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Highly Efficient Non-Catalytic Carboxylation of Diamines to Cyclic Ureas Using 2-Pyrrolidone as a Solvent and a Promoter

Junhyeok Hwang,[1] Donggu Han,[1] Jin Joo Oh, Minserk Cheong, Hyun-Joo Koo, Je Seung Lee* and Hoon Sik Kim*

Department of Chemistry and Research Institute of Basic Sciences, Kyung Hee University, 26 Kyungheedaero, Dongdaemun-gu, Seoul 02447, Republic of Korea
Tel: (+82)-2-961-0432; (+82)-2-961-0458
Fax: (+82)-2-959-6443; (+82)-2-961-0443
E-mail: khs2004@khu.ac.kr; leejs70@khu.ac.kr

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Abstract: Carboxylation reactions of diamines were found to proceed rapidly and non-catalytically, producing corresponding cyclic ureas in excellent yields and selectivities when 2-pyrrolidone (2-PY) was used as a solvent. A similar promoting effect with 2-PY was also observed for the carboxylation of monoamines by carbon dioxide (CO_2). Most notably, the carboxylation reactions of mono- and diamines conducted in 2-PY afforded 2-4 times higher yields of corresponding dialkyl ureas and cyclic ureas compared with those in *N*-methyl-2-pyrrolidone (NMP). Such a dramatic promoting effect using 2-PY is believed to be associated with the multiple hydrogen bonding interactions between 2-PY and the CO_2-containing species of amines. Due to such favorable interactions, carboxylation reactions seem to be more facilitated in 2-PY than in NMP.

Keywords: Cyclic ureas; CO_2 utilization; Diamines; Carboxylation; Tautomerization

Introduction

The direct carboxylation of diamines to cyclic ureas is considered to be one of the most promising routes for the transformation of carbon dioxide into valuable chemicals.[1] Of various cyclic ureas, ethylene urea (imidazolidin-2-one) finds uses as an organic intermediate in various chemical industries.[2] In particular, dimethylol ethylene urea, a condensation product of ethylene urea and formaldehyde, is used as an effective cross-linking agent for the treatment of cellulose-based fabrics and papers to inhibit wrinkle formation.[3] Ethylene urea is also used as a scavenging agent to reduce the free formaldehyde content in phenolic, melamine, glyoxal and urea formaldehyde resin systems for coatings, construction and textile industries.[4] Ethylene urea finds additional applications in the pharmaceutical industry; as an intermediate in the synthesis of a variety of new antibiotics, such as mezlocillin acid and azlocillin acid,[5] as an intermediate in anti-schistosomiasis drugs and as a basic material for the synthesis of third-generation penicillin derivatives.[6]

Cyclic ureas have been industrially manufactured by reacting diamines with urea under harsh conditions at around 250 °C, followed by quenching the resulting melt with water to give aqueous solutions containing the desired cyclic urea and NH_3.[7] However, the urea processes possess several drawbacks such as the formation of large amounts of water-insoluble by-products and the equipment corrosion arising from the handling of aqueous ammonia solutions.[8] Nonetheless, the urea process should not be disregarded because the process could be more competitive to other processes in terms of material cost and energy consumption.

Catalytic carboxylation processes employing CO_2 as a carbonyl source have also been investigated intensively.[1a,9] As a result, numerous homogeneous and heterogeneous catalysts and catalytic systems have been developed, including triphenylantimony oxide/phosphorous pentasulfide (Ph_3SbO/P_4S_{10}), tetramethylphenylguanidine/diphenylphosphoryl azide (PhTMG/DPPA), tungsten-based polyoxometalates ($TBA_2[WO_4]$), potassium hydroxide/polyethylene glycol (MW = 1000), and activated CeO_2.[1a,9b,9d-9f] However, most of the catalysts reported so far need further improvement with regard to the activity, stability and/or recyclability for their practical applications. Non-catalytic carboxylation processes have also been attempted, but they often require harsh reaction conditions to obtain reasonable cyclic urea yields, including high temperature of around 250 °C as well as high pressures.[2b,10]

Recently, we have reported that alkali metal carbonates and alkali metal bicarbonates are also effective catalysts for the synthesis of cyclic ureas

[1] These authors equally contributed.

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from the carboxylation of diamines in *N*-methyl-2-pyrrolidone (NMP), and the yields of cyclic ureas can be greatly enhanced by the addition of small amounts of ethylene urea as a promoter. Computational calculations suggest that catalyst-assisted keto-enol tautomerization of the ethylene urea is responsible for the increase of the cyclic urea yields.[11]

Being motivated by this result, we have investigated the effects of various tautomerizable compounds on the carboxylation of diamines. In this work, we report that cyclic ureas can be obtained in high yields and selectivities from the non-catalytic carboxylation of diamines using 2-pyrrolidone (2-PY) as a solvent.

Results and Discussion

Synthesis of cyclic ureas

The non-catalytic carboxylations of ethylene diamine (EDA) by CO_2 were conducted in various solvents at 200 °C and 5 MPa for 2 h. As shown in Table 1, the carboxylation of EDA in NMP produced ethylene urea in a yield of 21.1%. Surprisingly, the yield of ethylene urea increased dramatically by about 4 times from 21.1 to 83.0% when 2-PY was used as the solvent instead of NMP. The ethylene urea yield of 83.0% is even 9.6% higher than the yield achieved from the catalytic carboxylation reaction conducted in NMP using Cs_2CO_3, one of the most active carboxylation catalysts currently known (Table 1, entry 3). The yield of ethylene urea was further increased when the carboxylation of EDA was conducted in 2-PY with a catalyst. For instance, as can be seen in Table 1, the carboxylation of EDA in 2-PY proceeded almost quantitatively in the presence of K_2CO_3 or Cs_2CO_3, affording ethylene urea in yields of 98.1 and 99.0%, respectively (entries 9 and 10).

Table 1. Effect of solvent on the carboxylation reaction of mono- and diamines by CO_2.[a]

Entry	Solvent	Amine	Catalyst	Cyclic urea yield (%)
1	NMP	EDA	-	21.1
2		EDA[b]	K_2CO_3	48.2
3		EDA[b]	Cs_2CO_3	73.4
4		1,2-PDA	-	33.5
5		1,3-PDA	-	34.1
6		*n*-BA[c]	-	8.8
7		CHA[c]	-	2.5
8	2-PY	EDA	-	83.0
9		EDA[b]	K_2CO_3	98.1
10		EDA[b]	Cs_2CO_3	99.0
11		1,2-PDA	-	93.3
12		1,3-PDA	-	95.1
13		*n*-BA[c]	-	37.0
14		CHA[c]	-	16.0
15	CH_3OH	EDA[b]	K_2CO_3	5.8
16		1,2-PDA[b]	K_2CO_3	6.7

[a] Reaction condition: amine (100 mmol), P_{CO2} = 5 MPa, reaction temperature = 200 °C, reaction time = 2 h.
[b] Molar ratio of diamine/catalyst was set at 100.
[c] Reaction temperature = 170 °C, reaction time = 4 h.

Carboxylation of different amines

The carboxylation reactions of two propanediamine (PDA) isomers, 1,2-propanediamine (1,2-PDA) and 1,3-propanediamine (1,3-PDA), were also conducted in NMP and 2-PY at 200 °C for 2 h. As with EDA, the promoting effect of 2-PY was also observed in the carboxylation of 1,2-PDA and 1,3-PDA, yielding 4-methylimidazolidin-2-one and 1,3-diazinan-2-one, respectively. As shown in Table 1, the yields of 4-methylimidazolidin-2-one and 1,3-diazinan-2-one were found to increase from 33.5 and 34.1% to 93.3 and 95.1%, respectively when NMP was replaced by 2-PY (entries 4, 5 and 11, 12).

The promoting effect of 2-PY was further demonstrated in the carboxylation of monoamines. The carboxylation reactions of *n*-butylamine (*n*-BA) and cyclohexylamine (CHA) in NMP at 170 °C produced the corresponding dialkylureas, 1,3-dibutylurea and 1,3-dicyclohexylurea, in low yields of 8.8 and 2.5%, respectively (entries 6 and 7). In contrast, the yields of 1,3-dibutylurea and 1,3-dicyclohexylurea increased to 37.0 and 16.0%, respectively (entries 13 and 14) in 2-PY, confirming the beneficial role of 2-PY in the carboxylation of amines.

Spectroscopic investigation

To understand the excellent promoting effect of 2-PY on the carboxylation of diamines, the CO_2 absorption behavior of a diamines in 2-PY and NMP was investigated. To this end, 1,2-PDA is chosen as the diamine because its CO_2 adduct (**I**) is highly soluble

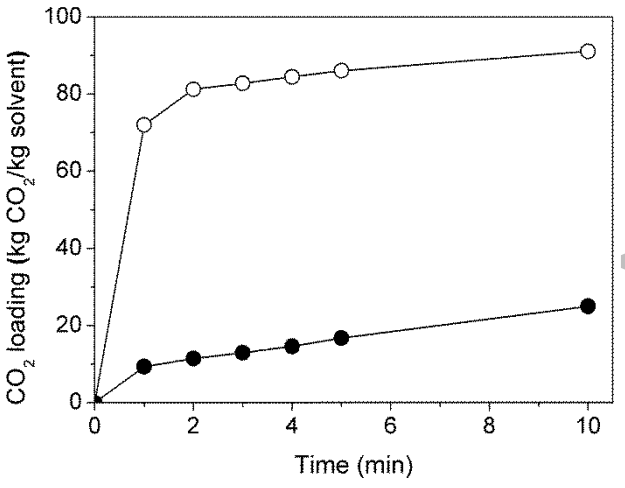

Figure 1. CO_2 absorption capacities of 1,2-PDA at 313 K and at 30 kPa CO_2 in NMP (-●-), and 2-PY (-○-).

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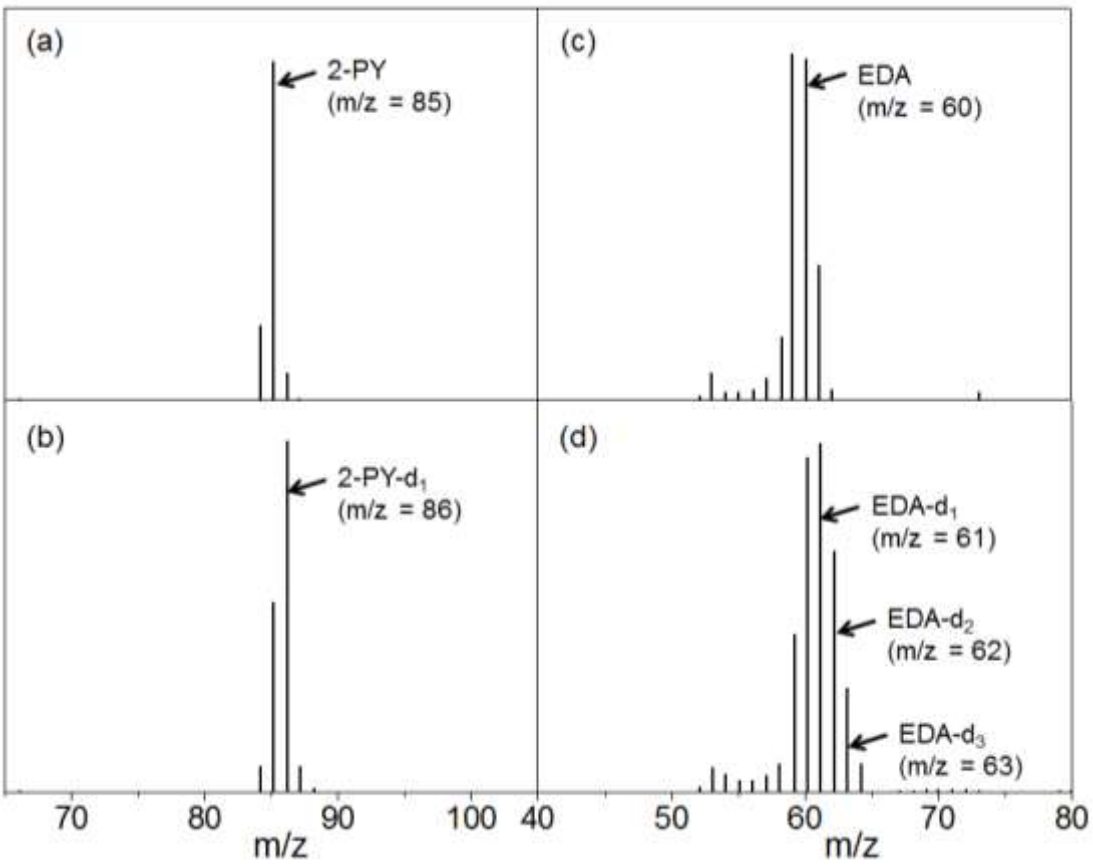

Figure 2. GC-Mass spectra of (a) 2-PY, (b) 2-PY-d_1, (c) EDA, and (d) EDA-d_x.

in 2-PY although its solubility in NMP is rather poor. As can be seen in Figure 1, the CO_2 absorption rate in a solution of 20wt.% 1,2-PDA in 2-PY was much faster than that observed in NMP. The CO_2 absorption capacity of the 1,2-PDA solution in 2-PY was also higher than that in NMP. Notably, the 1,2-PDA solution in 2-PY was transformed into a homogeneous, viscous solution upon absorption of CO_2, whereas the NMP solution of 1,2-PDA became turbid soon after contact with CO_2, generating insoluble gels (see Figure S1 in Supporting Information, SI). The only structural difference between 2-PY and NMP is that 2-PY has a protic hydrogen atom bonded to the nitrogen atom, whereas NMP possesses a methyl group bound to the nitrogen atom. Therefore, we infer that the N-H hydrogen atom of 2-PY is responsible for the higher CO_2 absorption rate and capacity in 2-PY than observed in NMP.

To gain a profound understanding of the role of 2-PY during the CO_2 absorption, kinetic isotope effect (k_H/k_D) was studied. (see Figure S42 and S43 in SI). As expected, the CO_2 absorption rate in a 1,2-PDA solution in deuterated 2-PY was significantly slower than that in un-deuterated 2-PY. It is likely that the N-H hydrogen atom of 2-PY contributes to the formation and stabilization of the carbonation species (**I**), possibly through a hydrogen bonding network. The plot of 1/[1,2-PDA] (where, [1,2-PDA] is the molarity of 1,2-PDA) versus time gives a straight line, indicating that the reaction of CO_2 with 1,2-PDA in 2-PY is a second order process with respect to [1,2-PDA] (see Figure S43 in SI). The rate constant for each absorption was obtained from the slope of the corresponding straight line, and deuterium kinetic isotope effect (k_H/k_D) for CO_2 absorption was calculated as 1.61.

The proton mobility of the N-H hydrogen atom of 2-PY was investigated by gas chromatography-mass spectrometry (GC-Mass). For this purpose, deuterated 2-PY (2-PY-d_1) and deuterated EDA (EDA-d_x, x = 1 ~ 4) were synthesized by allowing D_2O to interact with 2-PY and EDA for 2 h, respectively. As shown in Figure 2, deuterium incorporation into EDA was clearly observed after 2-PY-d_1 interacted with EDA. Such H-D exchange was also found to take place for the interaction between EDA-d_x and 2-PY (see Figure 2). H-D exchange studies with deuterated 2-PY and EDA using mass spectrometry demonstrate that 2-PY is capable of forming a hydrogen bond network through its peptide group, which could be beneficial to the carboxylation reaction of EDA. As expected, deuterium incorporation was not observed when D_2O was allowed to interact with NMP, which does not

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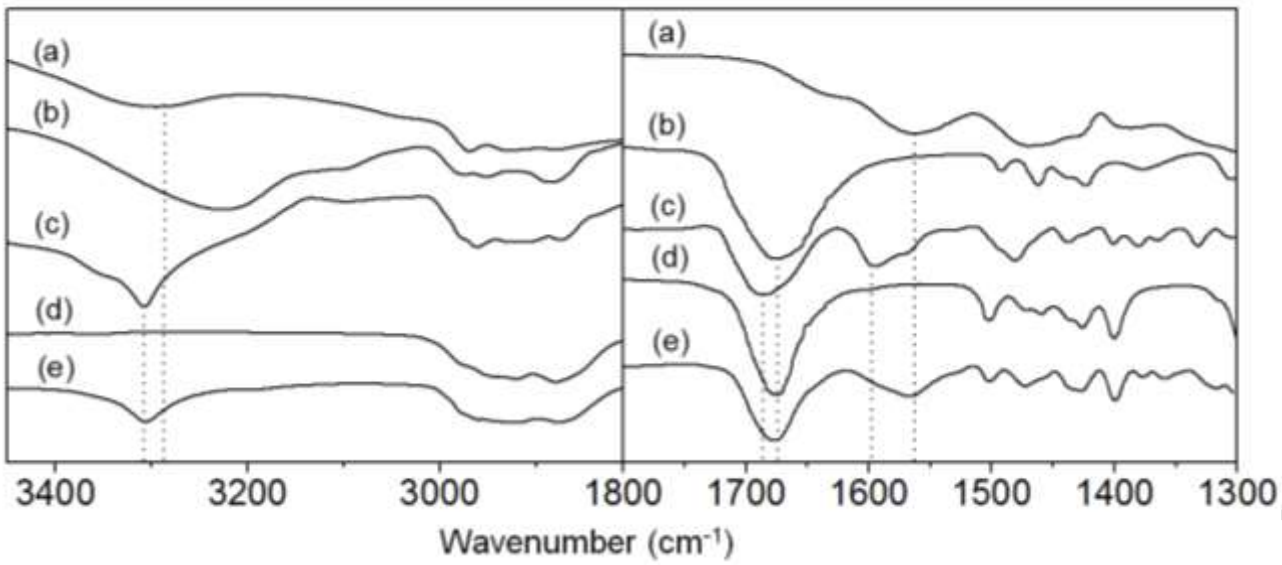

Figure 3. FT-IR spectra of (a) **I**, (b) 2-PY, (c) 20wt% **I** in 2-PY, (d) NMP, and (e) 20wt% **I** mixed with NMP.

possess a protic hydrogen atom. The GC-Mass results again support that the presence of the protic N-H hydrogen atom of 2-PY contributes to the acceleration of the carboxylation of amines. However, the yield of ethylene urea in a protic solvent, methanol was found to be extremely low below 7% even in the presence of a catalyst (Table 1, entries 15 and 16). These results strongly suggest that the presence of a labile proton in a solvent molecule is necessary, but not sufficient to be a good solvent for the carboxylation of diamines.[11] Comparison of the reactivity of EDA in methanol, NMP, and 2-PY reveals that the solvent of choice for carboxylation should be the one which possesses both proton donating and a proton accepting functional groups. In this context, cyclic amides bearing a peptide group could be regarded as effective solvents because they are able to function as proton shuttles through tautomerization. Among various cyclic amides, 2-PY is of particular interest because it is an inexpensive and thermally stable liquid. It has been reported that 2-PY can exist as a tautomer although the equilibrium constant for the keto to enol transformation is extremely low at room temperature (*vide infra*). Nevertheless, such a keto to enol transformation would be highly beneficial for the carboxylation of diamines, especially when 2-PY is present in large quantities at high temperatures (around 200 ºC) because the enol form of 2-PY can function as a better proton donor than the keto form. The promoting effect of 2-PY would be more pronounced if the enol form is stabilized by a carbonation species like **I**. It is worth mentioning here that the carboxylation of EDA to ethylene urea proceeds through a series of protonation-deprotonation steps.[11,12] Therefore, the stabilization of the enol form would enhance the proton donating ability of 2-PY to a certain extent, thereby facilitating the carboxylation of diamines and leading to cyclic ureas.

The hydrogen bonding interaction of 2-PY with the carbonation species (**I**) was further investigated by FT-IR spectroscopy. Figures 3(a) - (e) are the IR spectra revealing interactions of **I** with 2-PY and NMP. The absorption peaks at 1560 cm^{-1} in Figure 3(a) and 1675 cm^{-1} in Figure 3(b) can be assigned to the carbonyl stretching frequencies of **I** and 2-PY, respectively. Upon dissolution of 20wt% **I** in 2-PY, the carbonyl peak of **I** shifted by 35 cm^{-1} to a higher frequency at 1595 cm^{-1}. The carbonyl peak of 2-PY also moved by 12 cm^{-1} to a higher frequency at 1687 cm^{-1}, demonstrating strong interactions between **I** and 2-PY.

A similar phenomenon was also observed for the N-H absorption peaks of **I** and 2-PY. As shown in Figure 3, the peaks associated with the N-H stretching frequencies of **I** at 3296 cm^{-1} was found to shift to a higher frequency of 3307 cm^{-1}. These results indicate that there are multiple hydrogen bonding interactions between the ammonium group of **I** and the carbonyl group of 2-PY as well as between the carbonyl groups of **I** and the N-H group of 2-PY. This might suggest that the presence of a CO_2 adduct of a diamine like **I** could assist the migration of a H atom from the N-H to the carbonyl group of 2-PY. In other words, keto to enol transformation of 2-PY may proceed via interaction with **I**. Interestingly, the peak associated with the N-H stretching frequency of **I** was found to shift to a higher frequency with increasing temperature, implying that the degree of hydrogen bonding interaction between the ammonium group of **I** and the carbonyl group of 2-PY increases with increasing temperature (see Figure S3 in SI).

The carbonyl peak of **I** also shifted to a higher frequency at 1567 cm^{-1} upon dissolution of **I** in NMP as shown in Figure 3(e). However, as predicted from

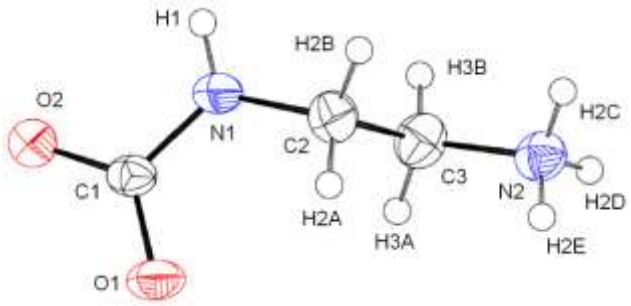

Figure 4. ORTEP drawing of the crystal structure of the 1:1 CO_2 adduct of EDA (**II**) displayed with thermal ellipsoids at 50% probability levels.

Scheme 1. Keto-enol tautomerization of 2-PY.

the significantly lower yield of cyclic ureas in NMP compared with that obtained in 2-PY, the extent of the peak shift was only 7 cm^{-1}, which is about one fifth of the value observed upon interaction with 2-PY.

Mechanistic consideration

EDA is known to react rapidly with CO_2, forming the zwitterionic carbamate species (**II**).[11] We have also confirmed the formation of **II** by X-ray crystallography and ^{13}C NMR spectroscopy. The crystal structure of **II** is shown in Figure 4 (see also Figure S4 and Tables S1-S3 in SI). The ^{13}C NMR spectrum of the crystals shows a characteristic peak at 164.5 ppm assignable to carbamate species (see Figure S15 in SI).

Two possible mechanisms can be proposed for the formation of cyclic urea from **II**: (**A**) nucleophilic attack of the amino group on the carbamate carbonyl carbon atom followed by the loss of water[12] and (**B**) the formation of an isocyanate intermediate from the carbamate by elimination of water followed by a nucleophilic attack of the amino group on the carbonyl carbon of the isocyanate intermediate.[13]

For the intramolecular nucleophilic attack of the second amine on the carbamate, **II** needs to be transformed into a neutral carbamic acid form (**III**) via a proton transfer from the ammonium cation (-NH_3^+) to the carboxylate anion (-CO_2^-), thereby enabling the nucleophilic attack of the amino group on the carbonyl group. However, the intramolecular proton transfer from ammonium to carbamate is not an easy process .

Such proton transfer can be facilitated in the presence of a base catalyst, which is capable of functioning as a proton shuttle.[11,14] In this context, alkali metal salts with a multivalent anion such as carbonate, bicarbonate, or phosphate anion can be regarded as the catalysts of choice because they can simultaneously accept and donate a proton from the carbonation species like **I** and **II**. However, for non-catalytic carboxylation reactions to take place smoothly, a solvent must play a role in assisting the proton transfer. The importance of a proton transfer in the carboxylation of amines is well described in the literature.[11,15] In this context, 2-PY, a five membered cyclic molecule, can be considered one of the most appropriate solvents because 2-PYcontains a peptide moiety (HN-C=O) comprising an acidic N-H proton and a basic C=O group, that can act as a proton donor and an acceptor, respectively. Therefore, 2-PY is capable of functioning as a proton shuttle. The proton transfer effect of 2-PY would be more pronounced if it could exist in an enol form. 2-PY is known to exist as a keto-enol tautomer through the migration of a labile N-H hydrogen atom from the ring nitrogen or oxygen atom as shown in Scheme 1, however, the equilibrium constant toward the enol form is calculated to be as low as 1.45×10^{-7} at 300 K.[16] Nonetheless, the equilibrium constant is expected to be greatly increased if the enol form of 2-PY is stabilized by a carbonation species like **I** or **II**.

If the presence of a N-H hydrogen atom is responsible for the outstanding performance of 2-PY as a promoter, the replacement of the N-H hydrogen atom by a deuterium atom is expected to decelerate the carboxylation rate of EDA at the early stage of the reaction. In this context, kinetic isotope effect was measured for the carboxylation of EDA using deuterated and un-deuterated 2-PY. The amount of ethylene urea (EU) produced in deuterated 2-PY was smaller than that in un-deuterated 2-PY during the period of reaction time up to 7 min, but became closer thereafter (see Figure S44 in SI). As shown in Figure S45 in SI, the plot of ln([EU]) versus time (s) gives straight lines. The rate constants for the carboxylation were obtained from the slopes of the straight lines. The deuterium kinetic isotope effect (k_H/k_D) was calculated as 0.89, demonstrating the involvement of N-H hydrogen atom in the carboxylation of EDA to ethylene urea at least to some extent. Although the kinetic isotope effect is not strong, the effect is still considered significant for a solvent. Such a small kinetic isotope effect is often observed for the reaction proceeded by a S_N2 mechanism.[17]

Computational calculations

To develop a better understanding of the promoting role of 2-PY, the synthesis of ethylene urea from the non-catalytic carboxylation of EDA in the presence of 2-PY was investigated by computational methods (Figure 5). As mentioned above, 2-PY could exist as a tautomer, but the equilibrium shift toward the enol form is negligible under normal conditions.[16b,16c] Therefore, calculation was more focused on the possible formation and stabilization of the enolate

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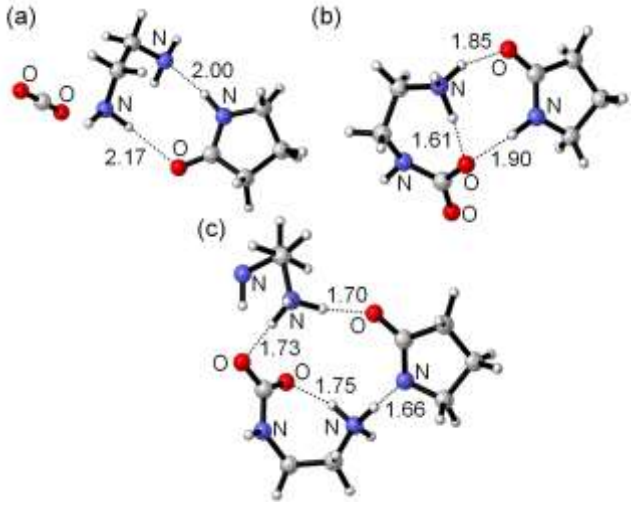

Figure 5. Optimized structures showing the interactions of EDA with CO_2 and 2-PY: (a) starting (ΔG = 0 kcal mol^{-1}), (b) **II** + 2-PY (keto form, ΔG = -6.8 kcal mol^{-1}), and (c) **II** + 2-PY + EDA (enolate species, ΔG = 10.3 kcal mol^{-1}).

species of 2-PY through the interaction with **II** and EDA. The enol form of 2-PY is highly unstable and thus it is reasonable to assume that the enol form would transform into ammonium enolate species as soon as it forms by reacting with free amine like EDA. As shown in Figure 5(b), the peptide functional group of 2-PY in its keto form is found to interact strongly with both the ammonium (-NH_3^+) and carbamate (-CO_2^-) groups of **II** via multi hydrogen bonding interactions.

The Gibbs free energy of formation (ΔG) for the interaction of the keto form of 2-PY with **II** to generate an intermediate species, $\mathbf{I_{1K}}$ was calculated as -6.8 kcal mol^{-1}. Interestingly, as shown in Figure 5(c), the intermediate species, $\mathbf{I_{1K}}$ can be transformed into an enolate species, $\mathbf{I_{1E}}$ upon interaction with another molecule of EDA. The Gibbs free energy of formation (ΔG) for the generation of the enolate species ($\mathbf{I_{1E}}$) was calculated as 10.3 kcal mol^{-1}. It has been reported that the equilibrium constant for the tautomerization of 2-PY is increased by 287 times from 1.45 × 10^{-7} to 4.16 × 10^{-5} when the temperature is raised from 27 to 187 °C.[16c] Therefore, it is expected that a ΔG of 17.1 kcal mol^{-1} for transformation of 2-PY from keto to enolate species could easily be overcome at an elevated reaction temperature around 200 °C. Once the enolate species, $\mathbf{I_{1E}}$ is generated, proton transfer can take place more effectively, thereby facilitating the nucleophilic attack and water removal processes.

As mentioned above, two pathways, **A** and **B** were considered in the calculations for the synthesis of ethylene urea from the carboxylation in 2-PY. The optimized structures of the intermediates and transition states for pathways **A** and **B** are shown in Figures 6 and 7, respectively. The energy profiles for both pathways are depicted in Figure 8. For both pathways, the formation of the enolate intermediate

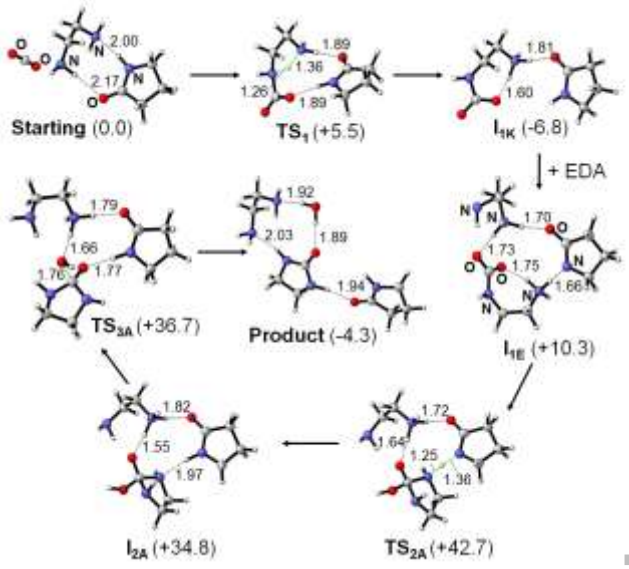

Figure 6. Optimized structures of intermediates, transition states and product involved in pathway **A**. The numbers in parenthesis are the Gibbs free energy of formation (ΔG) and transition state energy ($\Delta G^{\ddagger}$) are relative values with respect to that of the reactant complex (energies are in kcal mol^{-1}).

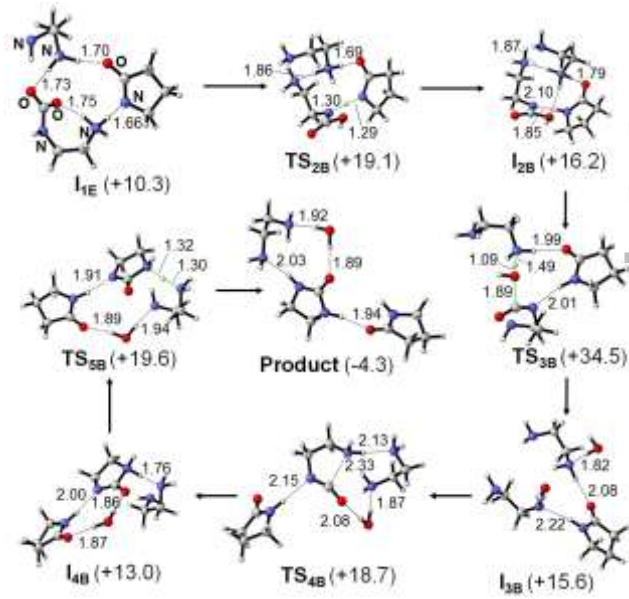

Figure 7. Optimized structures of intermediates, transition states and product involved in pathway **B**. The numbers in parenthesis are the Gibbs free energy of formation (ΔG) and transition state energy ($\Delta G^{\ddagger}$) are relative values with respect to that of the reactant complex (energies are in kcal mol^{-1}).

species, $\mathbf{I_{1E}}$ is likely to be the first step.

For the formation of ethylene urea via the pathway **A**, the intramolecular nucleophilic attack of the amino group on the carbamate carbonyl carbon atom should take place to generate a five membered ring intermediate species ($\mathbf{I_{2A}}$) where 2-PY exists as a keto form (Figure 6). The driving force for the nucleophilic

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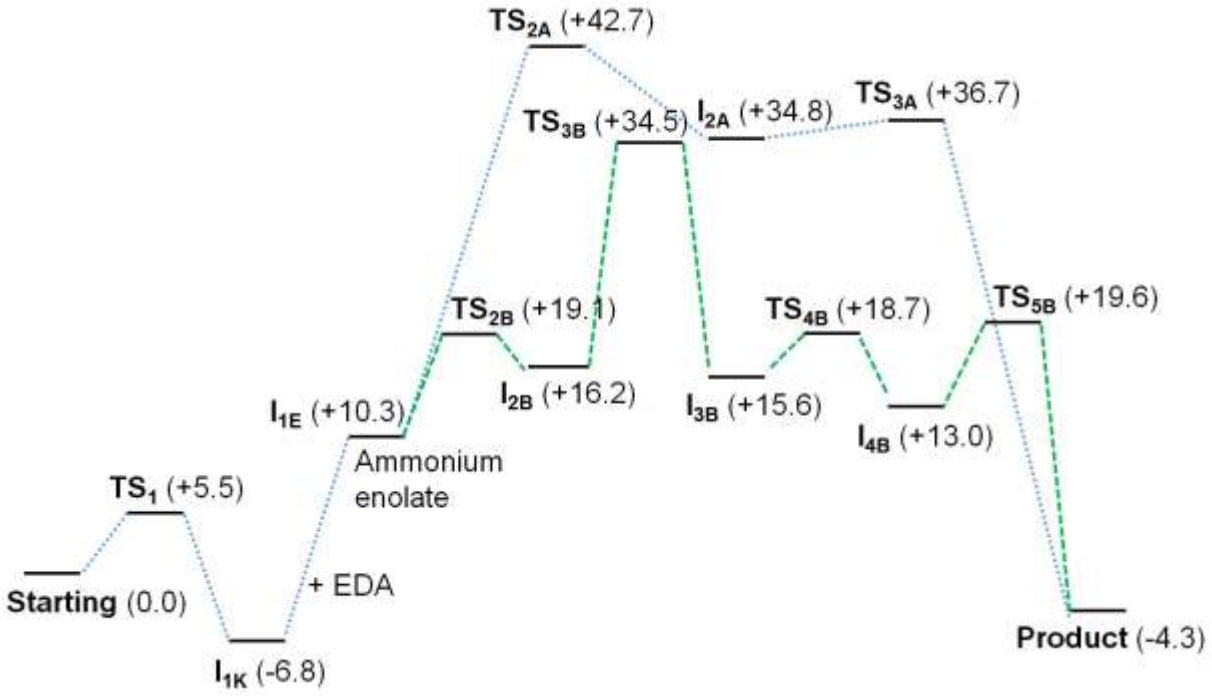

Figure 8. Reaction profiles of pathways **A** and **B**. The numbers in parenthesis are the Gibbs free energy of formation (ΔG) and transition state energy ($\Delta G^{\ddagger}$) are relative values with respect to that of the reactant complex (energies are in kcal mol^{-1}).

attack would be the proton transfer from the ammonium moiety of **II** to the nitrogen atom of the enolate species of 2-PY as well as the interaction of the ammonium cation of $[EDAH]^+$ with the carbamate anion via the transformation of 2-PY from the keto form to enolate species. Through such multi hydrogen bonding interactions, the electron density on the carbamate anion of **II** can be greatly reduced and the the nucleophilic attack of the amino group can be substantialized. The Gibbs free energies of the transition state (**TS_{2A}**) and intermediate species (**I_{2A}**) for this step were calculated as 42.7 and 34.8 kcal mol^{-1}, respectively. Further proton transfer from the ammonium cation to the ring moiety followed by the loss of water would produce the product along with the generation of EDA. The Gibbs free energies of the transition state (**TS_{3A}**) and the product were calculated as 36.7 and -4.3 kcal mol^{-1}, respectively. Based on the calculated energies, nucleophilic attack can be considered the rate determining step for the pathway **A**. However, the activation energy of 42.7 kcal mol^{-1} for **TS_{2A}** seems to be rather high for the nucleophilic attack to take place. Nonetheless, pathway **A** should not be ruled out because the reaction temperature at around 200 ºC is sufficiently high to overcome the activation barrier.

Figure 7 shows the optimized structures of transition states and intermediates involved in the formation of ethylene urea via the pathway **B**. Unlike the pathway **A**, the nucleophilic attack on the anionic carbamate is not necessary, and thus the primary role of the enolate species is to assist the intramolecular proton transfer from the ammonium moiety to the carbamate carbonyl carbon of **II** while simultaneously subtracting the N-H hydrogen atom bonded to the carbonyl group. The Gibbs free energies of the transition state (**TS_{2B}**) and the intermediate species (**I_{2B}**) were calculated as 19.1 and 16.2 kcal mol^{-1}, respectively. Further proton transfer from the ammonium cation followed by the loss of water would produce isocyanate intermediate species along with the generation of keto form of 2-PY and EDA. The Gibbs free energies of the transition state (**TS_{3B}**) and the intermediate species (**I_{3B}**) were calculated as 34.5 and 15.6 kcal mol^{-1}, respectively. Subsequent intramolecular nucleophilic attack of the amino group on the carbonyl carbon of the isocyanate group followed by loss of water and proton transfers would generate the same product shown in pathway **A**. The Gibbs free energies of the transition state (**TS_{4B}** and **TS_{5B}**) and the intermediate species (**I_{4B}**) involved for these steps were calculated as 18.7 and 19.6 kcal mol^{-1} for the transition states and 13.0 kcal mol^{-1} for the intermediate species, respectively. The rate determining step is the formation of isocyanate intermediate species. Like in the pathway **A**, the driving force seems to be the reversible transformation of 2-PY from the keto form into enolate species.

Comparison of the energy profiles shown in Figure 8 for the pathways **A** and **B** strongly suggests that the pathway **B** involving the formation of an isocyanate intermediate species is more favorable than pathway **A**. For instance, Gibbs free energies for the third transition state (**TS_{3B}**) for the rate determining step of the pathway **B** is calculated as 8.2 kcal mol^{-1} lower than that of **TS_{2A}** for the pathway **A**.

Table 2. Effects of reaction temperature and pressure on the carboxylation of EDA by CO_2.[a]

Entry	Temperature (°C)	P_{CO2} (MPa)	Yield (%)[b]
1	150	5	2.8
2	160	5	9.5
3	170	5	22.0
4	180	5	48.1
5	190	5	73.6
6	200	2	80.4
7	200	5	83.0
8	200	7	83.8
9	200	10	84.3
10	210	5	79.7
11	220	5	77.4

[a] Reaction condition: EDA (100 mmol), solvent (2-Py, 20 mL), reaction time = 2 h.
[b] Yield of ethylene urea.

Effects of reaction temperature and CO_2 pressure

Table 2 shows the effect of reaction temperature on the synthesis of ethylene urea via the carboxylation of EDA conducted in 2-PY for 2 h in the temperature range of 150 – 220 °C. The yield of ethylene urea increased rapidly with the temperature rise up to 200 °C, and slightly decreased thereafter. No sign of side product formation was observed by GC or GC-Mass analysis up to 220 °C. This is in contrast to the reaction in NMP, which shows the formation of small amounts of side products above 200 °C.[11]

In contrast to the temperature effect, the yield of ethylene urea did not vary substantially with pressure change. As can be seen in Table 2, the yield of ethylene urea was found to increase by only 3.9% from 80.4 to 84.3% when the pressure was increased from 2 to 10 MPa.

Conclusion

The non-catalytic carboxylation of mono- and diamines was greatly facilitated when 2-PY was used as a solvent. In general, the carboxylation of mono- and diamines produced 3-8 times higher yields of corresponding dialkylureas and cyclic ureas than those obtained in NMP.

H-D exchange studies with 2-PY and EDA using mass spectrometry clearly demonstrate that 2-PY is capable of playing roles as a proton donor as well as a proton acceptor. 1,2-PDA was found to interact with CO_2 much more rapidly in 2-PY than in NMP, forming a 1:1 CO_2 adduct of 1,2-PDA (1,2-PDA-CO_2, **I**). The carbonation species **I** was completely soluble in 2-PY, forming a homogeneous solution. In contrast, the species **I** was only slightly soluble in NMP, implying that the species **I** interacts much more strongly with 2-PY than with NMP, possibly via multi hydrogen bonding interactions.

Kinetic studies with deuterated 2-PY clearly demonstrates that the proton transfer proceeds involving the N-H hydrogen atom of 2-PY, and the N-H hydrogen atom is responsible for the drastic increase of the yield of cyclic ureas in 2-PY. Computational calculations also suggest that 2-PY plays a pivotal role in the carboxylation of amines through a reversible transformation from the keto form into enolate species.

In summary, the carboxylation of mono- and diamines to produce corresponding dialkylureas and cyclic ureas can be greatly accelerated even in the absence of a catalyst by using a solvent possessing a peptide functional group, which is capable of functioning as both a proton donor and a proton acceptor.

Experimental Section

Chemicals

NMP, 2-PY, and diamines including EDA, 1,2-PDA, 1,3-PDA were purchased from Aldrich Chemical Co., and used as received. Carbon dioxide (purity > 99.9%) was obtained from Sin Yang Gas Co. and used without further purification.

Absorption of CO_2

CO_2 absorption experiments were conducted inside a chamber maintained at 313 K using a 90 mL glass pressure reaction vessel (Fischer-Porter bottle) equipped with an inlet and outlet valves, a pressure gauge, and a thermocouple (Figure S1 in SI). In a typical experiment, the glass vessel was loaded with 18 g of 20wt% 1,2-PDA solution in 2-PY or NMP. CO_2 was then introduced into the vessel at 30 kPa from a 150 mL CO_2 reservoir cylinder equipped with a pressure regulator and a transducer. The reservoir cylinder was located inside the chamber, and the initial temperature and pressure in the cylinder were set at 313 K and 3.4 MPa, respectively. The change of the pressure inside the cylinder with the progress of the CO_2 absorption was monitored, and the weight change upon absorption of CO_2 was measured at certain intervals using a balance (OHAUS, EP613C) with an accuracy of 0.001 g. A blank test was also conducted with 18 mL water to precisely determine the amount of CO_2 in a 20wt% 1,2-PDA solution of NMP or 2-PY. The interactions of **I** (CO_2 adduct of 1,2-PDA) with 2-PY and NMP were studied using FT-IR spectrometer (Nicolet iS10). H-D exchange studies with deuterated and undeuterated 2-PY and EDA were investigated by GC-Mass spectrometer (Agilent 6890-5973, HP-MS capillary column).

Carboxylation of Diamines

All the carboxylation experiments were conducted in a 100 mL stainless steel bomb reactor equipped with a thermocouple and an electrical heater. The reactor was loaded with an amine (100 mmol) and a solvent (20 mL), and flushed three times with CO_2. The reactor was then heated to a desired temperature

under pressure of 1.0 MPa CO_2. At a specified temperature, CO_2 pressure was further increased to 5.0 MPa and maintained throughout the reaction by means of a CO_2 reservoir equipped with a high pressure regulator and a pressure transducer. Reactions were carried out for various periods of time, after which the reactor was cooled to room temperature and then depressurized. The product mixture was analyzed by NMR spectrometer (400 MHz, Bruker) and the yields of cyclic ureas were quantified using 1,4-dioxane as an internal standard.

Kinetic isotope effect

The kinetic isotope effect for the carboxylation of EDA was measured using deuterated 2-PY. To this end, the carboxylation reaction of EDA was performed in a specially designed 10 mL tube reactor at 200 ºC and 5 MPa of CO_2 in 2-PY and deuterated 2-PY, respectively (Figure S2 in SI). The tube reactor was charged with 2.4 g of EDA and 5 mL of deuterated or un-deuterated 2-PY, and pressurized with 5 MPa of CO_2. The reactor was then immersed in an oil bath maintained at 200 ºC and stayed for a specified period of time. The product mixture was analyzed by NMR and GC-mass spectrometer.

Crystallographic Data and Packing Diagrams

A 90 mL glass pressure bottle (Fisher-Porter vessel) was loaded with 6 g of EDA solution in 20 mL of 2-pyrroridone and pressurized with 0.3 MPa CO_2 with a gentle stirring to afford zwitterionic carbamate compound (**II**) as white solid precipitates. The precipitates were collected by filtration, washed with methanol, and dried at room temperature under vacuum. Single crystals suitable for X-ray crystallography were grown by diffusing methanol into an aqueous solution of **II**. Single crystal X-ray diffraction data for zwitterionic carbamate species (**II)** were collected on a Bruker SMART APEXII diffractometer equipped with a CCD area detector using graphite monochromated MoKα radiation (λ = 0.71073 Å). Preliminary orientation matrix and cell parameters were determined from three sets of ω scans at different starting angles. Data frames were obtained at scan intervals of 0.5º with an exposure time of 10 s per frame at 296 K. The reflection data were corrected for Lorentz and polarization factors. Absorption corrections were carried out using SADABS.[18] The structures were solved by direct methods and refined by full-matrix least-squares analysis using anisotropic thermal parameters for non-hydrogen atoms with the SHELXTL program.[19] All hydrogen atoms were calculated at idealized positions and refined with the riding models.

Crystal Data for II

$C_3H_8N_2O_2$, M = 104.11, orthorhombic, a = 12.8206(8) Å, b = 4.8279(3) Å, c = 8.2645(5) Å, α = 90.00°, β = 90.00°, γ = 90.00°, V = 511.54(5) Å^3, T = 296 K, space group *Pna2(1)*, Z = 4, 3713 reflections measured, 1232 independent reflections (R_{int} = 0.0406). The final R_1 values were 0.0406 ($I > 2\sigma(I)$). The final $wR(F^2)$ values were 0.0804 ($I > 2\sigma(I)$). The final R_1 values were 0.0322 (all data). The final $wR(F^2)$ values were 0.0742 (all data). The goodness of fit on F^2 was 1.065.

CCDC-1851007 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Center via www.ccdc.cam.ac.uk/data_request/cif.

Quantum mechanical calculations

Computations were made on the interaction of 2-PY with the CO_2 adduct of EDA, **II** using Gaussian 09 software.[20] All the geometries were optimized with the hybrid Becke, three-parameter, Lee–Yang–Parr (B3LYP) exchange–correlation functional with the 6-31+G* basis set for C, H, N, and O, Optimized geometries were subjected to full frequency analyses at the same level of theory to verify the nature of the stationary points. Equilibrium geometries were characterized by the absence of imaginary frequencies. B3LYP enthalpy and entropy corrections were used for all thermodynamic corrections. The effect of bulk solvent was taken into account in the single point calculations through the self-consistent reaction field theory (SCRF) based on the Polarizable Continuum Model (IEFPCM-UFF) implemented in the Gaussian 09 program. Since 2-PY and NMP are not available in the program package, *N*,*N*-dimethylacetamide (DMAc) was used instead in the calculation.

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FULL PAPER

Highly Efficient Non-Catalytic Carboxylation of Diamines to Cyclic Ureas Using 2-Pyrrolidone as a Solvent and a Promoter

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Junhyeok Hwang, Donggu Han, Jin Joo Oh, Minserk Cheong, Hyun-Joo Koo, Je Seung Lee* and Hoon Sik Kim*