAT}}$  distance is 1.42 Å) and the  $\text{H}_{\text{DME}}\text{-N}_{\text{DME}}$  bond is elongated from 1.03 Å to 1.16 Å, suggesting the bond is somewhat activated. At the same time, the  $\text{C}_{\text{URE}}$  atom connects to the  $\text{N}_{\text{DME}}$  atom which forms a weak  $\text{C}_{\text{URE}}\text{-N}_{\text{DME}}$  bond with the bondlength of 1.64 Å. Finally, the  $\text{C}_{\text{URE}}\text{-N}_{\text{URE}}$  bond dissociates to release an ammonia molecule, and the  $\text{H}_{\text{DME}}\text{-O}_{\text{WAT}}$  bond formed to restore the water. Apparently, water serves as an H transfer agent to mediate the ammonia removal by exchanging one of its H atoms with DMEDA. Such a route shortens the H migration pathway to implement easier kinetics. As a consequence, the activation barrier of forming **IM**<sup>1</sup> is considerably lowered down to  $33.86 \text{ kcal mol}^{-1}$ .

In principle, with or without water catalyzing, the thermodynamics should keep constant. However, in our calculations, due to the participation of water, the structural configurations differ slightly, which results in minor energy change for both the two ammonia elimination steps, as shown in Table 1. Although the kinetics becomes much facile due to the water catalyzing, the near thermoneutral nature (slight exothermic or endothermic) of the reactions does not change. It is also noteworthy from Table 1 that, such a thermoneutral nature does not vary even when including the implicit description of water surrounding environment. For the two ammonia elimination steps without water catalyzing, the solvent effect is almost invisible for the kinetic behaviors. Interestingly, once an explicit water molecule was introduced to the reaction, the solvent effect leads to significant barrier lower down, especially for the first ammonia elimination. The

**Fig. 2** The structure evolution of the cyclization process of N,N'-dimethyl-ethylenediamine with urea. **a** 1st  $\text{NH}_3$  elimination; **b** 2nd  $\text{NH}_3$  elimination



**Fig. 3** The structure evolution of the cyclization process of N, N'-dimethyl-ethylenediamine with urea using water as proton bridge. **a** 1st NH<sub>3</sub> elimination; **b** 2nd NH<sub>3</sub> elimination



coupling utilization of both implicit and explicit water plays a delicate role on influencing the energetics of the reactions involved in the current study. It is understandable that, in the whole real reaction, water, as a solvent, or a catalyst, always exists. Consequently, we can conclude that both the water catalyzing role and the solvent effect of water must always be considered for the present system. From this point of view, we invariably employed the solvent effect to explicitly describe the realistic water environment and thoroughly considered catalyzing effect of the explicit water throughout our calculations.

The intermediate IM<sup>1</sup> subsequently undergoes a cyclization process toward DMI. Since the eliminated ammonia molecule and the water molecule participated in the first step are intact to the second ammonia elimination step, for simplicity, we did not include the isolated ammonia and water molecule in IM<sup>1</sup>. The reaction pathways, without and with water as catalyst, are shown in Figs. 2b and 3b, respectively. Similar to the first ammonia removal, the H<sub>DME</sub><sup>2</sup> atom of IM<sup>1</sup> dissociates from the N<sub>DME</sub><sup>2</sup> atom and attaches to the N<sub>URE</sub><sup>2</sup> atom, leading to a secondary ammonia removal. Without water, the reaction energy and activation barrier is -3.21 kcal mol<sup>-1</sup> and 48.74 kcal mol<sup>-1</sup>, respectively. The energetics is very close to that of the first order ammonia removal without water catalyzing. From the initial structure, we can conclude that the high barrier is again due to the spatial configuration. The C<sub>DME</sub><sup>1</sup> – N<sub>DME</sub><sup>1</sup> bond is forced to rotate to allow the H<sub>DME</sub><sup>2</sup> atom to migrate to N<sub>URE</sub><sup>2</sup>, as indicated by the TS structure in Fig. 2b. Nevertheless, as water participates in the cyclization process as a proton exchange *bridge*, the activation barrier is considerably decreased to 29.81 kcal mol<sup>-1</sup>, slightly lower than that of the first ammonia removal with water catalyst. It can be concluded that, without water, synthesizing DMI through urea method is slightly exothermic and kinetically unfavorable and

the two steps have almost the same reaction rate. However, as water participates in the reaction, the kinetics becomes much facile which allows the reaction to occur under relatively mild temperature. The first ammonia removal can be considered as the rate determining step of the whole reaction.

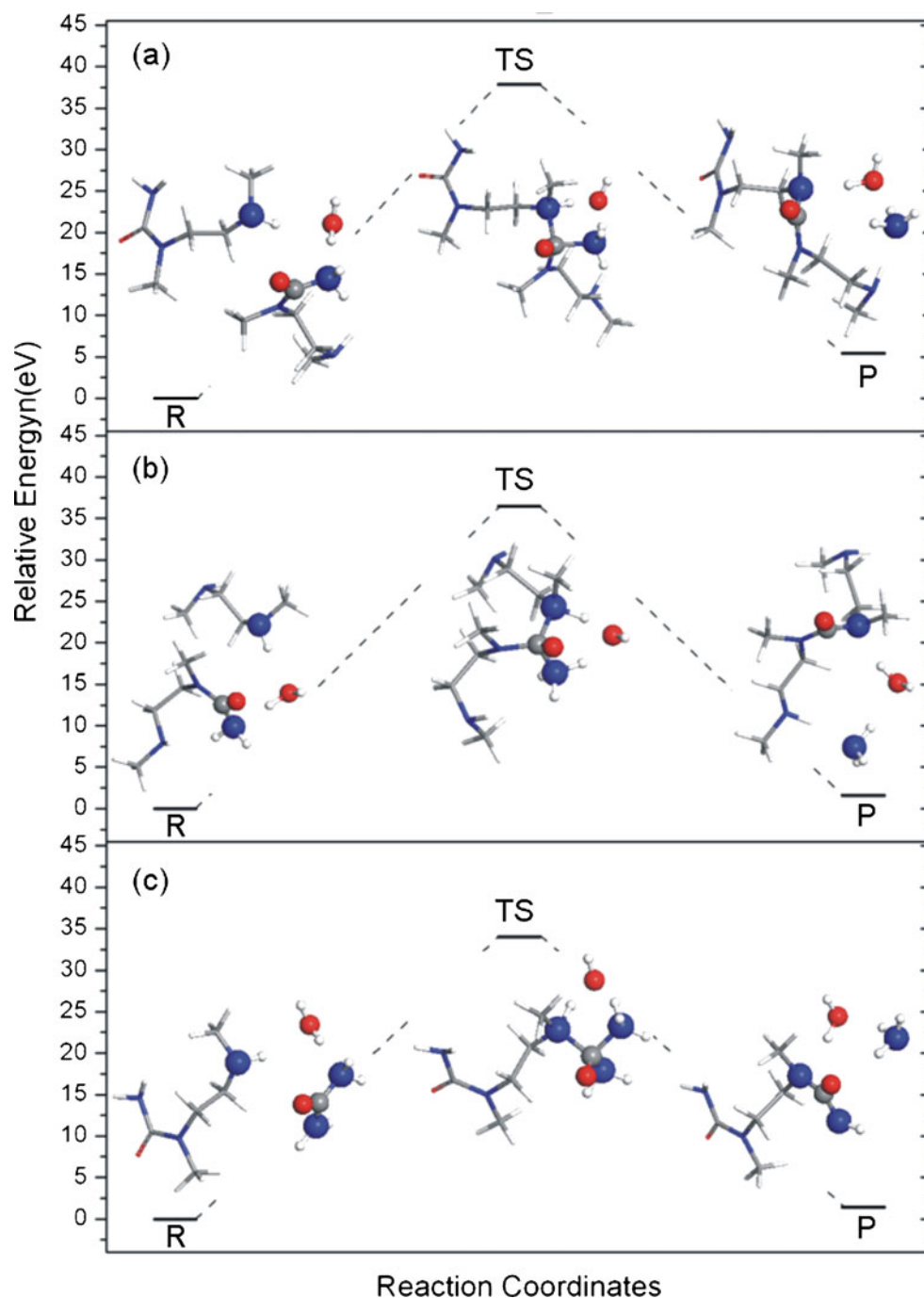
In fact, prior to the self-cyclization of IM<sup>1</sup>, there are three other possible side reactions for IM<sup>1</sup> to react with other species:

- Two adjacent IM<sup>1</sup> intermediates condensate with each other to form oligomers;
- An IM<sup>1</sup> intermediate reacts with an adjacent DMEDA molecule using the urea end (N<sub>URE</sub><sup>1</sup>);
- An IM<sup>1</sup> intermediate reacts with the adjacent urea molecule using the amine end (N<sub>DME</sub><sup>2</sup>).

Similar ammonia removal should occur for all these side reactions. Since the critical catalytic role that water plays for ammonia removal, we calculated all three reactions using water as the catalyst. The energy profile and the corresponding structures are shown in Fig. 4 and the energetics are listed in Table 2.

Mulliken charge analysis indicates that the N<sub>DME</sub><sup>2</sup> atom at amine end of IM<sup>1</sup> (Fig. 1d) is comparable to that in DMEDA, however, the C<sub>URE</sub> atom at urea end of IM<sup>1</sup> is more positive than that in pure urea. Compared with the first order ammonia removal, the nucleophilic reaction could occur more readily for IM<sup>1</sup> to react with itself, DMEDA or urea. We thus expected more favorable kinetics for the side reactions rather than the first order ammonia elimination. Our calculations suggested that all three side reactions are slightly endothermic. Side reaction A yields an oligomer structure which implies a chain growth could occur, leading to polymerization. The activation barrier of this condensation process is much higher than that of cyclization. Figure 1d

**Fig. 4** The structure evolutions of the three **a**, **b**, and **c** side reactions



**Table 2** Reaction barrier ( $E_a$ ) and reaction energy ( $\Delta E_r$ ) of the three side reactions and the typical cyclization reaction of IM<sup>I</sup>

Reaction	$E_a/\text{kcal}\cdot\text{mol}^{-1}$	$\Delta E_r/\text{kcal}\cdot\text{mol}^{-1}$
Cyclization	29.81	-4.56
Side reaction A	37.89	5.42
Side reaction B	36.47	1.60
Side reaction C	33.99	1.39

shows that the intramolecular distance between the urea end and the amine end in an IM<sup>I</sup> molecule is much shorter for implementing the proton transfer and the successive cyclization. For the condensation, the higher activation barrier should originate from the steric inhibition between adjacent IM<sup>I</sup> species, which leads to longer intermolecular distances and longer proton transfer pathway even catalyzed by water. On the other hand, in a real reaction process, the IM<sup>I</sup> species are relatively separated which gives rise to low probability for two IM<sup>I</sup> to meet with an appropriate

configuration. As a result, the polymerized species are seldom observed in experiments. The same situation can be extended to side reactions **B** and **C**, where the activation barrier of **B** is only slightly lower than that of condensation reaction **A** of  $IM^I$ , and the activation barrier of **C** is very approximate to that of the first order ammonia removal but higher than that of cyclization reaction. We consequently anticipated that the steric inhibition is the determining factor that controls all three side reactions. Thereby, the cyclization to form DMI should dominate the reaction through the urea method and using  $H_2O$  as catalyst. The prediction agrees well with experimental observation.

## Conclusions

We present a first-principles DFT study on the reaction mechanism of synthesizing DMI through urea method. Our calculations suggest that, the cyclization process toward DMI includes two ammonia removal steps. The first ammonia removal generates an intermediate state ( $IM^I$ ), which undergoes a secondary ammonia removal to implement the cyclization reaction. For both steps, the N atom of ethylenediamine attacks the C atom of urea and transfers its H atom to the N atom of urea simultaneously. The C-N bond of urea subsequently dissociates to release an ammonia molecule and a new C-N bond forms between urea and ethylenediamine. Both steps are slightly exothermic, while the activation barriers are relatively too high ( $\sim 50 \text{ kcal mol}^{-1}$ ) to achieve a good reaction rate without solvent/catalyst. The proton transfer from the N atoms of ethylenediamine to urea was deemed to be the rate determining factor. With the aid of water which serves as an exchange *bridge* to facilitate the proton migration by shortening the migration distance, the activation barriers are considerably lowered down to  $\sim 30 \text{ kcal mol}^{-1}$ , indicating that the reaction is significantly accelerated. In contrast, the three possible side reactions, even catalyzed by water, have higher activation barriers due to strong steric inhibitive effect and consequently become difficult to occur at the same condition. As a prototypical reaction, the current DFT elucidations can be readily applied to guide synthesizing imidazolidinone-based products through the urea method, especially for the asymmetric derivatives. It can be envisioned that we can achieve the products via tuning the substitution groups of ethylenediamine, or developing more effective and specific homogeneous solvents or heterogeneous catalysts to realize high-efficient synthesis of imidazolidinone derivatives.

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