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CO_2/Water-Regulating Transamidation of Urea and Amines

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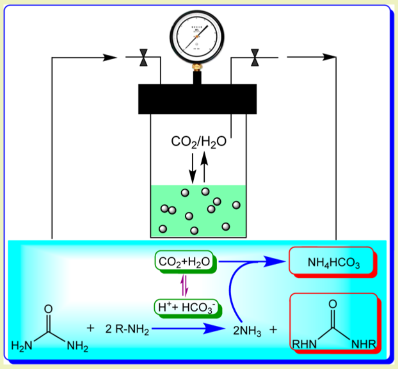
Supporting Information

ABSTRACT: The process of urea transamidation with amine to urea derivative has been developed in the presence of both carbon dioxide and water. Through the present reaction route, not only can the urea derivatives be obtained in high yield, but also inorganic salt ammonium bicarbonate (ABic) can be successfully isolated simultaneously from the reaction mixture. The phase behavior observed in situ by high pressure visual autoclave illustrated that the reaction occurred in biphasic conditions during the reaction. A number of verifying tests were conducted to investigate the role of carbon dioxide and water in the system. It was found that reaction temperature, total pressure, reaction time, and water played a crucial role in producing urea derivatives. The further investigation showed that the transamidation reaction between various amines and urea occurred successfully without the addition of any other catalysts in the presence of CO_2 and water. The acidity resulting from reaction of CO_2 with water facilitated the transamidation reaction.



KEYWORDS: *Carbon dioxide, Urea derivatives, Transamidation of urea, Ammonia scrubbing, Green chemistry*

INTRODUCTION

1,3-Disubstituted ureas and monosubstituted ureas, representative of an important class of carbonyl compounds, are significant subunits present in numerous naturally occurring compounds. They have found use in a wide variety of areas ranging from applications as dyes for cellulose fiber to the use as antioxidants in gasoline, corrosion inhibitors, and intermediates for the production of carbamates which represent raw materials for agrochemicals.[1] Several substituted ureas have also been reported to possess a marked inhibitory effect on HIV protease enzyme, which can be used for brain cancer treatment.[2] Trace amounts of urea derivatives have been shown to enhance photoreduction of nitrobenzene by catalyzing the rate-limiting proton transfer.[3]

Since Wöhler's synthesis of plain urea, numerous synthetic methods for the preparation of substituted ureas have been developed in recent years. The conventional synthetic routes of these compounds are phosgenation of amines, using highly toxic phosgene which is not environmental friendly. Over the last 80 years, a number of safer, milder, and easy-to-handle derivatives such as di*tert*-butyldicarbonate $(BOC)_2O$, bis(trichloromethyl) carbonate (BTC), dimethyl carbonate, ethylene carbonate, or methyl carbamate, have been utilized as alternative reagents to produce both symmetrical and unsymmetrical ureas, starting from primary amines.[4−8] However, they are too expensive to be cost-efficient. Further synthetic routes to substituted ureas involve noble metal[9−11] or transition metal-catalyzed carbonylation of amines with CO as the carbonyl source[12−14] and formation of ureas from CO_2 and amines via various catalysts.[15−21] Since the mixture of carbon monoxide and air is risky, CO_2 as a carbonyl source has been widely considered. Nevertheless, urea used as an activated form of CO_2 is easily available, cost-effective, and of low toxicity. Indeed, the transamidation of urea with amines into bis- or monosubstituted urea derivatives has been reported, and the process has been described as a new clean route that may be of significant value for the synthesis of a variety of urea derivatives with $Cu(OAc)_2$ as a catalyst.[22] In addition, a Brønsted acid such as concentrated H_2SO_4, hydrochloric acid, or Lewis acid such as $CeCl_3 \cdot 7H_2O/KI$ under conditions of microwave irradiation was used to catalyze the transamidation reaction and ammonia was released simultaneously during the reaction.[23]

As we have known, CO_2 in its liquid or supercritical state ($scCO_2$) is a very attractive medium because it has some unique features such as being nontoxic, nonflammable, abundant, cheap, and easily available.[24,25] In addition, a CO_2-tunable, biphasic, switchable solvent as a cleaner alternative to conventional solvent has been widely used.[26,27] It is also worth noting that the combination of CO_2 with water can afford acidity due to the formation and dissociation of carbonic acid, which could result in a low pH value of about 3.[28] Utilizing the binary system CO_2/water as a reaction and extraction medium has been of rising importance due to its advantages as a green solvent combination.[29] Furthermore, the CO_2/water system could replace conventional hazardous acids such as HCl and H_2SO_4 for the catalysis of some chemical reactions, and the solution can be easily neutralized by depressurization without requiring salt disposal.[30,31]

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On the basis of previous work, the present investigation focuses on synthesizing a series of urea derivatives directly from urea and organic amines and simultaneously obtaining ammonium bicarbonate (ABic) in the absence of other catalyst. CO_2/water media were found to act as a crucial acidic system to promote the first step reaction of urea and organic amine, and subsequently, ammonia released during reaction was captured in ABic by reacting with the compressed carbon dioxide and water. Through this approach, high value-added products like different types of urea derivatives and ABic can be obtained at the same time. Due to the obvious difference in chemical properties of organic urea derivatives and ABic, they could be easily isolated from reaction mixture only by solvent extraction. The present system makes full use of the acidity of CO_2 in water without adding other solid acid catalyst, and ammonia was transformed into ABic, leading to reducing pollutant emission.

EXPERIMENTAL SECTION

Materials. All chemicals were analytical grade and commercially available. They were used without further purification, unless otherwise stated. *N*-Butylamine (≥98.5%), *iso*-propylamine (≥98.0%%), and cyclohexylamine (≥98.5%) were obtained from Lingfeng Chemical Reagent Co., Ltd., Shanghai. CO_2 (>99.95%) and N_2 (>99.999%) were supplied by Shanghai Shangnong Gas Factory. All the other materials were obtained from SCRC (Sinopharm Chemical Reagent Co., Ltd., Shanghai).

GC analyses were performed on a Shimadzu GC-2014 apparatus equipped with a KB-50 column (30 m × 0.32 mm × 0.50 μm) and an FID detector. GC-MS analyses were conducted on Agilent-6890/GC-5973MS with a HP-5 column (30 m × 0.25 mm × 0.25 μm). All NMR spectra were recorded on a Bruker Avance III 400 instrument (400 MHz for ^{1}H, 100 MHz for ^{13}C) by using $CDCl_3$, D_2O, and [D_6]DMSO as solvents and TMS as reference. Chemical shifts (δ) are given in parts per million and coupling constants (J) in hertz. The elemental analysis of C, H, and N was performed on an Elementar Vario EI III Elementa. The UV/vis measurements were performed using a Varian Cary 500 spectrophotometer.

Methods. *N*-Butylamine (BA) was used as a model substrate. Organic products including 1,3-dibutylurea (DBU) and 1-butylurea (BU) were separated from inorganic salt ABic by extraction. The structure of the organic products was identified by ^{1}H NMR spectra and GC-MS. ABic was examined by ^{13}C NMR spectra and elemental analysis of C, H, and N. The absolute molar amounts (n_{DBU} or n_{BU}) were used throughout this work to denote the activity of the reaction (Supporting Information Figure 2S).

Nitrogen balance was determined in the reaction system (see the Supporting Information). The ammonia gas entrained in the CO_2 effluent was adsorbed by dilute sulphuric acid (0.025 M) to generate ammonium sulfate. The ammonium ion was then transformed into indophenol blue and analyzed quantitatively by UV/vis spectrophotometry.[32,33] Absorbance was measured in the wavelength of 697 nm, and the NH_3 concentration can be obtained according to the Beer–Lambert law. The amounts of organic compounds could be determined by GC analysis. Therefore, the total nitrogen after reaction can be gained by combining the amount of the organic compounds (BA, DBU, and BU) and the inorganic compounds (NH_3 and ABic) (Supporting Information Table 2S).

Observation of Phase Behavior. The phase behavior was directly observed during the whole reaction process by using a high pressure autoclave equipped with transparent glasses on opposite sides. The agitation was conducted by a magnetic stirring bar and a magnetic stirrer. The chamber of the autoclave is made of type 316 stainless steel, with tempered glasses on both sides to permit the passage of light, with an unobstructed view of the entire contents. Calibration of the vessel indicates a gross volume of 80 mL, and a working capacity of approximately 60 mL except for a glass liner tube. The unit can operate at a maximum temperature of 200 °C and a maximum pressure of 15 MPa.

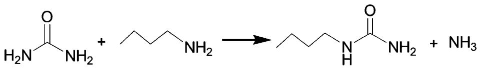
General Procedure for Catalytic Reactions. All reactions were performed in 50 mL stainless steel autoclaves with PTFE liner (working capacity of approximately 40 mL), equipped with pressure gauge and thermocouple. A typical reaction procedure for the synthesis of DBU from urea and BA in CO_2/water media is given as follows: 10 mmol urea was added to the solution containing 1.6 g BA (22 mmol) and 0.5 mL H_2O. The mixture was loaded into the autoclave equipped with a magnetic stirring bar. The reactor was closed and purged three times with dry CO_2. Then a certain amount of CO_2 was charged into the reactor to the desired pressure, and then the reactor was heated in a temperature-controlled heating jacket to the desired temperature. After the desired reaction time, the reaction was quenched by plunging the autoclave into cold water. CO_2 was released slowly by passing it through a cold trap containing ethyl acetate to absorb trace amounts of reactant and product entrained in the CO_2 stream.

Separation and Identification of Products. After depressurization, the reaction mixture in the reactor and ethyl acetate in the trap were transferred to a 25 mL vessel. Ethyl acetate (EA) was added to the mixture and then sonicated for 3 min whereby organic compounds were extracted into the EA phase while the crude inorganic products were insoluble and centrifuged to precipitate from the EA phase. The crude inorganic solid products were further washed with dichloromethane three times to wash off the residual carbamates or alkylammonium bicarbonate and dried overnight at room temperature. The dichloromethane phase was combined with the EA phase and then analyzed by GC and GC-MS to obtain n_{DBU} and n_{BU}. The organic phase was concentrated with rotary evaporator to afford the crude products, which were further chromatographed on silica gel column using 20% ethanol/petroleum ether as eluant. The purified organic compounds were subjected to ^{1}H NMR analysis. The as-obtained inorganic solids were analyzed by ^{13}C NMR spectra (D_2O as a solvent) and elemental analysis. All these results were shown in Figure 2b and c. For the sake of comparison, the pure urea was also treated under similar conditions and analyzed by ^{13}C NMR spectroscopy as well (Figure 2a).

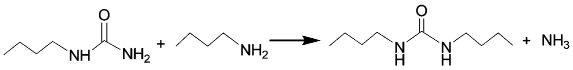
Safety Concerns. Solvents used (ethyl acetate, methylene chloride) should be used in a chemical fume hood and disposed of properly. Ammonia not fixed should be disposed of properly.

RESULTS AND DISCUSSION

In this work, the transamidation of urea with amine in pressurized CO_2/water media in the absence of any other additives has been investigated in detail. The possible reaction equations in the present reaction system are shown in eqs 1−1. Among them, the transamidation of urea with BA happened as indicated in eq 2, and in the meantime, the transformation of CO_2 with BA into DBU could take place as shown in eq 3. As we have known, in a ternary NH_3/CO_2/water system, the reaction equilibrium of 5−8 shifts to the right preferentially when the comparable amounts of CO_2 and NH_3 are present or an excess of CO_2 is loaded into the reaction system.[34,35]



(1)



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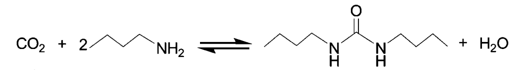

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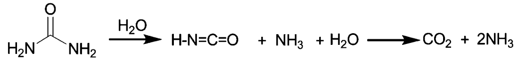


(4)

$$CO_2 + NH_3 + H_2O \rightarrow NH_4HCO_3 \tag{5}$$

$$CO_2 + H_2O \rightleftharpoons HCO_3^- + H^+ \tag{6}$$

$$HCO_3^- \rightleftharpoons CO_3^{2-} + H^+ \tag{7}$$

$$CO_2 + CO_3^{2-} + H_2O \rightleftharpoons 2HCO_3^- \tag{8}$$

The role of CO_2/water for the reaction was demonstrated, and the results were presented as follows.

Phase Behavior. The phase behavior of the reaction mixture was directly observed during the whole of reaction process by using a high pressure visual autoclave equipped with transparent glass. Figure 1 showed that the visual observations with temperature ranged from 25 to 170 °C at two different CO_2 densities (Figure 1a–h, low CO_2 density; Figure 1a′–h′, high CO_2 density). As shown in Figure 1, BA and water were miscible and the solution is transparent (Figure 1a), but when 15 mmol urea was added, the solid urea and a liquid phase coexisted (Figure 1b), which might result from the limited solubility of urea in the presence of a large of amount of BA. However, after the autoclave was purged three times with 0.1 MPa CO_2 and then charged with CO_2 up to 2.5 MPa at 25 °C, the solid urea disappeared and a colorless viscous liquid phase remained (Figure 1c). After further CO_2 addition at which the pressure reached up to 5.5 MPa at 170 °C, a vapor and a liquid phase could clearly be seen (Figure 1d and e). As shown in Figure 1f, some white solid product adhered at the reactor walls, which was suspended in the liquid phase through longer reaction times. Because DBU and BU should exist in a liquid state in the lower phase under the reaction conditions applied (melting points: 65 and 97 °C, respectively), the white solid formed is believed to be an inorganic solid (for identification, see the next paragraph). After the reaction mixture was cooled to 25 °C and depressurized, more solid products were accumulated on the inside wall or bottom of the liner (Figure 1g and h). On the other hand, if higher density CO_2 were initially charged at 25 °C (Figure 1a′), resulting in a total pressure of 7.0 MPa at 140 °C (Figure 1b′), a lot of bubbles appeared in the lower phase, indicating that chemically bonded CO_2 in the liquid phase is released into the gas phase at higher temperature. With the elevation of temperature, the pressure increased and the liquid phase was bubbled more violently (Figure 1c′ and d′). The pressure increased finally up to ca. 10.8 MPa after 2 h at 170 °C (Figure 1e′ and f′). However, the liquid phase was always transparent and no solid formed during the process, in contrast with that at lower CO_2 loading. After the reaction mixture was cooled to 25 °C, all the solid products were accumulated at the bottom of the liner (Figure 1g′). The solid was blown up during depressurizing which showed that the solid was quite light (Figure 1h′). From the visual observation under reaction conditions, it is very clear that the present reaction occurred in the two-phase condition. Inorganic solid was formed preferentially under lower pressure, which could be attributed to less ammonia being released under higher pressure.

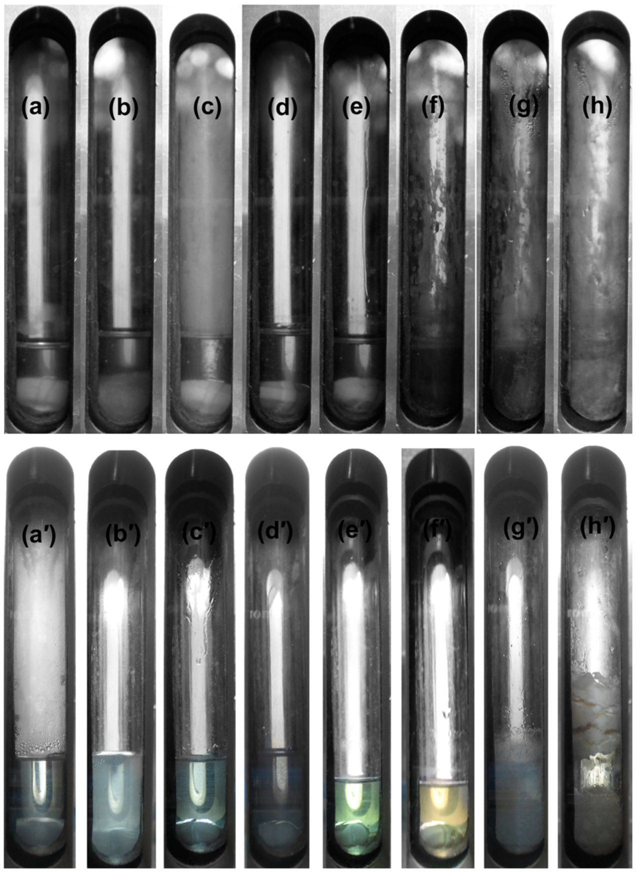


Figure 1. Visual observations of a reaction mixture containing urea, BA, H_2O, and CO_2 under reaction conditions, viewing the cell volume with a working volume of 60 mL, urea 15 mmol, BA 33 mmol, and H_2O 0.75 mL. CO_2 was charged at lesser amounts for a–h. (a) BA, H_2O, 25 °C; (b) BA, H_2O, urea, 25 °C; (c) BA, H_2O, urea, purging three times with 0.1 MPa CO_2 and then charged with CO_2 up to 2.5 MPa at 25 °C; (d) 5.5 MPa, 170 °C, 15 min; (e) 5.8 MPa, 170 °C, 2.0 h; (f) 5.8 MPa, 170 °C, 4 h; (g) 2.0 MPa, 25 °C, autoclave was cooled; (h) 0.1 MPa, 25 °C, CO_2 was released. For the sake of comparison, the only difference for a′–h′ was the greater loading of CO_2 in one batch at 25 °C. (a′) BA, H_2O, urea, 4.8 MPa, 25 °C; (b′) 7.0 MPa, 140 °C, 0.5 min; (c′) 8.0 MPa, 150 °C, 0.5 min; (d′) 10.0 MPa, 170 °C, 0.5 min; (e′) 10.8 MPa, 170 °C, 2 h; (f′) 11.0 MPa, 170 °C, 4 h; (g′) 3.8 MPa, 25 °C, autoclave was cooled; (h′) 0.1 MPa, 25 °C, CO_2 was released.

In order to identify the structure of inorganic solid, the inorganic solid was separated and then the ^{13}C NMR spectra were recorded with different reaction times. As shown in Figure 2a, when urea and water were treated for 10 h at 170 °C under N_2 atmosphere condition, two main distinct resonances appeared. The small signal at ca. 165.5 ppm can be attributed to the carbamate ion, while another resonance slightly shifted to lower frequencies ca. 161.0 ppm is ascribed to the carbon atoms of the carbonate and bicarbonate ions which are fast exchanging on the NMR time scale via proton scrambling.[36] From eqs 4 and 6, the reaction equilibrium shown in eqs 9 and 10 has been established in this case. However,

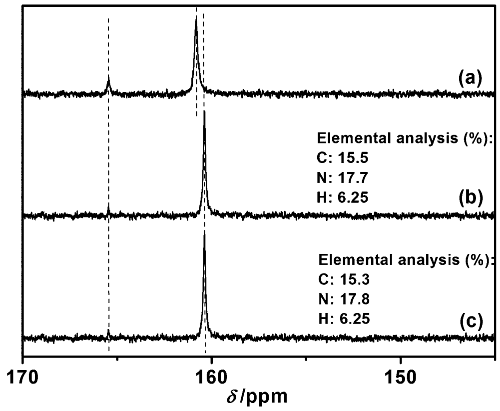


Figure 2. ^{13}C NMR spectra of the separated inorganic solids after reaction under different conditions: temperature 170 °C; 10 mmol Urea, 22 mmol BA, and 0.5 mL H_2O were added, repectively, if needed. (a) urea and H_2O, reaction time 10 h, N_2 pressure 4.9 MPa; (b) urea, BA and H_2O, reaction time 2 h, CO_2 pressure 4.9 MPa; (c) urea, BA, and H_2O, reaction time 10 h, CO_2 pressure 4.9 MPa.

Table 1. Transamidation of Urea and BA in the Presence of Conventional Brønsted and Lewis Acid Catalysts[a]

				substrates/mmol		products/mmol		
entry	catalysts	atmospheres	H_2O/mL	n_{Urea}	n_{BA}	n_{DBU}	n_{BU}	n_{abic}
1	none	N_2	0.5	10	22	2.8	0.03	trace
2	H_2SO_4	N_2	0.5	10	22	8.9	0.01	trace
3	$H_3PW_{12}O_{40}$	N_2	0.5	10	22	4.9	0.42	trace
4	$Zn(OAc)_2$	N_2	none	10	22	4.3	1.0	trace
5	$ZnBr_2$	N_2	none	10	22	3.8	0.64	trace
6[b]	none	CO_2	0.36[c]	none	22	1.4	0.3	8.1
7	none	CO_2	0.5	10	22	9.2	1.2	9.9

[a]Reaction conditions: Unless otherwise specified, all reactions were carried out in 50 mL stainless steel autoclaves. The total pressure was about all 4.9 MPa under reaction temperature 170 °C; reaction time 10 h. Unless otherwise specified, the amount of acids is 0.2 mmol. [b]The carbonylation reaction of BA with CO_2 in the presence of $NH_3 \cdot sH_2O$ (20 mmol). [c]Referred to the amount of H_2O contained in $NH_3 \cdot H_2O$ (30%).

$$NH_3 + HCO_3^- \rightleftharpoons NH_2CO_2^- + H_2O \qquad (9)$$

$$NH_3 + HCO_3^- \rightleftharpoons CO_3^{2-} + NH_4^+ \qquad (10)$$

when BA was added and the transamidation reaction happened. The separated inorganic solid exhibited one unique sharp resonance at ca. 160.4 ppm (Figure 2b and c). No other product was detected in the ^{13}C NMR spectra; in particular no biuret (δ = 158.1 ppm) and cyanuric acid (δ = 149.9 ppm) were detected.[37] The carbon atom of urea showed a signal at ca. 162.92 ppm in ^{13}C NMR,[38] while ABic afforded a single peak at 160.8 ppm,[36] and also the element analysis (EL) of the inorganic solids shown in Figure 2b and c was consistent with that of ABic. Combining the results of ^{13}C NMR and EL, we can see that no urea remained after 2 h and the separated inorganic solid was pure ABic. Meanwhile, it can be inferred that the present reaction process was mostly based on eqs 5−8. Furthermore, the nitrogen distribution for the products was determined. The NH_3 in CO_2 effluent for depressurization has been analyzed by Indophenol blue spectrophotometry (see the Supporting Information). The results showed that the distribution of total nitrogen contents in BA, DBU, BU, ABic, and NH_3 was over 95% (Supporting Information Table 2S, entries 1−3).

Transamidation Catalyzed by Acid Catalysts. The transamidation of urea was primarily carried out in the presence of conventional Brønsted and Lewis acids. The results were shown in Table 1. Under the N_2 atmosphere, the transamidation reaction of urea and amine showed poor activity without any catalyst (Table 1, entry 1). While typical Brønsted acid like sulfuric acid was quite efficient for the transamidation of urea (Table 1, entry 2), which afforded 8.9 mmol of DBU when 10 mmol of urea was used. Heteropoly acid ($H_3PW_{12}O_{40}$) and Lewis acids like $Zn(OAc)_2$ and $ZnBr_2$ showed lower activity than sulfuric acid toward producing DBU (Table 1, entries 3−5). It is also worthy of noting that when CO_2 and BA, together with $NH_3 \cdot H_2O$, were employed but no urea was present, n_{DBU} or n_{BU} was very low, which indicated the reaction of BA with CO_2 as shown in eq 3 happened hardly under the present conditions (Table 1, entry 6). However, a large amount of DBU, together with ABic was formed simultaneously in CO_2/water media in the absence of any other conventional acid (Table 1, entry 7). Carbon dioxide is a weak acid and may have the unfortunate side effect of forming carbamic acid and/or carbamate which takes away amine groups.[39] Hence, H_2SO_4 catalysis, without CO_2, gives near-complete conversion without formation of a carbamate, a substantially better result than that obtained with CO_2 (Table 1, entries 2 and 7). If a certain amount of water was absent or replaced by the organic solvents such as tetrahydrofuran (THF) or acetonitrile under the same conditions (Supporting Information Table 3S), the n_{DBU} dropped down considerably. This demonstrated that both water and CO_2 were crucial for the transamidation reaction.

Most importantly, water will contribute to in situ acid formation through the formation of carbonic acid soluble in the viscous liquid thereby promoting the transamidation reaction. In addition, water could adsorb ammonia formed in the process and CO_2 to produce ABic. On the other hand, water reacting with the carbamate salt may afford alkylammonium bicarbonate, which has been proven by ^1H NMR spectra. As shown in Figure 3, when BA was bubbled with CO_2 and was subjected to the analysis of ^1H NMR spectra directly, the chemical shifts of α-methylene protons are downfield (Figure 3b), implying that the primary amine group of BA has been protonated due to the formation of carbamate salt. Moreover, if CO_2 was charged

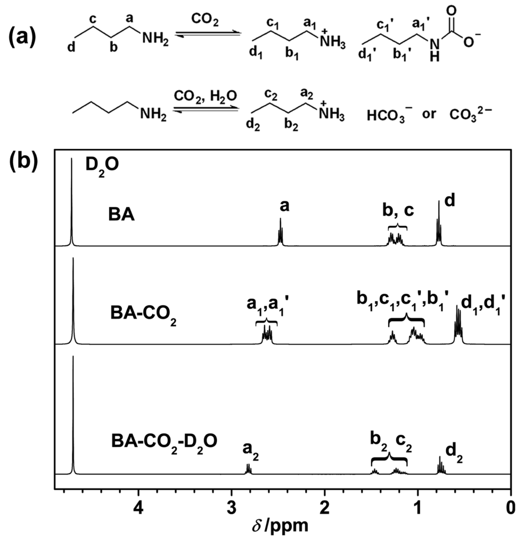
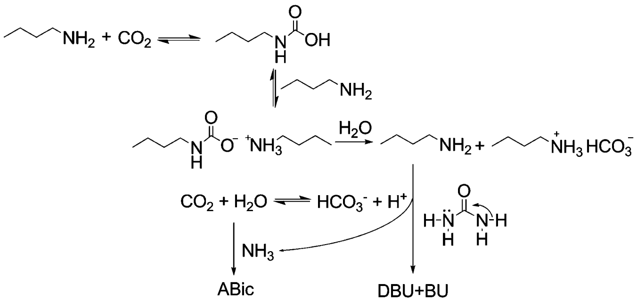


Figure 3. (a) CO_2-switchable chemical structure changes of BA. (b) Comparison of the ^1H NMR spectra of BA (22 mmol) before and after exposure to CO_2 and CO_2/D_2O (0.5 mL). The top line was the ^1H NMR of 1.0 M BA deuterium aqueous. The middle line denoted that, after BA was bubbled with CO_2 at 0.1 MPa for 30 min in Schlenk flask, the as-obtained white solid was dissolved in D_2O (1.0 M) for ^1H NMR analysis directly. The bottom line represented that after the BA and D_2O was mixed in 50 mL stainless steel autoclave with PTFE liner, CO_2 was charged into the autoclave and stirred continuously for 4 h. After CO_2 was released slowly, the as-obtained viscous liquid was diluted with D_2O and was subjected to ^1H NMR analysis.

into the mixture BA and D_2O, and then stirred for 4 h, the chemical shifts of α-methylene protons were further downfield, indicating that carbamate salt can be converted into alkylammonium bicarbonate after a longer reaction time.[40−42] On the basis of above discussion, the whole reaction route was shown in Scheme 1, which demonstrated that water played an important role in transformation of carbamate salt into more active alkylammonium bicarbonate.[43,44] Obviously, the current approach provided unique advantages over the conventional acidic catalysts, in that after reaction, CO_2 was released and then urea derivatives (mainly DBU), even ABic were separated and collected, respectively.

Scheme 1. Urea Transamidation with Amine with Binary CO_2/Water as Reaction Media



Reaction Parameters. In the next step, the transamidation of urea with BA was carried out in binary CO_2/water media. As shown in Figure 4, the overall reaction pressure was found to play a crucial role in producing DBU. The value of n_{DBU} increased with pressure with a maximum amount up to 9.2 mmol around 4.9 MPa, which is about three times higher than that without CO_2 (Table 1, entry 1). Nevertheless, n_{DBU} decreased sharply as the pressure exceeded 7.0 MPa. Higher CO_2 pressure (<7.0 MPa) would enhance the dissolution and adsorption of CO_2 in the lower phase, resulting in the reaction as illustrated in eqs 6 and 7,[45] where it was indicated that the concentration of carbonic acid was dependent on the amount of dissolved CO_2 and the dissociation of carbonic acid is the key step to produce acidity in the CO_2/water system.[46] Obviously, the reaction proceeded, smoothly catalyzed by the gradually enhanced acidity at lower pressure (<7.0 MPa). From the observed phase behavior, more addition of CO_2 led to the expanded volume and thus dilution of substrate in the liquid phase (Figure 1a′−d′), which decreased the activity of transamidation reaction. Additionally, higher density CO_2 will also lead to more formation of carbamic acid decreasing the nucleophilicity of the nitrogen atom and make it less reactive in reaction media.[39,47] Besides, increasing the amount of CO_2 will drive the formation of the carbonic acid but simultaneously reduce the dielectric constant of the lower liquid phase and thereby decrease acid dissociation.[28,48] Therefore, n_{DBU} decreased sharply under higher pressure. The results above indicated clearly that the pressure has a significant influence on the reaction activity. It should be noticed that reaction of CO_2 and amine may occur under the same conditions, and the results were also plotted in Figure 4, which indicated that n_{DBU} resulted from CO_2 and BA increasing monotonically with pressure below 6.0 MPa but leveling off above 6.0 MPa and only about 3.5 mmol of DBU was obtained under high pressure.

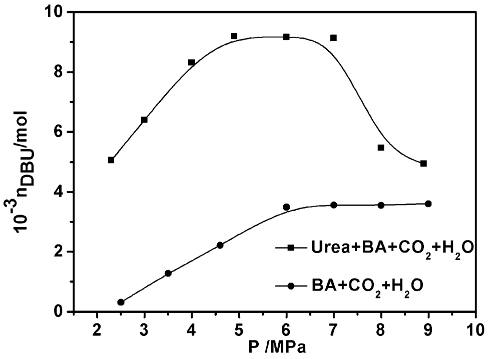


Figure 4. Effect of CO_2 pressure on n_{DBU}: urea 10 mmol; BA 22 mmol; H_2O 0.5 mL; time 10 h; temperature 170 °C.

Figure 5 showed that the n_{DBU} increased with temperature ranging from 120 to 180 °C along with the decrease of n_{BU}, from which it can be inferred that the lower temperature was favorable for the initial formation of BU and then the sequential reaction of BU with BA would result in producing DBU at a higher temperature. However, if the reaction was carried out at too high temperature (>170 °C), DBU was unstable and the reaction equilibrium was shifted to hydrolysis of DBU. Similarly, the hydrolysis of urea accompanied with condensation polymerization, such as formation of biuret, was more prone to happen at high temperature.[49] Considering the results in Figure 6, which showed that the n_{DBU} decreased if the reaction time was too long, we can infer that the product DBU would undergo successive reaction(s) itself at too high

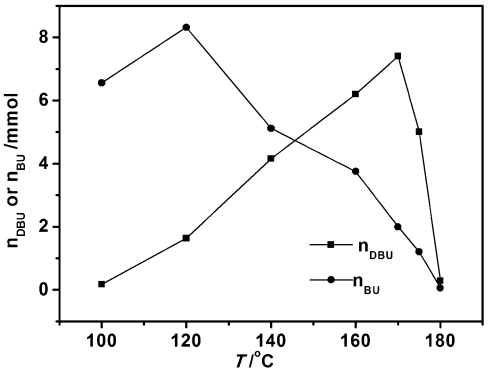


Figure 5. Effect of reaction temperature on n_{BU} and n_{DBU}: urea 10 mmol, H_2O 0.5 mL, time 10 h, BA 22 mmol, CO_2 pressure 3.5 MPa.

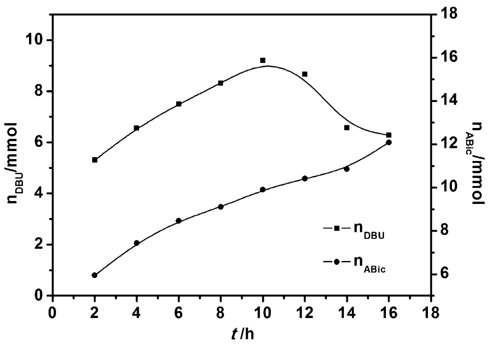
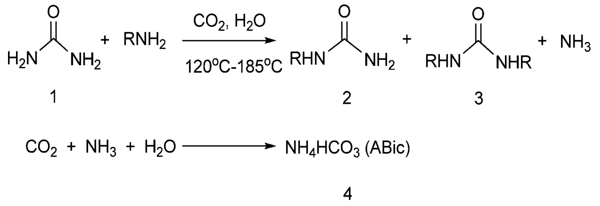
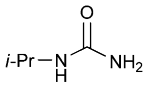
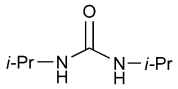
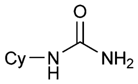
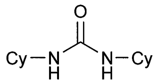
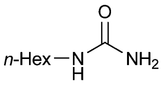
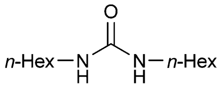
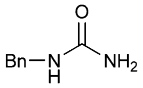
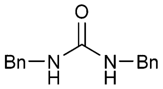
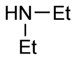
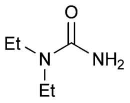
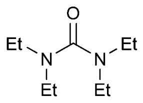


Figure 6. Values of n_{DBU} and n_{ABic} as functions of reaction time: urea 10 mmol, BA 22 mmol, H_2O 0.5 mL, temperature 170 °C, CO_2 pressure 4.9 MPa.

Table 2. CO_2-Catalyzed Transamidation of Urea with Other Amines[a]



Entry	Substrates	Products/ mmol [g]		n_{ABic}/ mol [h]
1[b]	*i*-Pr—NH_2 1a	 2a (5.7)	 3a (2.1)	5.4
2[c]	Cy—NH_2 1b	 2b (9.9)	 3b (1.67)	5.9
3[d]	*n*-Hex—NH_2 1c	 2c (Trace)	 3c (9.8)	11.3
4[e]	Bn—NH_2 1d	 2d (Trace)	 3d (9.9)	7.8
5[f]	 HN(Et)—Et 1e	 2e (none)	 3e (none)	9.1

[a] Reaction conditions: urea (10 mmol), amine (22 mmol), and H_2O (0.5 mL). [b] *iso*-Propylamine, 120 °C for 2 h with 4.6 MPa pressure. [c] Cyclohexylamine, 170 °C for 10 h with 4.8 MPa pressure. [d] *N*-Hexylamine, 170 °C for 10 h with 4.9 MPa pressure. [e] Benzylamine, 185 °C for 10 h with 5.0 MPa pressure. [f] Diethylamine, 170 °C for 10 h with 6.0 MPa pressure. [g] Data was obtained by GC. [h] ABic was precipitated by adding ethyl acetate and methylene chloride, and then it was isolated.

temperature or long time.[16] In addition, high temperature resulted in the decrease of CO_2 solubility in the expanded bottom phase,[50] which was unfavorable for the reaction. Hence, the appropriate temperature was required for the transamidation reaction to proceed to high activity within reasonable time.

As we have known, the amount of adsorbed CO_2 in amine solution is dependent on temperature, partial pressure of CO_2 in the gas phase, and the concentration of the amine.[51,52] The n_{DBU} and n_{ABic} were plotted as a function of reaction time in CO_2/water system under constant temperature and pressure (Figure 6). As shown in Figure 6, the n_{DBU} increased smoothly with the reaction time at the beginning of reaction and reached a maximum of 9.2 mmol at 10 h, while the n_{ABic} versus reaction time gradually increased all along within 16 h. Obviously, the formation of ABic was much slower than t1e generation of DBU. The amount of BA detected from the GC-MS increased with the decrease of n_{DBU} after 10 h indicating the hydrolysis of DBU for a long reaction time. Thus the optimized transamidation reaction conditions are ca. 170 °C, 4.9 MPa for 10 h.

Transamidation of Urea with Different Amines. Different amines such as linear or branched chain aliphatic amines, cyclohexylamine, and benzylamine were all employed for the transamidation reaction in CO_2/water system. The effect of temperature, time, and pressure on the reaction for different substrates has been screened, and the optimal reaction conditions were shown in Table 2. It was observed that the reactivity of branched chain *iso*-propylamine was the lowest and the main product was monosubstituted urea rather than bis-substituted urea (Table 2, entry 1). In addition, the reactivity of cyclohexylamine was quite good and the main product was also monosubstituted urea, although a small amount of bis-substituted urea was also present (Table 2, entry 2). Meanwhile, the *n*-hexylamine and benzylamine showed better reactivity and the dominant product was bis-substituted urea (Table 2, entries 3–4). However, the secondary amine diethylamine showed no activity for substituted ureas (Table 2, entry 5). Hence, the present transamidation reaction could proceed by following an addition/elimination mechanism,[53] which would be in line with the finding that carbon dioxide is rather unreactive toward DBU and BU and the finding that sterically hindered amines reacting with urea only gave the monosubstituted product. With all listed amines, ABic can be easily isolated by capturing the released NH_3 with CO_2, in spite of a small difference in the capture efficiency.

In conclusion, we have developed an environmentally friendly CO_2/water system to catalyze the transamidation of urea with a variety of amines, which afforded higher-valued monosubstituted or bis-substituted ureas and captured the released NH_3 as ABic by the compressed CO_2 without using any conventional acid catalysts. The Brønsted acid catalyst was in situ formed through the dissociated of carbonic acid generated from CO_2 and water. The phase behavior observed in situ by high pressure visual autoclave confirmed that the reaction mixture existed in biphasic condition during the whole process of reaction. The formation of monosubstituted urea was favorable at lower temperature, and that of bis-substituted urea, at higher temperature. The pressure also has a significant influence on reaction. Although the present rate of catalytic formation of urea derivative is low for industrial applications and the efficiency of absorption of ammonia was less efficient, we have proven that the reaction can be accelerated with a CO_2/water system without using any conventional acid catalysts. Studies are in progress to find more efficient catalysts and to optimize the process.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Data concerning the determination of total nitrogen balance, solvent effect, and all ^1H NMR and MS spectra of the different products. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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