Mechanism of Formation of Organic Carbonates from Aliphatic Alcohols and Carbon Dioxide under Mild Conditions Promoted by Carbodiimides. DFT Calculation and Experimental Study

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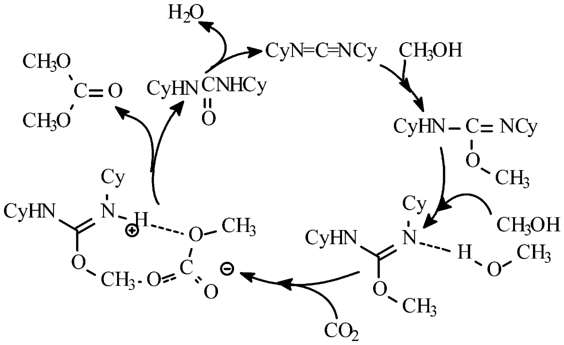

Dicyclohexylcarbodiimide (CyN=C=NCy, DCC) promotes the facile formation of organic carbonates from aliphatic alcohols and carbon dioxide at temperatures as low as 310 K and moderate pressure of CO_2 (from 0.1 MPa) with an acceptable rate. The conversion yield of DCC is quantitative, and the reaction has a very high selectivity toward carbonates at 330 K; increasing the temperature increases the conversion rate, but lowers the selectivity. A detailed study has allowed us to isolate or identify the intermediates formed in the reaction of an alcohol with DCC in the presence or absence of carbon dioxide. The first step is the addition of alcohol to the cumulene (a known reaction) with formation of an *O*-alkyl isourea [RHNC(OR′)=NR] that may interact with a second alcohol molecule via H-bond (a reaction never described thus far). Such an adduct can be detected by NMR. In alcohol, in absence of CO_2, it converts into a carbamate and a secondary amine, while in the presence of CO_2, the dialkyl carbonate, $(RO)_2CO$, is formed together with urea [CyHN−CO−NHCy]. The reaction has been tested with various aliphatic alcohols such as methanol, ethanol, and allyl alcohol. It results in being a convenient route to the synthesis of diallyl carbonate, in particular. *O*-Methyl-*N*,*N*′-dicyclohexyl isourea also reacts with phenol in the presence of CO_2 to directly afford for the very first time a mixed aliphatic−aromatic carbonate, (MeO)(PhO)CO. A DFT study has allowed us to estimate the energy of each intermediate and the relevant kinetic barriers in the described reactions, providing reasonable mechanistic details. Calculated data match very well the experimental results. The driving force of the reaction is the conversion of carbodiimide into the relevant urea, which is some 35 kcal/mol downhill with respect to the parent compound. The best operative conditions have been defined for achieving a quantitative yield of carbonate from carbodiimide. The role of temperature, pressure, and catalysts (Lewis acids and bases) has been established. As the urea can be reconverted into DCC, the reaction described in this article may further be developed for application to the synthesis of organic carbonates under selective and mild conditions.

Introduction

Molecular organic carbonates (Figure 1) are expected to experience a considerable expansion of their market

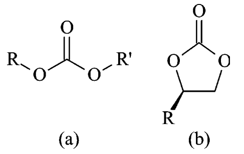

FIGURE 1. Linear (a) and cyclic (b) molecular organic carbonates.

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in the coming years, due to their growing use in the chemical (as solvent and reagent[1]), pharmaceutical (as intermediates[2]), and polymer industries.[3] Also, the use of dimethyl carbonate (DMC) as an additive to gasoline[4] will increase its market by nearly 2 orders of magnitude to an expected 30 Mt per year.[5] To satisfy the market demand, new synthetic technologies need to be developed that are not based on phosgene,[6] a chemical banned in several countries. The search for newer, safer, environmentally friendly synthetic methodologies has attracted the attention of a large scientific community. Either CO[7,8] or CO_2 are used as substitutes of phosgene in the scientific and patent literature for the synthesis of linear carbonates, cyclic monomeric carbonates, or polycarbonates.[9,10]

The direct carboxylation of alcohols (eq 1) responds to the requisites of sustainable chemistry. Such a reaction shows acceptable thermodynamics when R is an aliphatic group, but has such a high positive free energy when R is phenyl or, in general, an aromatic group, that thus far the synthesis of aromatic carbonates according to eq 1 was prevented.

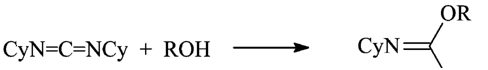
$$\underset{R = Me,\ \mathbf{1a};\ Et,\ \mathbf{1b};\ Allyl,\ \mathbf{1c}}{2\,ROH + CO_2} \rightarrow \underset{\mathbf{1}}{(RO)_2CO} + H_2O \qquad (1)$$

A few reports in the recent literature show that the equilibrium concentration of conversion of methanol into DMC (eq 1) is as low as 2%.[11] This is also true for ethanol and allyl alcohol.[12] A limiting factor, beyond the thermodynamics, is represented by water formed in the reaction that may push the equilibrium to the left or destroy the catalyst, when the latter is an alkoxo metal derivative.[13] To prevent such a negative effect, water traps are needed, either chemical- or process-based. Inorganic materials such as zeolites can be used as water traps, but the (surface)-hydroxo groups formed upon reaction with water are acidic enough to protonate the carbonate at the reaction temperature and convert it back into methanol and CO_2. It is possible to prevent such back reaction by cooling to ambient temperature the reaction mixture that, after dewatering, can be heated again to the reaction temperature. This procedure is very energy-intensive and does not meet the economic and environmental targets. Alternatively, there have been attempts to run separately the reaction that causes the water formation from the process of synthesis of the carbonate. To this end, ortomethylesters, acetals,[14] and ketals[15] have been reacted with $scCO_2$ to afford DMC. A single report describes the use of carbodiimide as "water trap" in the carboxylation of methanol in $scCO_2$ (323 K, 12 MPa),[16] but the reaction mechanism has not been investigated.

In this article, we discuss the reaction of dicyclohexylcarbodiimide, CyN=C=NCy, **2** (DCC), with several alcohols in the absence or presence of carbon dioxide, the formation of carbonates from aliphatic alcohols and CO_2 mediated by DCC and the role of the latter. The mechanism of formation of dialkyl carbonates is also discussed, highlighting the influence of temperature and pressure. The details of the reaction mechanism are revealed from the results of density functional calculations. Several intermediates have been isolated or identified using spectroscopic techniques. The effect of working in the presence of Lewis acids such as transition metal systems is also presented.

Discussion

Carbodiimides **2** have been known for some time to react with methanol (eq 2, R = Me) to afford *O*-methyl isoureas **3** as addition products. The chemistry of the latter compounds has been only moderately investigated. **3** has been reported to behave as an alkylating agent toward acids and alcohols,[17] but no detailed studies are reported that describe its behavior varying the reaction conditions.



(2)

2 **3a-c**

R= Me, **3a**; Et, **3b**; Allyl, **3c**

We have carried out an extended study on the behavior of DCC toward various alcohols and under different conditions and shown the reaction path and the role of *O*-alkyl isoureas in the synthesis of organic carbonates from alcohols and CO_2 under very mild conditions. Such reaction turns out to be a paradigm case for the formation of carbonates from alcohols and CO_2.

Reaction of DCC with Alcohols. DCC reacts with aliphatic alcohols to produce *O*-alkyl isoureas according to eq 2. The latter is a quite effective agent for the conversion of organic acids into the relevant alkylesters[17] at room temperature and of phenols into their ethers at

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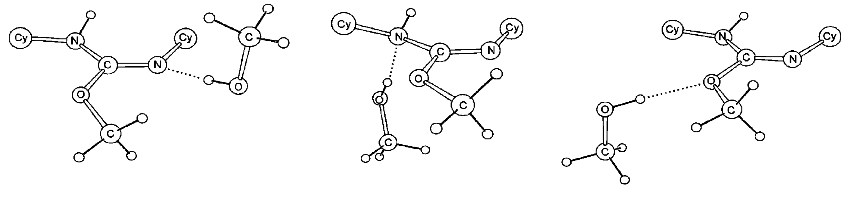
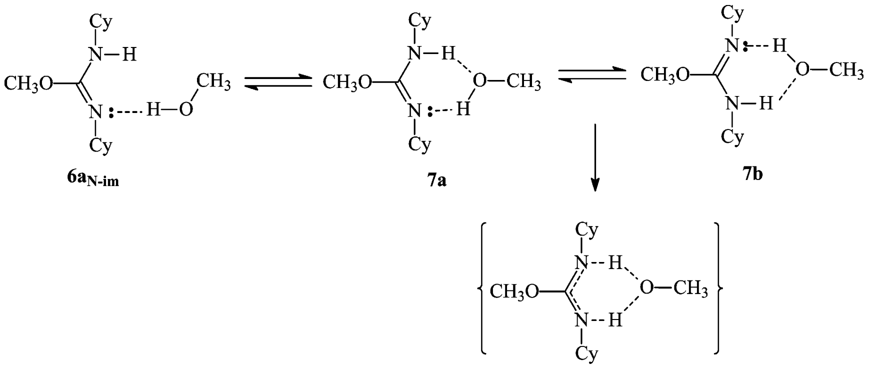


6a$_{N\text{-im}}$ (6.8) **6a**$_{N\text{-am}}$ (3.7) **6a**$_O$ (3.4)

FIGURE 2. H-bonded adducts formed between isourea **3a** and MeOH as obtained from DFT calculations. The predicted binding energies (in kcal/mol) are given in parentheses.

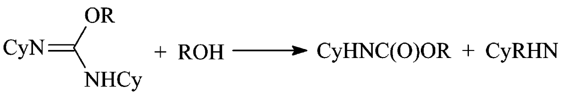
SCHEME 1. Methanol Interaction with 3a



6a$_{N\text{-im}}$ **7a** **7b** **7**

380 K, with quantitative yield. We have shown that such alkylating properties can be used for the selective alkylation of the acid with respect to the alkoxo functionality in the same molecule. In fact, **3a**–**c** can promptly (>99%) alkylate 4-OH-benzoic acid to 4-OH-benzoic alkylester at ambient temperature with high selectivity.

Such alkylation reactions are relevant to the mechanism of formation of DMC, or dialkyl carbonates in general, from alcohols and CO_2. Therefore, we have investigated in detail the factors that influence the yield and selectivity of eq 2. The rate of the process of alkylation of **2** to afford **3** (eq 2) is dependent on the nature of the alcohol used: at 330 K using a stoichiometric mixture of alcohol and DCC, the trend is $CH_3 > C_2H_5 > CH_2{-}CH{=}CH_2 \gg Ph$. Phenol reacts very little, and the corresponding *O*-phenyl isourea could not be isolated at 330 K, while other alkyl isoureas were isolated in very good yield (R = Me, >98%; R = Et, >96%; R = allyl, >95%). The reaction rate of the addition of alcohols to the C=N bond in general increases with the temperature and is influenced by the presence of a catalyst. We have found that $ZnCl_2$ and CuO or Cu_2I_2 are catalysts as good as CuCl, already described.[17] Zinc acetate is also active, but it generates the acetate alkyl ester formed upon reaction of alcohol with the acetate moiety linked to Zn, which is converted into $Zn(OH)_2$, isolated at the end of the reaction as an insoluble white solid. We have further investigated the reaction of *O*-alkyl isoureas with the relevant alcohol, a reaction that was never described before. We have found that while *O*-alkyl isoureas are stable in aromatic aprotic solvents, chlorinated solvents, and CH_3CN, also at temperatures above 373 K, they quite easily undergo a further reaction with alcohols to afford carbamates (**4**) and secondary amines (**5**) (eq 3).

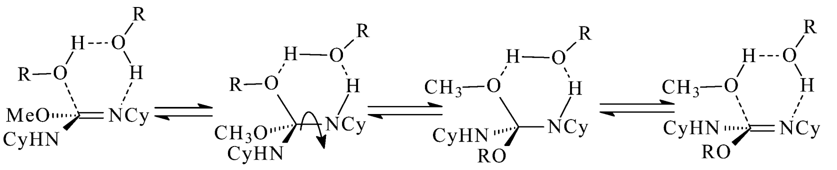


$$\underset{\mathbf{3}}{CyN{=}C(OR)(NHCy)} + ROH \longrightarrow \underset{\mathbf{4}}{CyHNC(O)OR} + \underset{\mathbf{5}}{CyRHN} \qquad (3)$$

Density functional calculations show that this reaction is strongly exothermic, because **4a** + **5a** is predicted to lie 29.2 kcal/mol below the energy of **3a** + MeOH. A second alcohol molecule may interact with isourea through an H-bond to either the aminic or iminic nitrogen or to the methoxy oxygen atom (see Figure 2), affording $[CyHNC(OR){=}NCy\cdots HOCH_3]$, **6** (R = Me, **6a**; Et, **6b**; Allyl, **6c**).

Of the three possible adducts, **6a**$_{N-im}$ represents the most stable structure (the calculated binding energy is 6.8 kcal/mol), which is due to the enhanced basicity of the iminic N atom in **3a**. The other two H-bonds are significantly weaker, the corresponding binding energies being in the range 3–4 kcal/mol. Infrared spectroscopy (IR) is not able to show such interaction. Conversely, a ^1H NMR study on the equimolar mixture isourea alcohol in CH_3CN has clearly shown the formation of an adduct. In fact, when methanol is added to an acetonitrile solution of isourea, a net change of the ^1H NMR spectrum is observed. While the methoxo group of the isourea can still be distinguished from the incoming $HOCH_3$ (CH_3 resonances of 3.55 and 3.29 ppm singlet, respectively), the proton signals of the N–C–H moiety of the two initially different cyclohexyl rings of **3a** (multiplets centered at 2.92 (1H) and 3.25 ppm (1H)) disappear, while a single multiplet at 1.72 ppm appears. Also, the signal due to the single N–H proton of **3a** (found at 3.95

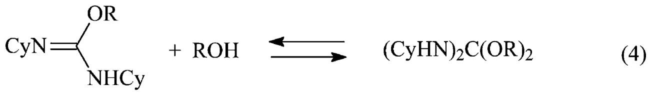
SCHEME 2. Exchange Mechanism of OMe to OR in Isoureas



3a +2ROH **8** **8'** **3b(c)**+MeOH+ROH

ppm) disappears, and a new broad signal is found at 2.6 ppm. Similarly, the ^{13}C spectrum confirms the equivalence of the two cyclohexyl groups. The equivalence of both N−H and N···H−O protons can be explained with the initial formation of adduct **6a**$_{\mathbf{Nim}}$ from which the resonance structures **7a**,**b** can be generated (Scheme 1) in which the N−H and N···H−O hydrogens become equivalent, while the methoxo groups remain different.

Heating **3** in an excess of alcohol allows eq 3 to occur. To gain more insight into this reaction, we have reacted CyHNC(OMe)=NCy with a heteroalcohol ROH (R = Et or Allyl) and found that CyHNC(OR)=NCy and methanol are formed. This exchange can be explained on the basis of the equilibria depicted in Scheme 2. The involvement of more than one alcohol molecule (two, as shown in Scheme 2) recalls the pathway proposed for the hydration of carbodiimides.[18] Scheme 2 shows that the conversion of **3a** into **3b**(**c**) passes through the formation of intermediate **8**, which can be considered the monosolvated form of the product of addition of a molecule of alcohol to the C=N bond of isourea **3a**, as shown in eq 4. Our calculations predict that **8a** lies only 4.8 kcal/mol above **3a** + MeOH (11.6 kcal/mol less stable than the hydrogen-bonded complex **6a**$_{\mathbf{N-im}}$).



$$\mathrm{CyN{=}C(OR)(NHCy)} + \mathrm{ROH} \rightleftharpoons \mathrm{(CyHN)_2C(OR)_2} \quad (4)$$

3 **8**

R = Me, **3a-8a**; Et, **3b-8b**; Allyl, **3c-8c**

A low energy transition state for the direct addition of a MeOH molecule to **3a** to give **8a** was not found, which might be an indication that eq 3 does not involve a single alcohol molecule, but rather a network of H-bonded alcohols as reported in Scheme 2. The alkyl group exchange is, thus, consistent with the intermediacy of the metastable ureal **8**, which was not isolated although several reaction conditions were tried.

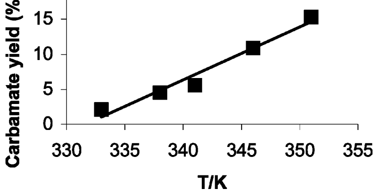
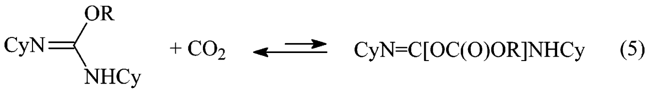


FIGURE 3. Influence of the temperature on the yield of carbamate. Molar ratio MeOH/DCC = 15:1, P_{CO2} = 5.0 MPa.

A study carried out using different alcohols (i.e., methanol in the synthesis of the alkyl isourea and ethanol for the following reaction) has shown that both *O*-methyl and *O*-ethyl carbamate and the chiral amines NHMeCy and NHEtCy are formed and can be isolated very pure. The same is true if allyl OH is used instead of EtOH. This trend is consistent with the alkyl-exchange reaction (Scheme 2). Increasing the temperature favors the formation of the carbamate that is not formed below 332 K (Figure 3). This is of relevance to the presence of **4** and **5** in the reaction mixture of carboxylation of alcohols in the presence of DCC at temperature above 340 K. The concentration of the reacting alcohol plays a key role. In fact, if isourea (50 mM) and alcohol are reacted in a solvent such as toluene or CH_3CN, no reaction takes place if the concentration of the alcohol is lower than 500 mM, independent of the solvent used.

Reaction of *O*-Alkyl Isoureas with Alcohols in the Presence of CO₂. *O*-Alkyl isourea **3** does not show any tendency to react directly with CO_2 either in organic solvents at 330 K under 6.0 MPa of CO_2 or under supercritical conditions (350 K and 12 MPa).



$$\mathrm{CyN{=}C(OR)(NHCy)} + \mathrm{CO_2} \rightleftharpoons \mathrm{CyN{=}C[OC(O)OR]NHCy} \quad (5)$$

3 **9**

Equation 5 is shifted to the left under the above conditions. In agreement with such an observation, DFT calculations show that the insertion of CO_2 into the C−O bond of O-methyl isourea to give **9a** (R = Me) is an endothermic process (**9a** is predicted to lie 17.7 kcal/mol above **3a** + CO_2). Clearly **9** is not an intermediate in the formation of carbonates, which are easily formed from alcohols and CO_2 in the presence of DCC.

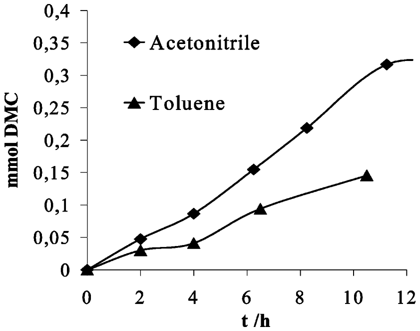


FIGURE 4. Influence of the solvent on the carboxylation rate of methanol in the presence of **3a**: the reaction is faster in polar solvents. The molar ratio solvent/CH_3OH/**3a** is 50:15:1, while P_{CO2} = 0.1 MPa and T = 323 K.

The carboxylation of alcohols shows an induction time during the first 2 h (Figure 4), and then the rate

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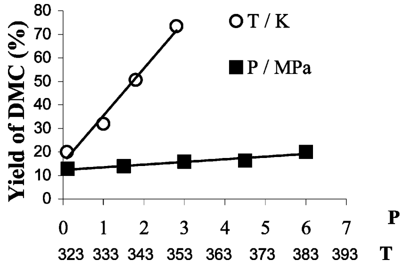


FIGURE 5. Effect of temperature and pressure on the yield of DMC formed by reacting methanol and CO_2 in the presence of DCC (methanol as solvent). The temperature effect is studied at a pressure of carbon dioxide of 5.0 MPa, while the influence of pressure is investigated at 323 K.

TABLE 1. Influence of the Alkyl Group on the Yield of Formation of Dialkyl Carbonates from the Relevant Alcohols and CO_2 in Presence of DCC[a]

alcohol	yield (selectivity) % starting from DCC	yield (selectivity) % from the relevant isourea
MeOH	11 (84)	32.6 (92)
EtOH	1 (93)	15.3 (96)
allyl OH	14.8 (94)	90.1 (95)

[a] Reaction condition: 323 K, 5.0 MPa, 6 h.

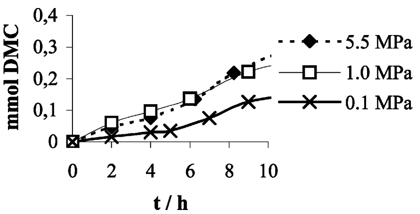


FIGURE 6. Influence of the P_{CO2} on the rate of formation of DMC by reacting methanol with CO_2 in the presence of *O*-methyl-*N,N′*-dicyclohexyl isourea in CH_3CN (solvent/CH_3OH/isourea = 50:15:1, T = 323 K).

TABLE 2. Influence of the Reaction Conditions on the Yield of Formation of Carbonates from Alcohols or Isoureas

entry	reagent	catalyst	carbonate yield (%) 6 h	12 h	24 h
		In Methanol			
1	DCC[a]	no	11.0		
2	DCC[a]	CuCl	30.2	53.0	83.3
3	methyl isourea[a]	no	32.6	52.0	76.4
4	methyl isourea[a]	MeOC(O)ONa	33.4	51.8	80.3
5	methyl isourea[a]	CuCl	29.4	46.8	76.0
6	DCC[b]	no	22.8	36.4	
7	DCC[c]	no	62.2		
		In Ethanol			
8	DCC[d]	no	1.0		
9	DCC[d]	CuCl	14.0	37.1	46.1
10	ethyl isourea[d]	no	15.3	37.5	45.8
11	ethyl isourea[d]	CuCl	14.1	37.8	44.8

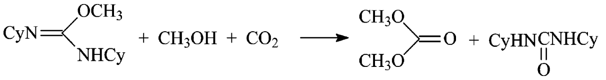
[a] 338 K, 5.0 MPa of CO_2, r = 100 (alcohol/DCC molar ratio). [b] 338 K, 5.0 MPa of CO_2, r = 5 (alcohol/DCC molar ratio). [c] 353 K, 5.0 MPa of CO_2, r = 5 (alcohol/DCC molar ratio). [d] 338 K, 5.0 MPa of CO_2, r = 70 (alcohol/DCC molar ratio).

increases. The rate of the reaction is sensitive to the nature of the solvent, the reaction being faster in polar solvents such as CH_3CN or the alcohol itself. Moreover, while in polar solvents the carboxylation readily occurs also under 0.1 MPa of CO_2, and in apolar solvents the reaction rate is sensitive to the CO_2 pressure, being close to zero at 0.1 MPa.

An increase of pressure from 0.1 to 6.0 MPa does not greatly influence the yield using the reagent alcohol as solvent. Conversely, the temperature plays a much more important role (Figure 5).

The use of $scCO_2$ at moderate temperature does not give better results with respect to working in alcohol as solvent. Table 1 shows that the alkyl group may influence the yield of the reaction.

Using the preformed *O*-alkyl isourea, we improved both yield and selectivity. The explanation is that when *O*-alkyl isourea is used, a shorter reaction time is necessary for the carboxylation to occur, which prevents the conversion of isourea into the relevant carbamate (see above). To observe the best selectivity toward the carbonate, the carboxylation reaction should be run at the lowest possible temperature to prevent eq 3 from occurring. Figure 6 shows the influence of pressure on the rate of formation of DMC from methyl isourea, methanol, and CO_2 in CH_3CN (eq 6).


$$CyN{=}C(OCH_3)(NHCy) + CH_3OH + CO_2 \longrightarrow (CH_3O)_2C{=}O + CyHNC(O)NHCy \qquad (6)$$

An increase in the CO_2 pressure above 1 MPa does not produce an increase of the conversion yield. As a matter of fact, the yield and selectivity are optimized working in alcohol under 1.0 MPa of CO_2 at 330 K. Under these conditions, the rate of conversion of DCC into the carbonate increases in the order: AllylOH > MeOH > EtOH, which is not the same trend observed for the addition of the alcohol to DCC (MeOH > EtOH > Allyl OH).

When *O*-alkyl isoureas are used as starting materials, the same trend is observed as that for DCC and alcohol, which demonstrates that the conversion of isourea and alcohol + CO_2 into the carbonate is the rate-determining step. We have also found that when allyl alcohol is used, a new reaction product (diallyl ether) is observed. The ether is preferentially formed at temperature above 330 K, in both the presence and absence of CO_2.

The allyl inversion, a possible process in both the formation of ether and carbonate, has been excluded using crotyl alcohol, which affords only dicrotyl carbonate without any trace of the inversion product (the (crotyl)-(1-methyl-1-propenyl)-carbonate). The rate and selectivity of the ether-forming reaction are positively affected by an increase of temperature: below 330 K the ether yield is less than 1%, while it is 50% at 350 K.

Use of Catalysts. To ascertain if a Lewis acid, such as CuCl, $CuCl_2$, Cu_2I_2, CuO, $ZnCl_2$, or Zn(acetate)$_2$, improves the rate of formation of the carbonate, we have compared the conversion yield and selectivity of the carboxylation of alcohols using either DCC or preformed alkyl isoureas. Both reactions were carried out in the presence or absence of catalysts (Table 2). The experimental results (Table 2) suggest that the addition of the first methanol unit to DCC is catalyzed by Lewis acids (entries 1 and 2), while the following steps are not. (Compare entries 1 and 2 (effect of catalyst), 2 and 3, and 3–5 in Table 2.)

TABLE 3. Reactivity Trend in the Case of Allyl Alcohol[a]

					reaction mixture composition (%)			
entry	*r′*	*r″*	*T* (K)	*t* (h)	DAC	DAE	diallyl ether	DCC unreacted
1	60	/	338	6	14.8	2	trace	82
2	60 (isourea)	/	338	2	91	7	trace	0
3	56	2	338	6	3.3	>90	trace	trace
4	31	40	338	6	56.4	40	trace	trace
5	15	215	338	3	61	21	15	3
6	15	412	313	8	45	3	40	9
7	15	412	338	2	81	7	8	2
8	15	500	323	5	49	5	35	9
9	15	400[b]	338	5	16	1.06	42	38
10	15	670[c]	338	4	75	7.05	12	3
11	15	206[d]	338	4	71	15	9	4
12	15	500[d]	338	4	93	6	/	0.4

[a] *r′* is the molar ratio “alcohol/DCC” (with the exception of entry 2, where it represents the “alcohol/isourea” ratio). *r″* is the ratio “DCC/catalyst (CuCl)”. [b] $CuCl_2$ is used as catalyst. [c] CuO is used. [d] Cu_2I_2 is used, DAC = diallyl carbonate, DAE = diallyl ether.

Entries 6 and 7 in Table 2 show the influence of temperature on the conversion yield. The comparison of entries 1 and 2 with 8 and 9, and 3−5 with 10 and 11 of Table 2 demonstrates that methanol is more reactive than ethanol.

Table 3 shows the figures relevant to a detailed study performed with allyl alcohol. Comparing entries 1 and 2 in Table 3 to entries 1 and 3 in Table 2 it is evident that allyl alcohol is more reactive than methanol. The best yield and selectivity are those relevant to entries 2 and 12. In other cases, the formation of diallyl ether is significant (entries 5−11), or the yield in carbonate is low (entries 3 and 4).

Basic catalysts such as $NaOCH_3$ (obtained from the reaction of methanol with sodium metal) or the product of its reaction with CO_2, $NaOC(O)OCH_3$,[19] **10**, does not cause an increase in the conversion yield with respect to DCC alone (see entries 3 and 4 in Table 2).

The Mechanism of Formation of Dialkyl Carbonates and the Role of DCC. The information gathered with the systems described above helps to draw the reaction mechanism of formation of dialkyl carbonates from alcohols and CO_2 in the presence of DCC. Two pathways can be envisaged:

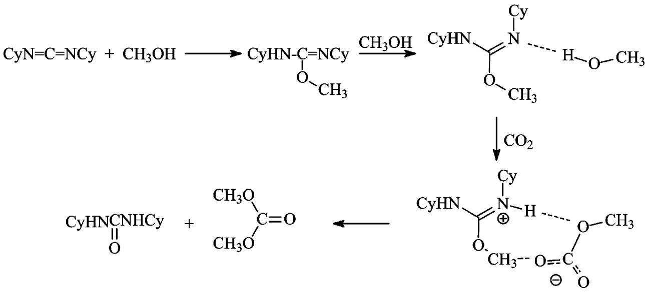
(i) A preliminary interaction of CO_2 with methanol (eq 7) to afford the monomethyl ester of carbonic acid (**11**), which is then methylated by the alkyl isourea.

$$CH_3OH + CO_2 \rightleftharpoons \underset{\mathbf{11}}{HOC(O)OCH_3} \qquad (7)$$

(ii) The direct pseudo “three-center” interaction of alkyl isourea with alcohol and CO_2.

The first route is ruled out because the CO_2 insertion into the O−H bond of CH_3OH does not take place.[19] We propose the reaction mechanism depicted in Scheme 3 for the conversion of DCC and methanol under CO_2 into DMC and urea.

SCHEME 3. Reaction Mechanism for the Formation of Organic Carbonates from DCC and Alcohols in the Presence of CO_2



To elucidate the mechanistic details of the CO_2 activation part of the reaction, we have examined possible reaction intermediates and related transition states from the H-bonded $6a_{N-im}$ complex toward the final products. The structures of the stationary points located on the potential energy surface are collected in Figure 7. The calculations indicate that the reaction between CO_2 and the $\mathbf{6a}_{N-im}$ complex takes place in two steps. The first step corresponds to the proton transfer from the alcohol to the iminic nitrogen of isourea, promoted by CO_2, which interacts with the methoxy anion giving rise to the “ion pair” intermediate **12a** (eq 8). In the second step, the positively charged methyl group of isourea migrates to the hemicarbonate anion $^-OC(O)OCH_3$ to afford the DMC molecule and urea (eq 9).

$$\underset{\mathbf{3a}}{CyHNC(OCH_3){=}NCy} + HOCH_3 \xrightleftharpoons{CO_2} \underset{\mathbf{12a}}{CyHN{-}C^+(OCH_3){-}NHCy} \; {}^-OC(O)OCH_3 \qquad (8)$$

$$\underset{\mathbf{12a}}{CyHC^+(OCH_3){-}NHCy \; {}^-OC(O)OCH_3} \rightarrow CyHNC(O)NHCy + (CH_3O)_2CO \qquad (9)$$

Calculations were used to examine the first step in detail. The precursor state of this step is a three-component adduct $\mathbf{6a}_{N-im}\cdots CO_2$ involving an initial weak electrostatic interaction between CO_2 and MeOH (the interaction energy between $\mathbf{6a}_{N-im}$ and CO_2 is 2.4 kcal/mol). The reaction is initiated by the O−H···N → O···H−N hydrogen shift that increases the negative charge of the methoxo oxygen, causing a strengthening of the $O{-}CO_2$ bond. When CH_3OD, instead of CH_3OH, is reacted with isourea and CO_2, an isotopic effect equal to 1.8 is observed that supports that the H (D) transfer is

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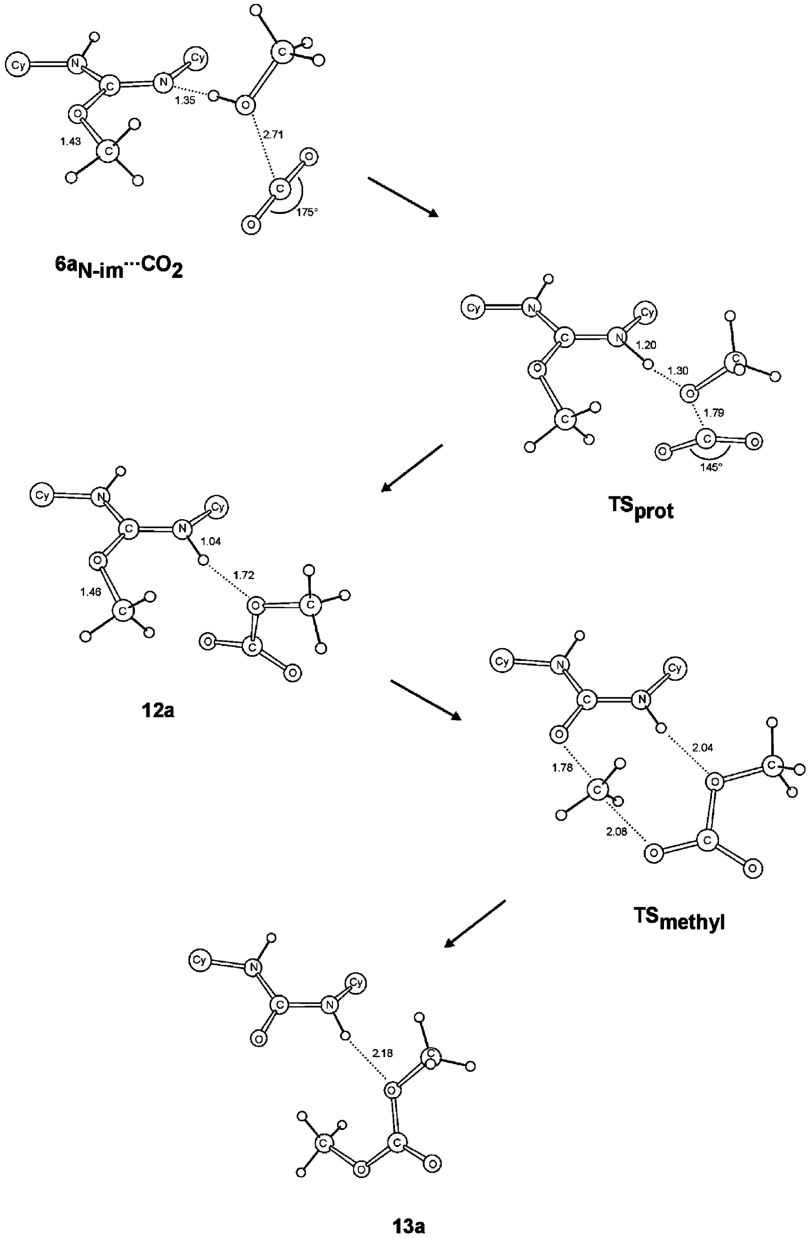

FIGURE 7. Optimized structures of stationary points involved in the reaction of isourea with CH_3OH and CO_2 (bond lengths in Å, angles in degrees).

the rate-determining step.[20] The concerted mechanism of the proton shift and the O−C bond formation is clearly born out by the structure of the transition state $\mathbf{TS_{prot}}$, in which the proton is between nitrogen and oxygen, while the O−C bond distance is 1.79 Å and CO_2 is bent. Therefore, the presence of CO_2 in the reaction medium converts the alkoxo- into the hemicarbonate form, which is more stable than the former due to charge delocalization over the two oxygen atoms of the COO− group.

Calculations carried out for the interaction of a methoxy anion with carbon dioxide show that CO_2 addition to CH_3O^- anion occurs spontaneously (with no energy barrier), and the formation of the CH_3OCOO^- anion is exothermic by 40.4 kcal/mol, underlying the importance of stabilization introduced by the presence of CO_2. The protonation of the iminic−N of isourea weakens its O−CH_3 bond as indicated by the O−C bond distances in $\mathbf{6a_{N-im}}\cdots CO_2$ and **12a** (1.43 versus 1.46 Å, respectively). This favors the methyl transfer to the $^-OC(O)OMe$ moiety, a step represented by $\mathbf{TS_{methyl}}$. The nearly planar CH_3 group is positioned between the two O atoms, and the N−H···O hydrogen bond is much weaker than that in the ion pair. Since the migrating CH_3 group carries a positive charge, both components of **13a** become neutral, and the final state is characterized as an H-bonded complex formed between the *cis*−*trans* isomers of urea and DMC. The relative energies of the stationary points are summarized in Figure 8.

Because of the ionic nature of **12a**, we found it important to incorporate the solvent effects into the energetics, and therefore we estimated the solvation energies for the five stationary points in terms of the polarizable continuum model (PCM) model and corrected

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[20] O'Ferral R. A. *J. Chem. Soc. B* **1970**, 785−790.

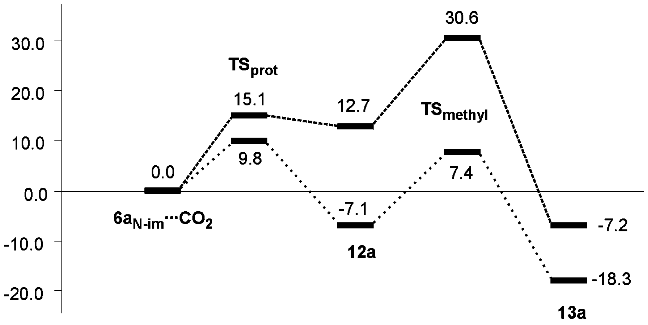

FIGURE 8. Energy profile of the $\mathbf{6a_{N-im}} \rightarrow \mathbf{13a}$ reaction pathway as obtained by the gas phase (dashed) and solvated (dotted) models. The dielectric constant of the polarizable medium was set to $\epsilon = 32.6$ to model methanol as a solvent.

the relative energies by solvent effects. As Figure 8 shows, the two models provide rather different energy profiles. While the gas-phase calculations predict the ion pair to be well above the $\mathbf{6a_{N-im}}\cdots CO_2$ adduct, this step clearly becomes energetically permitted in the solvated model; therefore, the energy of $\mathbf{TS_{methyl}}$ shifts to a lower value. The energy barriers for the two steps of the reaction are predicted to be 9.8 and 14.5 kcal/mol with the solvated model, which are reasonably low, and we may conclude that the two-step reaction mechanism represents a conceivable low energy route between $\mathbf{6a_{N-im}}\cdots CO_2$ and **13a**. Furthermore, these results are consistent with the fact that the reaction takes place faster in polar solvents, since the stability of the ion-pair intermediate and the gap of the proton shift appear to be sensitive to the polarity of the solvent.

We have attempted to find experimental evidence for such a mechanism with NMR and IR studies. When CO_2 is added to a CH_3CN solution containing **3a** and methanol in equimolar amounts (see above for the NMR data of the system **3a** + MeOH), a new signal located at 3.41 ppm appears due to the proton of the methyl group of the hemicarbonate moiety. At room temperature, no further change is observed with time, but upon heating this solution to 330 K the typical DMC signal at 3.70 ppm appears. As reported above, IR cannot prove the formation of $\mathbf{6a_{N-im}}$, but when an acetonitrile solution of methanol and isourea is exposed to CO_2, new bands attributed to the symmetrical and asymmetrical carbonyl stretching of the methyl carbonate anion appear at 1585 and 1283 cm^{-1}. The position of the bands and the difference of 302 cm^{-1} between the *sym* and *asym* carbonyl stretching frequency confirm that the methyl carbonate is not monodentate and behaves as a μ^2-OO bidentate ligand,[12] a more stable form (**12a′**), as shown in Figure 9. **12a′** is not able to give rise to the formation of DMC at 300 K. After heating such a solution above 330 K, we find that a new signal centered at 1755 cm^{-1} appears (C═O asymmetrical stretching due to the dimethyl carbonate), which increases with time until complete disappearing of the C═N stretching of isourea (1660 cm^{-1}). The GC−MS analysis of this solution confirms the formation of DMC. Our B3LYP/6-311++G** calculations reveal that indeed **12a′** is 19.8 kcal/mol more stable than **12a**, which is attributed to the formation of the double H-bond and also to the internal structural rearrangement of the protonated isourea moiety (Figure 9). The relative stability of **12a′** is rather similar in energy to that of **13a**, as the bidentate complex is predicted to lie 3.5 kcal/mol above **13a** in the gas-phase model, and it even becomes 0.8 kcal/mol more stable when solvent effects are included. We point out, however, that the two components in **13a** (urea and DMC) can also rearrange to their global minima (i.e., w-shape structures), and as a result, the final products become about 7 kcal/mol more stable than the bidentate H-bonded complex. These results are in line with the observation reported above that the ion pair identified as a stable form at 298 K can be converted into urea + DMC when the temperature is increased up to 330 K.

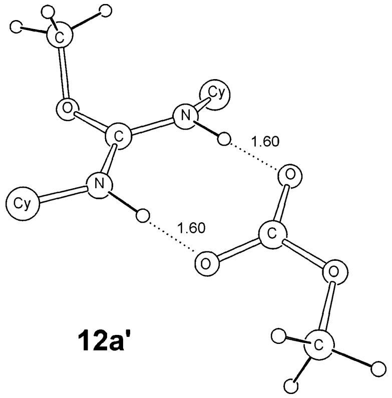

FIGURE 9. Optimized structure of the bidentate ion pair formed between the protonated isourea and the hemicarbonate anion (bond lengths in Å).

It is noteworthy that phenol and CO_2 can react with methyl isourea to afford methylphenyl carbonate. This is the first evidence of formation of a carbonate containing the phenyl moiety starting from phenol and CO_2. As reported earlier in this article, the formation of diphenyl carbonate from CO_2 and phenol has not been achieved thus far, most likely because it is not thermodynamically permitted. What may prevent the formation of diphenyl carbonate from phenol and CO_2 in the presence of DCC is the fact that phenol does not give a stable addition product to DCC (see above). The formation of methylphenyl carbonate occurs because CH_3^+ is transferred to the $^-OC(O)OPh$ anion. DFT calculations reveal that the formation of methylphenyl carbonate + urea is exothermic by 13.5 kcal/mol relative to isourea + PhOH + CO_2 (the exothermicity of the reaction with MeOH is 21.2 kcal/mol), and the energy gap represented by the transition state of the methyl transfer step is about 6 kcal/mol higher for PhOH as compared to the reaction with MeOH. All these data are in agreement with our experimental observations.

However, we have clearly demonstrated that the role of DCC in the reaction of alcohols with CO_2 to afford dialkyl carbonates can be identified in the following specific actions:

(i) DCC reacts with the alcohol to afford the *O*-alkyl isourea, which is the precursor of the CH_3^+ moiety that will be used in the methylation step. With respect to this, it is noteworthy that phenol does not react with DCC under the same conditions as aliphatic alcohols, despite being a better acid ($pK_a = 10$) than methanol ($pK_a = 16$), ethanol, and allyl alcohol.[21] This means that the stability of the NC(OR)=N moiety is very important for the isolation of the isourea. This reaction is catalyzed by metal systems such as CuCl, $ZnCl_2$, CuO, Cu_2I_2, and $Cu(OAc)_2$. The conversion of DCC into the isourea is quantitative, and the latter can be easily isolated and used as a reagent. The temperature plays a key role: to have good selectivity together with high yield, the reaction should be carried out at a temperature close to 330 K. Above this temperature, carbamates are formed from isourea and alcohols, lowering the selectivity.

(ii) The isourea reacts at 332 K with methanol and CO_2 to afford dimethyl carbonate, a reaction not requiring any catalyst and stepping through the simultaneous interaction of a second alcohol moiety with **3** and CO_2 with subsequent intramolecular methyl transfer to afford the carbonate. This reaction already occurs at 310 K and 0.1–6.0 MPa of CO_2, with high selectivity and good yield. Temperatures higher than 330 K increase the reaction rate but lower the selectivity as they promote the conversion of **6** into the relevant carbamate and amine. This reaction does not need a Lewis acid as catalyst. In fact, the reaction proceeds through a "base activation" of methanol to afford the methoxo group: the relevant role is played by the iminic nitrogen of isourea.

DCC may, thus, produce the reaction of alcohols with carbon dioxide to occur under temperature and pressure conditions that are much milder than those encountered for metal-catalyzed reactions.[11–15] In fact, the latter require 420–470 K under sc-conditions for reaching a 2% concentration of carbonate at the equilibrium. However, there is no sense in using DCC as a water trap in combination with metal systems as DCC itself promotes the carboxylation reaction in milder conditions than metal systems. The identification of the intermediates has made it possible to fully describe the reaction path. DFT calculations provided an energy profile for the reaction. Such a detailed study has no precedent and can result in being a paradigm for the carboxylation of alcohols as well as giving information useful for metal-catalyzed reactions. Because the resulting urea can be reconverted into DCC,[22] our findings may find practical application.

Experimental Section

All alcohols, starting reagents (DCC, metal catalysts, etc.), and solvents were commercial products. Alcohols and solvents were dried, distilled,[23] and stored under dinitrogen. Carbon dioxide was 99.999% pure.

Nuclear magnetic resonance experiments were carried out with a 300 MHz apparatus using deuterated solvents. Infrared spectra were recorded with an FTIR apparatus. High-pressure reactions were carried out in a 70-mL autoclave thermostated with an electric heating jacket. The autoclave was equipped with an inner glass reactor for avoiding metal contamination of the reagents and with a valve for continuous withdrawing of liquid samples. Reactions in supercritical carbon dioxide were carried out in equipment with automatic temperature and pressure control.

GC–MS analyses were carried out with a gas chromatograph (capillary column: 30 m; MDN-5S; ∅ 0.25 mm, 0.25-μm film) coupled to a QP5050 A mass spectrometer. Quantitative determinations on the reaction solutions were recorded using a GC–FID (capillary column: 30 m; MDN-5S; ∅ 0.25 mm, 0.25-μm film).

Synthesis of *O*-Alkyl-*N*,*N*′-dicyclohexyl Isourea (R = Me, Et, and Allyl). A quantity of 2 g of DCC (9.71 mmol) was dissolved in 10 mL of alcohol (methanol or ethanol or allyl alcohol) in the presence of catalytic amounts of Cu_2I_2 (10 mg, 0.05 mmol of Cu) (or CuO or $ZnCl_2$). The solution was stirred at room temperature until the complete conversion (generally 15 h at room temperature) of DCC in the relevant isourea (GC–MS test) was observed. The residual alcohol was distilled under vacuum (0.1 mm of Hg) at 300 K, while *O*-alkyl isourea was distilled at 410–440 K (depending on the alkyl group) under vacuum. MS pattern, infrared, and NMR data for *O*-methyl, *O*-ethyl, and *O*-allyl isoureas are in agreement with literature data.[24]

Methylation of 4-Hydroxybenzoic Acid. A quantity of 0.5 g of 4-hydroxybenzoic acid (3.62 mmol) was placed under stirring in 10 mL of diethyl ether. To the white suspension, an ether solution of **3a** (0.86 g, 3.62 mmol, in 10 mL of diethyl ether) was added dropwise. The reaction mixture obtained was analyzed by gas chromatography with a GC–FID (quantitative analysis using anisole as internal standard) and with GC–MS (qualitative analysis) showing that 98.7% of 4-hydroxybenzoic acid was converted in the relevant methyl ester. Only traces of $MeOC_6H_4(p\text{-}COOMe)$ were detected.

Reaction of *O*-Alkyl-*N*,*N*′-dicyclohexyl Isourea (R = Me, Et, and Allyl) with Alcohols. (a) Reaction at 300 K. A quantity of 0.050 g of *O*-alkyl isourea was dissolved in 0.7 mL of dry CD_3CN in an NMR tube, and the NMR spectrum was taken. To the solution, the stoichiometric amount of the relevant alcohol was added, and the proton spectrum was immediately recorded. The spectral data are reported in the Discussion section.

(b) Reaction at 350 K. A quantity of 0.5 g of *O*-alkyl isourea was placed in 5 mL of the relevant alcohol under stirring for 24 h at 350 K under a dinitrogen atmosphere. The formation of the alkylated primary amine and the relevant carbamate was shown by GC–MS analysis. The amine and carbamates were fully characterized by distillation of the alcoholic phase and column (0.5 m, 3 cm i.d.; hexane–diethyl ether 50/50 v/v) chromatographic separation, as already reported.[25]

(c) Alkyl Exchange Reaction. A quantity of 0.11 g of **3a** (0.46 mmol) in toluene (5 mL) was reacted at 333 K with a 5-fold molar excess of either ethanol or allyl alcohol. After a few minutes, the solution was analyzed by GC–MS, showing the presence of *O*-alkyl isourea (ethyl or allyl) and methanol. The reaction was complete in 15 h.

Reaction of DCC with Alcohols and Carbon Dioxide. The following general procedure was used for all reactions. A quantity of 1.0 g of DCC (4.85 mmol) was placed in a glass reactor with the reagent alcohol (10 mL). Toluene (20 μL) was added as internal standard, and the catalyst (Cu_2I_2, CuCl, Cu_2O, $ZnCl_2$) was eventually added. The reactor was placed in a stainless steel autoclave that was closed and pressurized with carbon dioxide at the desired pressure. The system was heated at different temperatures and for different times. After reaction, the autoclave was cooled to room temperature and depressurized, bubbling the gas phase in a cold DMF solution. The GC analysis of such solution allowed us to determine the amount of dialkyl carbonate that had possibly left the autoclave with the gas phase. The reaction solution was filtered for recovering the formed urea, and the clear solution was analyzed by GC or GC–MS to determine the formed carbonate

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and residual DCC. The recovered urea was washed with diethyl ether (2 × 5 mL), dried, and weighted for a double check on the conversion yield of DCC.

Influence of the Solvent on the Carboxylation of Alcohols. A quantity of 0.2 g of **3a** (0.84 mmol) was dissolved in 5 mL of toluene or acetonitrile in a glass reactor under an atmospheric pressure of carbon dioxide. Naphthalene (12.0 mg, 0.094 mmol) was added as internal standard. To the solution, 0.25 mL of methanol (6.23 mmol) was added, and the reactor was closed and heated in an oil bath at 328 K. The reaction was followed by gas chromatography for the due time. The results are reported in Figure 4.

Reaction of DCC with Crotyl Alcohol and Carbon Dioxide. A quantity of 2 g of DCC (9.7 mmol) and 12 mg of Cu_2I_2 (0.063 mmol of Cu) was added to 10 mL of crotyl alcohol (*cis*−*trans* isomer mixture) in a glass reactor that was placed in a stainless steel autoclave under 6.0 MPa at 338 K. After 2 h, the autoclave was depressurized, and the solution was filtered to afford the relevant urea that was washed with diethyl ether (2 × 10 mL). The reaction solution was treated with distilled water (10 mL) to extract the copper salts and the organic phase was separated, dried over anhydrous Na_2SO_4, and distilled to afford a dark-yellow liquid that was characterized as dicrotyl carbonate (1.04 g, 6.1 mmol, isolated yield 63.9%). The GC−MS and NMR analysis confirmed the total absence of the product originated by allyl inversion.

Mass pattern (*m/z*): 55, 71, 72, 108, 116. Infrared data recorded on the neat compound with KBr disks: 3025 (w), 2932 (s), 2856 (m), 1745 (s), 1450 (m), 1392 (m), 1251 (s), 1081 (m), 1042 (m), 967 (m), 924 (m), 793 (m), 590 (m). ^{1}H NMR (second-order spectrum: all signals are undefined multiplets): 5.79 (1H), 5.62 (1H), 4.51 ppm (2H), 1.70 ppm (3H). ^{13}C NMR: *C*H_2 at 68.6 ppm, *C*H at 132.2 ppm, *C*H at 125.1 ppm, *C*H_3 at 17.9 ppm, and O*C*(O)O signal at 155.3 ppm.

Spectroscopic Evidence of the Reaction of 3a with Alcohols and CO_2. A quantity of 0.1582 g of **3a** (0.665 mmol) was dissolved in 3 mL of CD_3CN under a dinitrogen atmosphere. To this solution, 50 μL of methanol (1.25 mmol) was added. The ^{1}H NMR was recorded, the dinitrogen atmosphere was replaced with CO_2, and the spectrum was again recorded. The results are reported in the Discussion section. All steps were also monitored by FTIR and GC−MS.

Study of the Isotopic Effect in the Reaction of CH_3OH/CH_3OD with 3a. A quantity of 0.22 g of **3a** (0.92 mmol) was dissolved in 5 mL of toluene under an atmosphere of carbon dioxide, and 250 μL of CH_3OH (or CH_3OD) was added. The composition of the reaction mixture was monitored by GC−FID, and the kinetic curve of formation of DMC was obtained. The k_H and k_D were determined, and an isotopic effect of 1.8 was calculated.

Synthesis of Methylphenyl Carbonate. A quantity of 1.0 g of **3a** (4.20 mmol) was placed in the $scCO_2$ reactor with 1.0 g of phenol (10.64 mmol) at 333 K under 20.0 MPa of carbon dioxide for 4 h. After being cooled and depressurized, 5 mL of THF was added to dissolve the reaction mixture. A GC−MS analysis showed the formation of methylphenyl carbonate, for which retention time and MS pattern fragmentation are identical with those of an authentic sample. Working in a solvent (toluene or CH_3CN or an excess of phenol) under 6 MPa of CO_2 does not afford any mixed carbonate.

Synthesis of Mixed Carbonates from 3a and Ethanol or Allyl Alcohol. A quantity of 0.2 g of **3a** (0.84 mmol) was dissolved in 5 mL of CH_3CN. Ethanol (250 μL, 4.35 mmol) or allyl alcohol (3.67 mmol) was added under an atmosphere of carbon dioxide. The solution was heated to 333 K. The reaction mixture was analyzed by GC−MS, confirming the formation of methyl ethyl- and methyl allyl carbonate, respectively. Continuous monitoring showed that the selectivity of the reaction decreases with time because of the trans-alkylation of methyl isourea with subsequent formation of diethyl- and diallyl carbonates.

Computational Details

DFT calculations were carried out to obtain information on the structures and relative energies of energy minima and transition states relevant to possible reaction pathways. First we located the stationary points using a smaller model, where the dicyclohexylcarbodiimide was simplified to dimethylcarbodiimide. These structures were used to construct the realistic model compounds by replacing the methyl groups with the experimentally used cyclohexyls and repeated the geometry optimizations for these realistic models. The nature of the stationary points obtained from the geometry optimizations was verified by subsequent vibrational frequency analysis. Intrinsic reaction coordinate (IRC) calculations were performed from the located transition states to check whether these structures indeed connect the appropriate minima on the proposed reaction pathways.

The calculations were carried out with Becke's three-parameter B3LYP hybrid exchange-correlation functional[26] using the Gaussian 98 software package.[27] For the geometry optimizations, frequency calculations, and IRC calculations, we used the standard 6-31G* basis set; however, to obtain accurate energetics, single-point energy calculations were performed at each stationary point using the extended 6-311++G** basis set. For some of the structures, in cases where we expected considerable solvent effects on the energetics, we estimated the solvation energies in terms of the PCM.[28] In these calculations, we used methanol as a solvent with a dielectric constant of $\epsilon = 32.6$. The energies given in the article generally refer to B3LYP/6-311++G** gas-phase values, except those where the solvent effects are examined explicitly. The structures and the total energies of all located stationary points are given in the Supporting Information.

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Supporting Information Available: Cartesian coordinates and total energies of located stationary points relevant to the title reaction. This material is available free of charge via the Internet at http://pubs.acs.org.

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