Mechanistic Insights into the Bazarov Synthesis of Urea from NH_3 and CO_2 Using Electronic Structure Calculation Methods

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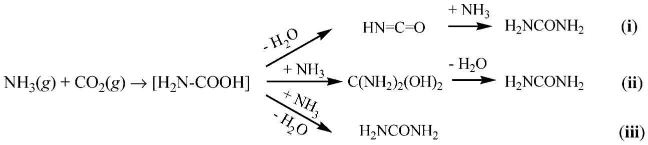
The mechanism of the noncatalyzed and reagent-catalyzed Bazarov synthesis of urea has extensively been investigated in the gas phase by means of density functional (B3LYP/6-31G(d,p)) and high quality ab initio (CBS-QB3) computational techniques. It was found that the first step of urea formation from NH_3(g) and CO_2(g) corresponds to a simple addition reaction leading to the carbamic acid intermediate, a process being slightly endothermic. Among the three possible reaction mechanisms considered, the addition−elimination−addition (AEA) and the double addition−elimination (DAE) mechanisms are almost equally favored, while the concerted (C) one was predicted kinetically forbidden. The second step involves the formation of loose adducts between NH_3 and carbamic acid corresponding to an ammonium carbamate intermediate, which subsequently dehydrates to urea. The formation of "ammonium carbamate" corresponds to an almost thermoneutral process, whereas its dehydration, which is the rate-determining step, is highly endothermic. The Bazarov synthesis of urea is strongly assisted by the active participation of extra NH_3 or H_2O molecules (autocatalysis). For all reaction pathways studied the entire geometric and energetic profiles were computed and thoroughly analyzed. The reaction scheme described herein can be related with the formation of both isocyanic acid, H−N═C═O, and carbamic acid, H_2N−COOH, as key intermediates in the initial formation of organic molecules, such as urea, under prebiotic conditions.

Introduction

Urea or carbamide, H_2N−C(O)−NH_2, was first discovered in human urine by H. M. Rouelle in 1773, while half a century later, in 1828, Friedrich Wöhler[1] synthesized urea accidentally when he attempted to prepare ammonium cyanate. In 1870, the Russian chemist A. Bazarov[2] prepared urea by heating solid ammonium carbamate, NH_2COONH_4, in a sealed vessel at high pressure and temperature, in a laboratory process that provided the basis for the current industrial process of urea's production. Nowadays, urea is alternatively produced by (i) the well-known procedure based on the addition of NH_3 to phosgene, $COCl_2$, (ii) the newly discovered metal-catalyzed process involving the direct carbonylation of NH_3,[3] and (iii) the use of ionic liquids under mild conditions.[4]

Bazarov synthesis of urea is a synthetic process with great commercial significance for many decades. However, although a number of models describing the thermodynamic equilibrium of Bazarov's reaction have been developed and proposed,[5−9] the details of the complete reaction scheme are still not well understood.[5] It is generally accepted that the reaction proceeds via formation of ammonium carbamate as an intermediate, which in turn is dehydrated to yield urea. It is also assumed that the ammonium carbamate intermediate is formed in the gas phase, while its dehydration occurs in the liquid phase. At pressures above the dissociation pressure, the formation of ammonium carbamate is very fast, highly exothermic and goes essentially to completion under normal industrial processing conditions. On the other hand, the dehydration of ammonium carbamate corresponds to a slower, endothermic process, which does not reach thermodynamic equilibrium under processing conditions. Furthermore, it is believed that ammonium carbamate, carbamic acid and ammonia are in equilibrium, while at the first step of the reaction of CO_2(g) with NH_3(g), carbamic acid is formed as a transient intermediate. Both the ammonium carbamate[10,11,12] and carbamic acid[13] decompositions have been thoroughly studied in the past, even though carbamic acid has never been observed experimentally. Buckingham et al.[14] investigated the formation of urea from NH_3(g) and CO_2(g) at a primitive level using Hartree−Fock-based computational techniques, while recently the very own hydrolysis of urea has thoroughly been investigated and the presence of water solvent has been assessed.[15]

SCHEME 1



Considering the industrial importance for the production of urea and the biochemical importance of urea in living organisms,[15] we attempted herein to shed light on the mechanistic details of urea's formation from the inorganic species NH_3(g) and CO_2(g), using high quality electronic structure calculation methods. Along this line, three different possible reaction pathways (Scheme 1) following the *addition−elimination−addition* (*AEA*) mechanism (i), the *addition−addition−elimination* or *double addition−elimination* (*DAE*) mechanism (ii), and the *concerted* (*C*) mechanism (iii) have been thoroughly investigated. Moreover, the reagent-catalyzed (e.g., the water-

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TABLE 1: Intermolecular N···C Distance (Å) and Dipole Moment (D) of the $H_3N\cdots CO_2$ van der Waals Complex Computed at the B3LYP Level of Theory Using Various Basis Sets

method	basis set	N···C distance	dipole moment
B3LYP	6-31G(d,p)	2.846	2.43
(CBS-QB3)//B3LYP	6-311G(2d,d,p)	2.865	2.16
B3LYP	cc-pVTZ	2.956	2.13
B3LYP	cc-pVQZ	3.003	2.05
expt[a]		2.987	1.77

[a] Taken from ref 28.

and ammonia-catalyzed) reactions of the aforementioned reaction pathways have also been explored.

Methods and Computational Details

Three possible reaction pathways have been investigated (Scheme 1): (i) the addition−elimination−addition (AEA) mechanism, (ii) the addition−addition−elimination or double addition−elimination (DAE) mechanism, and (iii) the concerted (C) mechanism. All the calculations were performed using the Gaussian03 suite of programs.[16] The equilibrium and transition structures were fully optimized using the B3LYP hybrid functional[17−19] in conjunction with the 6-31G(d,p) basis set. For transition-state geometry determination quasi-Newton transit-guided (QSTN) computations were performed.[20] Moreover, the correct transition states have been confirmed by intrinsic reaction coordinate (IRC) calculations, while intrinsic reaction paths (IRPs) were traced from the various transition structures to make sure that no further intermediates exist.[21,22] To check the reliability of the DFT energetic results, the improved complete-basis-set CBS-QB3 model chemistry was also employed.[23,24] In some cases, the reliability of the B3LYP method was checked against MP2 calculations.[20,25−27]

Results and Discussion

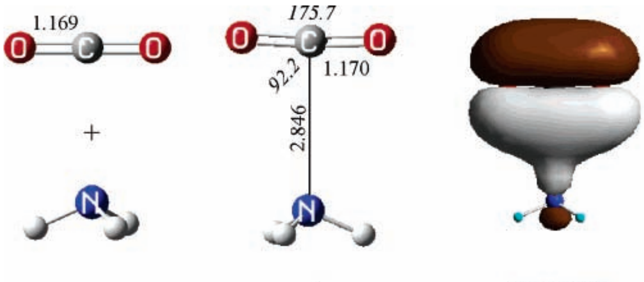
1. Modeling Bazarov's Synthesis of Urea in the Gas Phase. At the molecular level the synthesis of urea by reacting NH_3(g) with CO_2(g) in 2:1 ratio consists of three distinct, elementary reactions (Scheme 1), corresponding to two ammonia additions (aminolysis steps) and one water elimination (dehydration step).

1.1. The H_3N- - -CO_2 van der Waals Complex. Carbamic acid is unambiguously the first transient intermediate that is formed solely from the NH_3(g) addition to CO_2(g) (aminolysis of CO_2). The electronic structure calculations showed that a loose van der Waals complex $H_3N\cdots CO_2$, **1** (Figure 1), the structure of which has previously been identified by means of rotational spectroscopy,[28] is the preassociation complex of the process. Interestingly, the largest cc-pVQZ basis set reproduces well the experimental value of the N···C separation distance and the dipole moment of **1** (Table 1).

The equilibrium geometries of the reactants and the van der Waals complex **1** along with the molecular orbital (MO) contributing to their association computed at the B3LYP/6-31G(d,p) level of theory are depicted schematically in Scheme 2. Complex **1** seems to be slightly more stable than the separate NH_3(g) and CO_2(g) molecules ($\Delta H_f = -2.5$ and -1.1 kcal·mol^{-1} at the B3LYP/6-31G(d,p) and CBS-QB3 levels of theory, respectively), but its formation does not correspond to a spontaneous process ($\Delta G_f = +2.9$ and $+3.1$ kcal·mol^{-1}, respectively).

1.2. The Carbamic Acid Formation. Because of the volatility of these low-molecular weight molecules, it is safe to assume that even under industrial conditions the first reaction step takes place in the gas phase. It was found that the formation of carbamic acid surmounts a quite high activation barrier of about 50 kcal·mol^{-1} (Figure 1), while the change in enthalpy is almost zero ($\Delta H(CO_2 + NH_3 \rightarrow$ **3a**$) = -1.0$ and $+1.0$ kcal·mol^{-1} at the two levels of theory). Further searching of the potential energy surface (PES) of the [CNO_2H_3] system revealed that there are two conformers of carbamic acid, $H_2N-COOH$, and four conformers of isocarbamic acid, $HN{=}C(OH)_2$ (see Supporting Information).[29] The conformer resulting from the aminolysis of CO_2(g) is characterized as *anti*-carbamic acid, **2**, and it is found to be less stable than the syn form, **3**, by about 7 kcal·mol^{-1}. The anti → syn transformation corresponds to an almost "barrier-free" process (Figure 1).

SCHEME 2



1 **HOMO-5**

Carbamic acid, in either neutral or zwitterionic form, has previously been postulated as an indispensable intermediate of the reversible ammonium carbamate decomposition.[10] Its decomposition back to NH_3(g) and CO_2(g) has an activation barrier of about 35 kcal·mol^{-1}, and it is favored by both the energetic and entropic effects. Similar values (in terms of free energy) have also been calculated by Ramachandran et al.[10] at the MP2/6-31+G(d) level of theory.

1.3. The Elimination—Addition (AEA) Mechanism. The energetic and geometric profiles of the two reactions of the AEA mechanism are depicted pictorially in Figure 1i. Note that even though there are totally three different possible pathways for the addition of NH_3 to the unsaturated bonds of isocyanic acid, the one affording directly urea has been found to be the most favorable one.[30] Structure **5** was traced through IRC calculations to be the preassociation complex, even though the global minimum corresponds to the structure H_3N- - -$H-N{=}C{=}O$, which lies 5.9 kcal·mol^{-1} lower.[31,32] The calculated $\Delta_rH°$ of the reaction $CO_2 + NH_3 \leftrightarrows HN{=}C{=}O + H_2O$ is 20.9 and 18.3 kcal·mol^{-1} at the B3LYP/6-31G(d,p) and CBS-QB3 levels of theory, respectively. The calculated $\Delta_rH°$ values are in excellent agreement with the experimental[33] one of 22.9 kcal·mol^{-1}. Finally, the overall process of urea formation is estimated to be slightly endothermic ($\Delta_rH° = 3.6$ and 2.2 kcal·mol^{-1} at the two levels) and not spontaneous ($\Delta_rG° = 14.2$ and 13.3 kcal·mol^{-1}) at 298 K and pressure 1 atm. Note that according to experimental enthalpy values,[33] the $\Delta_rH°$ of the reaction CO_2(g) + $2NH_3$(g) $\leftrightarrows$ $H_2N-CO-NH_2$(g) + H_2O(g) (in the gas phase) amounts to 1.9 kcal·mol^{-1}.

1.4. The Addition—Elimination (DAE) Mechanism. For the second consecutive NH_3 addition to the carbamic acid intermediate to occur, a preassociation complex, $H_3N\cdots$*syn*-H_2NCOOH, must first be formed. The calculations revealed that there are totally three relevant complexes of this type, labeled **7**, **8** and **9** (Figure 1). In contrast to complex **9**, complexes **7** and **8** have a local C_s symmetry exhibiting a planar [$CN_2O_2H_4$] nuclear framework, resembling the planarity of the H_2N-COO^- anion in the solid ammonium carbamate.[34] The structures of

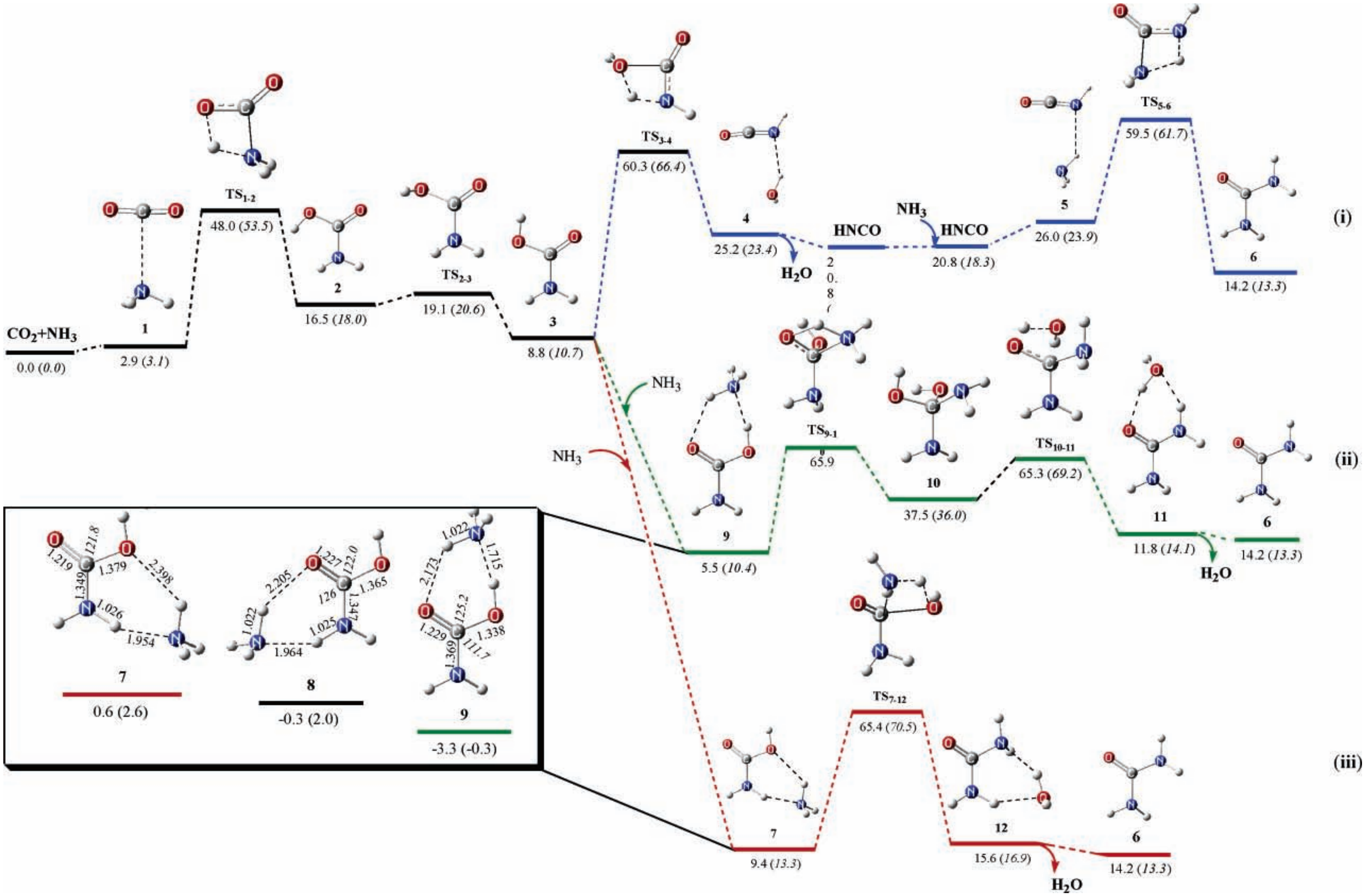


Figure 1. Energetic profile (ΔG_{298}, kcal·mol^{-1}) of the noncatalyzed pathways of urea formation from CO$_2$(g) and NH$_3$(g) calculated at the B3LYP/6-31G(d,p) and CBS-QB3 (figures in parentheses) levels of theory: the elimination−addition (AEA) mechanism (i); the addition−elimination (DAE) mechanism (ii); the concerted (C) mechanism (iii). Structural parameters and relative energies of complexes **7**−**9** are also given (the free reactant molecules were considered at the zero level).

7−**9** correspond to the structure of the intermediate "ammonium carbamate" which dehydrates to urea and could be considered as intermediates in the decomposition of crystalline ammonium carbamate, since they constitute the simple acid−base reactants between the $[H_2NCOO]^-$ and $[NH_4]^+$ ions. Thus, the sequence "crystalline $[H_2NCOO^-][NH_4]^+$ → **7**−**9** → carbamic acid → $NH_3(g) + CO_2(g)$" may constitute a possible pathway for this peculiar decomposition process.

It was found that **9** is the reactant in the second NH_3 addition step leading to the unstable (diamino)(dihydroxy) methane intermediate, $C(NH_2)_2(OH)_2$, **10**, which then dehydrates to urea (Figure 1). Finally, **10** can be first dehydrated to isourea, which could then be transformed into urea through a simple prototropic tautomerization. The theoretical results illustrated that there are two different pathways for this transformation, both of which are energetically more demanding than the dehydration step already examined (see Supporting Information).

1.5. The Concerted (C) Mechanism. The third reaction pathway for the synthesis of urea is the simplest one, involving the simultaneous water elimination and NH_3 addition to carbamic acid. The calculations indicated that this reaction pathway proceeds through $\mathbf{TS_{7-12}}$ (Figure 1) with an activation energy of about 57 kcal·mol^{-1}, while the $H_3N\cdots$*syn*-H_2NCOOH complex **7** is formed as a precursor in the reaction. Thus, the energy results predict that this mechanism competes the other two stepwise mechanisms in the noncatalyzed ractions.

2. Urea Synthesis Catalyzed by NH_3 or H_2O Molecules. Bazarov synthesis of urea is carried out in the presence of steam and in excess of ammonia, which are partially in the liquid phase and partially gaseous under the industrial conditions, with variable H_2O/NH_3 volume ratio. Further theoretical investigation of urea's formation has shown that extra H_2O or NH_3 molecules can actively participate in all possible pathways, resulting in substantial decrease of the activation barriers of the reactions. The extra H_2O/NH_3 molecules have the ability to act as a proton shuttle, facilitating the formation of a strain-free six-center or even eight-center transition state. Such catalytic phenomena taking place in hydrolysis or aminolysis reactions have already been well documented and the magnitude of the catalytic effects have been estimated at various levels of theory for a variety of reactions.[15,30,35,36] It is generally proved that six-membered cyclic transition states are sufficient for the proton transfer to occur strain-free, while additional H_2O molecules on the active site bring about nothing but marginal decrease in the activation energy. Recently, however, Lewis et al.[37−39] demonstrated that the placement of an extra, "spectator" H_2O molecule *opposite* the site of the proton transfer in the hydration of CO_2 results in considerable charge stabilization of the transition state, thereby further decreasing the activation energy of the reaction. Hereto we are going to apply the same strategy to some of the reactions of urea formation, and thoroughly test the effects of microsolvation.

2.1. Catalytic Formation of Carbamic Acid. The catalytic hydration of carbon dioxide has been the subject of extensive theoretical studies in the past, and it was found that the participation of extra H_2O molecules hydrogen bonded to CO_2 results in significant lowering of the activation barrier.[35] We have found that the NH_3 addition to CO_2 follows the same trend, since it is being catalyzed not only by additional H_2O molecules, but also by additional NH_3 molecules. This functionality of NH_3 molecules acting like H_2O in catalysis has already been demonstrated in Wöhler's synthesis of urea[30] and other analogous reactions.[10,36] The catalytic effects of the extra NH_3 and H_2O molecules in the NH_3 addition to CO_2 are presented in Figure 2, parts a and b, respectively. The activation barrier ($\Delta G^{\ddagger}$) of the reaction is now remarkably decreased by about 24 kcal·mol^{-1} at both the CBS-QB3 and B3LYP/6-31G(d,p) levels of theory. Similar values have also been obtained for the noncatalyzed and the one-water-catalyzed hydration of CO_2 at the QCISD(T)/6-31G(d,p)//MP2/6-31G(d,p) level,[35] while the addition of a second water molecule was found to cause no significant further decrease. Noteworthy is the excellent agreement between the computed $\Delta G^{\ddagger}$ and ΔG values of 30.9 and 8 kcal·mol^{-1}, respectively, at the CBS-QB3 level and the MP2/6-31G(d) values of 30 and 11.4 kcal·mol^{-1} reported by Ramachandran et al.[10] Finally, the presence of one extra, "spectator" H_2O molecule, opposite to the active site of the proton transfer (Figure 3a), was found to slightly facilitate the reaction, reducing further the activation barrier by 4.3 kcal·mol^{-1}. Obviously, microsolvation effects play a considerable role in the NH_3 addition to CO_2, as well.

2.2. The Catalytic Elimination—Addition Mechanism. Both reactions that constitute the AEA mechanism can be assisted—catalyzed—by extra water or ammonia molecules, as it is clearly illustrated in Figure 3. More specifically, it was found that the activation barrier of the dehydration of *syn*-carbamic acid is reduced from 55 kcal·mol^{-1} for the noncatalyzed reaction to approximately 40 kcal·mol^{-1} (at the CBS-QB3 level) for the catalyzed ones. Despite the substantial decrease of the activation barrier, it still remains quite high, even higher than the activation barrier of the catalyzed aminolysis of CO_2. On the other hand, the pattern of the second reaction changes radically not only in terms of activation barriers, but also in terms of its elementary steps. Quite interestingly, a thorough examination of the catalyzed NH_3 addition to $HN{=}C{=}O$ revealed that the reaction is completed in two successive steps, in contrast to the one-step reaction for the noncatalyzed case. The activation barrier is dramatically reduced from 38 kcal·mol^{-1} to a maximum value of 14.6 kcal·mol^{-1} for the NH_3-catalyzed and 13.4 kcal·mol^{-1} for the H_2O-catalyzed case. We have also corroborated the existence of these new, rather peculiar intermediates (labeled **17** and **28**) at the higher MP2/6-311++G(d,p) level (in the gas phase), while a similar to **28** intermediate (labeled **I6** in ref 15) was reported for the two-water-catalyzed NH_3 elimination from urea in solution.[15] Intermediates **17** and **28** correspond to loose associations of NH_3 and HNCO, which are stabilized by additional NH_3 and/or H_2O molecules through formation of hydrogen bonds. The Mulliken bond overlap population of the $C\cdots NH_3$ bond was estimated to be 0.082 and 0.086 for **17** and **28**, respectively, while the bond overlap population of the C=N bond of the HNCO moiety is 0.523 and 0.492 for **17** and **28**, respectively. Detachment of the extra NH_3 and/or H_2O molecules results in the "free" NH_3 and HNCO molecules. According to the natural bond orbital (NBO) population analysis[40] the bonding σ(C−N) interaction between the C atom of HNCO and N atom of NH_3 in **17** is constructed from an $sp^{5.08}$ hybrid (83.39% p-character) on C atom, $h_C = -0.4037(2s)_C - 0.4807(2p_x)_C - 0.7764(2p_y)_C$, interacting with an $sp^{3.33}$ hybrid (76.89% p-character) on N atom, $h_N = -0.4804(2s)_N + 0.4766(2p_x)_N + 0.7354(2p_y)_N$, thus having the form $\sigma(C-N) = 0.5111h_C + 0.8596h_N$. Similarly, the bonding σ(C−N) interaction in **28** is constructed from an $sp^{4.95}$ hybrid (83.04% p-character) on C atom, $h_C = 0.4080(2s)_C - 0.4346(2p_x)_C + 0.8009(2p_y)_C$, interacting with an $sp^{3.35}$ hybrid (77.00% p-character) on N atom, $h_N = 0.4793(2s)_N + 0.4527(2p_x)_N - 0.7510(2p_y)_N$, thus having the form $\sigma(C-N) = 0.5141h_C + 0.8577h_N$.

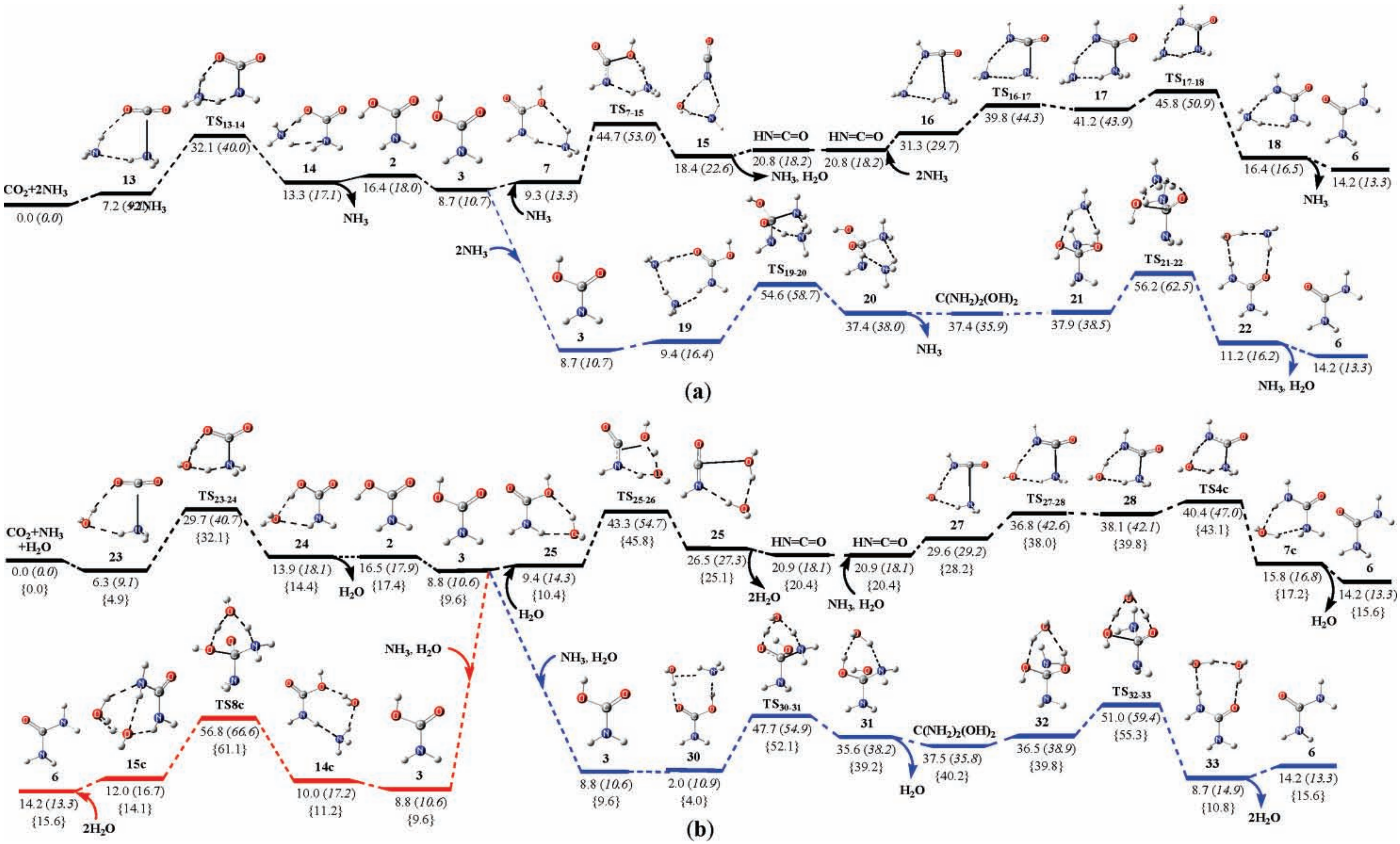


Figure 2. Energetic profile (ΔG_{298}, kcal·mol^{-1}) of the NH_3-catalyzed (a) and the H_2O-catalyzed (b) pathways of urea formation from CO_2 and NH_3, calculated at the B3LYP/6-31G(d,p) and CBS-QB3 (figures in parentheses) levels of theory. Values in braces are the B3LYP/6-31G(d,p) free energies (ΔG, kcal·mol^{-1}) calculated at pressure 200 atm and temperature 473 K.

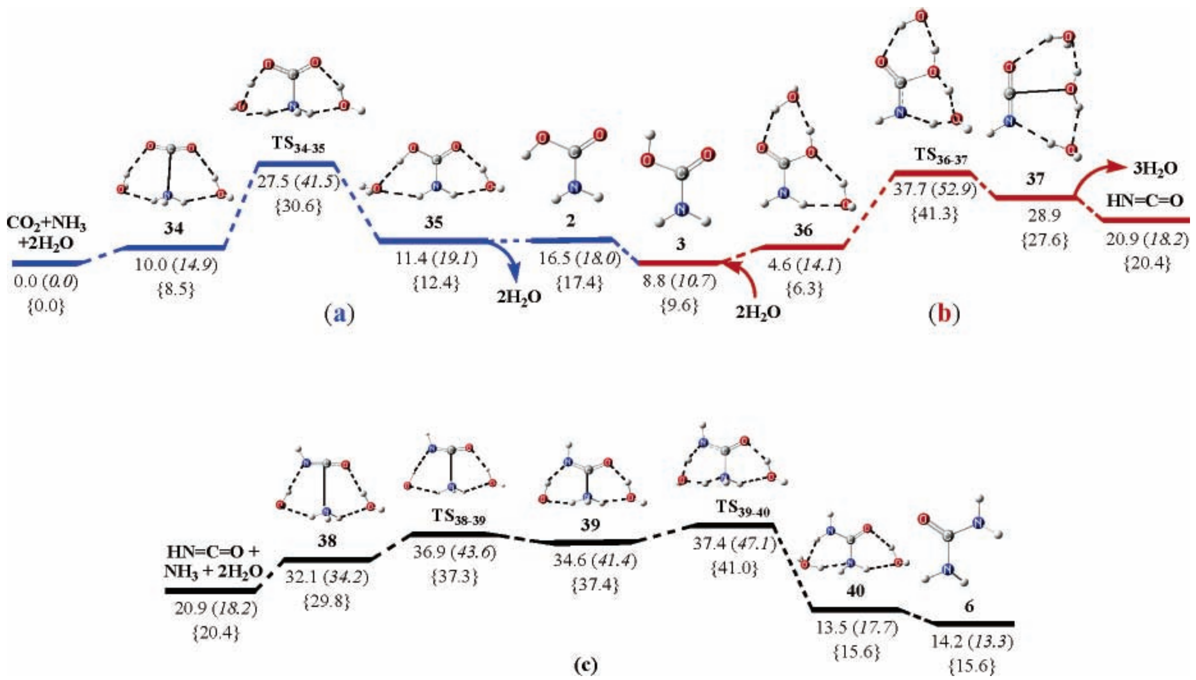


Figure 3. Energetic profile (ΔG_{298}, kcal·mol^{-1}) of the H_2O-catalyzed *addition* (a)−*elimination* (b)−*addition* (c) mechanism of urea formation from CO_2 and NH_3, at the presence of one extra “spectator” H_2O molecule opposite to the site of the proton transfer, calculated at the B3LYP/6-31G(d,p) and CBS-QB3 levels of theory. Values in braces are the B3LYP/6-31G(d,p) free energies (ΔG, kcal·mol^{-1}) at pressure 200 atm and temperature 473 K.

Finally, the effect of an extra, “spectator” H_2O molecule *opposite* to the active site of the proton transfer was investigated for the two reactions of the AEA mechanism (Figure 3b,c). For the dehydration reaction the decrease of the activation barrier was found to be negligible when the extra, “spectator” H_2O molecule is added (1.6 kcal·mol^{-1} at the CBS-QB3 level). On the other hand, for the NH_3 addition to HN═C═O the first higher activation barrier is further decreased by 5 kcal·mol^{-1}, while the second activation barrier remains almost unchanged at the same level of theory. Thus, we find that isocyanic acid resembles CO_2 in aminolysis reactions, being kinetically facilitated by microsolvation effects.

Similarly, in the hydration of isocyanic acid, following the reverse processes to those illustrated in Figures 2 and 3, microsolvation effects decrease the activation barrier by 8 kcal·mol^{-1} at the B3LYP/6-31G(d,p) level. In summary, it is predicted that the catalytic *addition*−*elimination*−*addition* mechanism involves the formation of small molecules, such as carbamic and isocyanic acid, and that the rate-determining step of the overall mechanism corresponds to the dehydration of carbamic acid, having an activation barrier of 39 kcal·mol^{-1}. Moreover, the first step of urea formation involving the NH_3 addition to CO_2, which is common for all three mechanisms, has a considerable activation barrier of about 27 kcal·mol^{-1}.

2.3. The Catalytic Addition—Elimination Mechanism. Both reactions can be assisted—catalyzed—by extra water or ammonia molecules. Interestingly, it was found that the addition step could be accomplished through two different transition states depending on which of the initial complexes between carbamic acid and the NH_3/H_2O molecules is considered as the reactant. The computed activation barriers range from 42.3 to 46.4 kcal·mol^{-1}. These barriers are lower than the barrier of the noncatalyzed reaction by about 15 kcal·mol^{-1}. For the sake of simplicity, only the two most favorable reactions are presented in Figure 2, while the other two are given as Supporting Information.

After formation of the unstable intermediate $C(NH_2)_2(OH)_2$, urea could be formed by elimination of one water molecule, which is assisted by additional NH_3 or H_2O molecules. The calculations predicted that the dehydration process has to surmount an activation barrier of about 20 kcal·mol^{-1} (at the CBS-QB3 level) a value being much lower than the barrier of the noncatalyzed reaction (33.2 kcal·mol^{-1} at the same level). The relatively low activation barrier can be partially attributed to the instability of the gem−diol−gem−diamine $C(NH_2)_2(OH)_2$ intermediate.

To summarize both catalytic *AEA* and *DAE* mechanisms demand comparable activation barriers (39 vs 42 kcal·mol^{-1}) illustrating that both mechanisms compete with each other, even though the first one seems to be marginally in favor.

2.4. The Catalytic Concerted (C) Mechanism. In the concerted mechanism, the formation of urea can also be assisted with extra water molecules (Figure 2), whereas for the NH_3-catalyzed reaction all attempts to locate the respective transition state using either the B3LYP or MP2 computational techniques were unsuccessful. The activation barrier of the H_2O-catalyzed reaction is lowered by only 8 kcal·mol^{-1}, with respect to the noncatalyzed one. In effect, the activation barrier is decreased to approximately 50 kcal·mol^{-1}, which is much higher than those of the other two stepwise reaction pathways. Therefore, the concerted mechanism seems to be energetically forbidden. It should be noticed that the concerted mechanism of a reagent-catalyzed addition−elimination reaction being higher in energy than the stepwise one both in a vacuum and in solution has been observed earlier and the solvent effects were found to leave the qualitative results unchanged.[36] In summary, urea’s formation both in a vacuum and in solution via the concerted mechanism could not be regarded as a favorable option.

Finally, we performed calculations of the PESs of the Bazarov’s synthesis of urea under the industrial conditions, e.g., high temperature (T = 473 K) and pressure (200 atm) and the results are also given in Figures 2 and 3 (figures in brackets).

It can be seen that under industrial conditions the calculated ΔG values are only marginally higher than those computed at the standard conditions, indicating that the reaction energetics are adequately described by the gas-phase calculations under standard conditions.

3. Considering the Reverse Process: The Hydrolysis of Urea. Following the same strategy the possible mechanism of the catalyzed hydrolysis of urea to NH_3 and CO_2 in the gas phase was also elucidated. More specifically, the AEA mechanism in its reverse direction consists of three successive reaction steps: (i) NH_3 elimination (deamination) from urea affording isocyanic acid, (ii) H_2O addition to HN═C═O (hydrolysis) affording carbamic acid, and (iii) NH_3 elimination from carbamic acid yielding CO_2. The catalyzed deamination of urea corresponds to a two-step reaction which demands a minimum of 29.3 kcal•mol^{-1} for the first step (Figure 3, **40** → **39**), while the second step is virtually barrierless. The subsequent hydration of HN═C═O has already been discussed in paragraph 2.2 with the activation barrier of the reaction predicted to be approximately 10 kcal•mol^{-1} at the B3LYP/6-31G(d,p) level of theory, which suggests a value of about 20 kcal•mol^{-1} at the more accurate CBS-QB3 level. In the third and final reaction step, which is common for all three molecular mechanisms, the catalyzed carbamic acid decomposition into NH_3 and CO_2 has an activation barrier of 22.4 kcal•mol^{-1} (Figure 3a), while the *syn*-H_2NCOOH transformation into its less stable anti- conformer requires an activation energy of 10 kcal•mol^{-1} at the CBS-QB3 level (Figure 2, **3** → **2**). It should be noted that the extra "spectator" H_2O molecule has no effect on the activation barrier of the NH_3 elimination from *anti*-H_2NCOOH, even though it slightly facilitates the reverse process.

Reversing the DAE mechanism, the following successive reaction steps occur: (i) H_2O addition to urea affording $C(NH_2)_2(OH)_2$ and (ii) NH_3 elimination from $C(NH_2)_2(OH)_2$ affording carbamic acid. The minimum activation barrier of the first reaction is estimated to be 44.5 kcal•mol^{-1} at the CBS-QB3 level, while the minimum barrier of the second one is estimated to be 16.7 kcal•mol^{-1} (Figure 2). Comparing AEA with DAE mechanism in their reverse direction, it is clear that the first one is energetically more favorable than the second one (29.3 vs 44.5 kcal•mol^{-1}).

Finally, in the catalyzed C mechanism (Figure 2) the simultaneous NH_3-elimination/H_2O-addition to urea affording directly carbamic acid has an activation barrier of 50 kcal•mol^{-1}, a value being quite high compared with the activation barriers of the other two stepwise mechanisms. The elimination pathway was also predicted to have lower activation barrier than the hydrolytic one ($\Delta G^{\ddagger} = 22$ kcal•mol^{-1}) at the solvent-corrected MP2/6-311++G** level of theory for the one-water catalyzed urea deamination.[15]

An overall clear picture of the mechanistic details of the noncatalyzed, the NH_3-catalyzed and the H_2O-catalyzed Bazarov synthesis of urea is given in Table 2.

Conclusions

From the comprehensive study of the mechanism of the noncatalyzed, the NH_3-catalyzed, and the H_2O-catalyzed Bazarov synthesis of urea the following conclusions can be drawn:

The reactants NH_3(g) and CO_2(g) considered as separate molecules lie lower in energy relative to the $H_2N{-}C(O){-}NH_2$ and H_2O products; the computed ΔH_f of the Bazarov's synthesis of urea was predicted to be 2.8 kcal•mol^{-1} at the CBS-QB3 level. The overall process is not spontaneous ($\Delta G_f = 13.3$ kcal•mol^{-1} at the same level) indicating that high temperatures

TABLE 2: Summary of the Activation Barriers ($\Delta G^{\ddagger}$, kcal·mol^{-1}) and Free Energies (ΔG, kcal·mol^{-1}) of the Noncatalyzed and Catalyzed Pathways of Bazarov Synthesis of Urea from NH_3(g) and CO_2(g), Computed at the B3LYP/6-31G(d,p) and CBS-QB3 Levels of Theory

mechanism	reaction	noncatalyzed		NH_3-catalyzed		H_2O-catalyzed		H_2O-cat. + spectator H_2O	
		$\Delta G^{\ddagger}$	ΔG	$\Delta G^{\ddagger}$	ΔG	$\Delta G^{\ddagger}$	ΔG	$\Delta G^{\ddagger}$	ΔG
AEA	NH_3 addition to CO_2	45.1 (50.4)[a]	13.6 (14.9)	24.9 (30.9)	6.1 (8.0)	23.4 (31.6)	7.6 (9.0)	17.5 (26.6)	1.4 (4.2)
	H_2NCOOH tautomerization	2.6 (2.6)	−7.7 (−7.3)						
	H_2NCOOH dehydr	51.5 (55.7)	16.5 (12.6)	35.4 (39.7)	9.1 (9.3)	33.9 (40.4)	17.1 (13.0)	33.2 (38.8)	24.3[b]
	NH_3 addition to HN═C═O	33.5 (37.8)	−11.8 (−10.5)	(i) 8.5 (14.6)	9.9 (14.1)	(i) 7.2 (13.4)	8.4 (12.9)	(i) 4.8 (9.4)	2.6 (7.2)
				(ii) 4.6 (7.0)	−24.8 (−27.3)	(ii) 2.3 (4.9)	−22.4 (−25.4)	(ii) 2.8 (5.7)	−21.1 (−23.6)
DAE	NH_3 addition to H_2NCOOH	60.4[b]	32.1 (25.6)	45.2 (42.3)	28.1 (21.7)	45.6 (43.8)	30.3 (23.8)		
	$C(NH_2)_2(OH)_2$ dehydr	27.8 (33.2)	−25.6 (−21.9)	18.2 (24.0)	−26.8 (−22.3)	14.5 (20.5)	−27.7 (−24.1)		
concerted	NH_3 addition/H_2NCOOH dehydr	56.0 (57.2)	6.2 (3.6)	*c*	*c*	46.8 (49.4)	2.0 (−0.6)		

[a] Figures in parentheses refer to the values computed at the CBS-QB3 level. [b] No stationary points were located at the CBS-QB3 level. [c] No saddle point was located at both levels of theory.

are necessary to be applied for the reaction to be accomplished. Moreover, as expected, these results are compatible with the high spontaneity of the reversible process—the hydrolysis of urea—which is hydrolyzed in vivo by only one enzyme without consuming energy, whereas its synthesis requires many successive steps, the participation of many enzymes and the consumption of three high-energy phosphate bonds (ATPs).

The first step of urea formation from NH_3(g) and CO_2(g) corresponds to a simple addition reaction leading to the carbamic acid intermediate, a process being moderately endothermic. The loose adducts formed between NH_3 and carbamic acid can be regarded as the form of the intermediate ammonium carbamate that dehydrates to urea. From the three mechanisms examined, the *concerted* (*C*) one was predicted kinetically disfavored. On the other hand, the *addition−elimination−addition* (*AEA*) and the *double addition−elimination* (*DAE*) mechanisms, are almost equally favored. However, for the reverse process, the hydrolysis of urea into the volatile NH_3(g) and CO_2(g) species, the hydrolytic pathway is predicted to be energetically favored.

The synthesis of urea using the Bazarov's procedure is assisted by the active participation of extra NH_3 or H_2O molecules (reagent−catalysis). The barriers for the uncatalyzed reactions are too high to be viable.

Finally, considering that the synthesis of urea in the industrial scale is carried out under high temperature and pressure, conditions closely resembling those of the prebiotic atmosphere on our planet, the reaction scheme described herein reveals that both isocyanic acid, H−N═C═O, and carbamic acid, H_2N−COOH, were actually key intermediates in the initial formation of organic molecules, since they are both connected with urea formation. Taking into account that NH_3 addition to HN═C═O, according to the AEA mechanism, proceeds almost without any appreciable barrier, we can claim that urea is actually formed by "ammonium carbamate" dehydration, as has been postulated for many decades. The "ammonium carbamate" dehydration is, indeed, the rate-determining step in this mechanism characterized simultaneously by high endothermicity.

Supporting Information Available: Energies (Tables S1 and S2) and Cartesian coordinates (Table S3) of all stationary points, energetic and geometric profiles of the isocarbamic conformers (Figure S1), the noncatalyzed dehydration of $C(NH_2)_2(OH)_2$ to isourea (Figure S2), the tautomerization of isourea to urea (Figure S3), and the NH_3-catalyzed dehydration of $C(NH_2)_2(OH)_2$ to isourea (Figure S4). This material is available free of charge via the Internet at http://pubs.acs.org.

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