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Understanding the mechanism of the *N*-heterocyclic carbene-catalyzed ring-expansion of 4-formyl-β-lactams to succinimide derivatives

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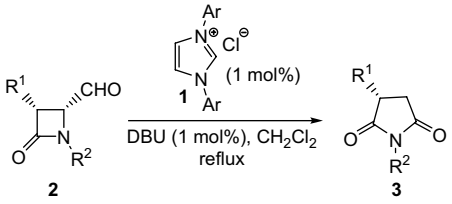
ABSTRACT

The mechanism of the *N*-heterocyclic carbene (NHC)-catalyzed ring-expansion of 4-formyl-β-lactams to succinimides has been studied using DFT methods at the B3LYP/6-31G** level. The first step is the nucleophilic attack of NHC to the aldehyde to yield the zwitterionic intermediate, which by a proton-transfer process affords the Breslow intermediate. The lactam N–C breaking bond in this intermediate yields an enol-amidate, which by a keto–enol type equilibrium becomes the ketone form. The subsequent ring-closure achieved by the nucleophilic attack of the amidate to carbonyl carbon allows the formation of the five-membered ring. Finally, elimination of NHC affords the succinimide. Analysis of the nucleophilicity index correctly explains the behaviors of the NHCs and the Breslow intermediates in the *umpolung* reactivity of aldehydes.

1. Introduction

Succinimides constitute an important compound class due to their wide profile of biological activity.[1] Besides, the succinimide nucleus is a useful building block for the synthesis of natural as well as unnatural products.[2] On the other hand, the use of 2-azetidinones as chiral building blocks in organic synthesis is now well established.[3] Although many efforts have been made in these fields, the preparation of the succinimide ring from the β-lactam nucleus has not been much studied. Recently, Alcaide et al.[4] studied the tetrabutylammonium cyanide-catalyzed ring-expansion of 4-(arylamino)methylazetidin-2-ones to succinimide derivatives.

N-Heterocyclic carbene (NHC) catalysts are being extensively utilized for a variety of transformations by the means of *umpolung*,[5] reversing of the reactivity of aldehydes, providing an unconventional access to some important target molecules.[6,7] Very recently, You[8] and Alcaide[9] have reported that in presence of NHC catalysts, *cis*-4-formyl-β-lactams undergo a ring-expansion to succinimide derivatives (see Scheme 1). Thus, when the *cis*-4-formyl-β-lactam **2** (R^1=Ph, R^2=PMP) was treated with 1 mol % of the imidazolium chloride **1** (Ar=Mes) and DBU, it was smoothly converted to the succinimide **3** in 7 h at reflux in 99% yield.[8a]



Scheme 1.

A plausible catalytic cycle was proposed as illustrated in Scheme 2.[8,9] The NHC **4** would be formed in situ by deprotonation of imidazolium chloride **1** in the presence of DBU, at its most acidic position. The resulting imidazol-2-ylidene, **4**, the actual catalyst, reacts with 4-formyl-β-lactam **2** to give the enoldiamine **5**, which undergoes the ring-opening of 4-formyl-β-lactam releasing the nucleophilic amidate **6**. The nucleophilic amidate **7**, the carbonyl form of **6**, experiments an intramolecular cyclization to give succinimide derivative **8**, which releases the NHC catalyst **4** to yield the succinimide **3**.

The key step of this catalyst cycle is the formation of the enoldiamine **5**, which permits the cleavage of the N1–C4 lactam ring through a *umpolung* reactivity of the aldehyde carbon atom. The N1–C4 cleavage on the 4-formyl-β-lactam **2** will generate a very energetic zwitterionic intermediate **ZW1** in which the C4 positive charge is located closer to the carbonyl carbon atom of the formyl group (see Scheme 3). This unfavorable arrangement prevents the corresponding ring-cleavage on the 4-formyl-β-lactam **2**. However,

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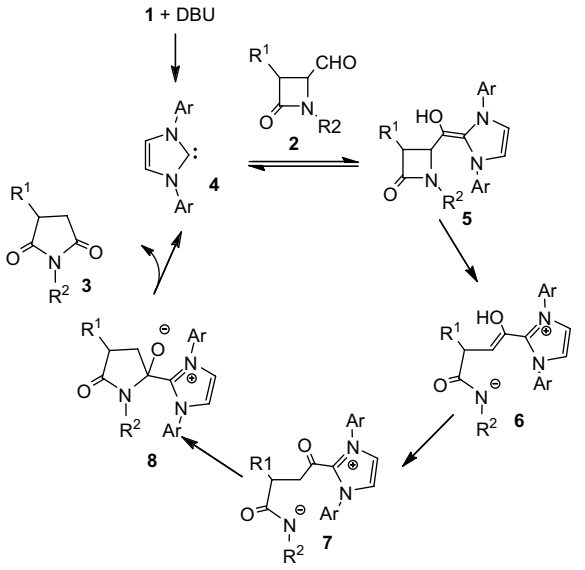
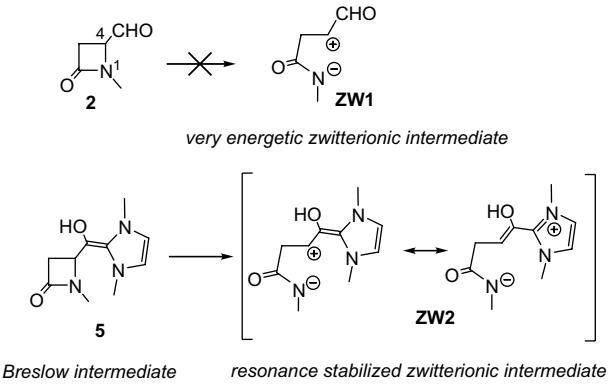


Scheme 2.

the presence of the 2-methyleneimidazole group on **5** favors the corresponding N1–C4 cleavage by a favorable charge delocalization on the C4 carbocationic center, which is being generate along the heterolytic N1–C4 breaking bond.



Scheme 3.

The enoldiamines as **5**, know as Breslow intermediates,[10] are proposed as the key intermediates on the NHC *umpolung* reactivity of aldehydes, because the electron-deficient carbonyl carbon becomes as an electron-rich center to occupy the β-position of the enoldiamine (see Chart 1).

In 1958 Breslow[10] studied the mechanism of the thiazolium catalyzed benzoin condensation. It stated that the key intermediate was compound **12**, which acts as nucleophile like the α-hydroxyl carbanionic intermediate on the cyanide-catalyzed reaction of benzaldehyde to benzoin.[11] These intermediates are highly appreciated d^1-synthons in the *umpolung* reactivity of the aldehydes. In 1964, Lemal et al.[12] proposed that the true mechanism of the benzoin condensation involves the dimerization of the thiazolin-2-ylidene **10** to **15**, and the subsequent addition to benzaldehyde to form, after a proton-transfer process on the adduct **16**, the carbanion **17**. The subsequent C–C breaking bond in **17** will afford the Breslow intermediate **12**. Experimental evidences reported by Lopez-Calahorra et al.[13] indicated that the bis(thiazolin-2-ylidene) **15** acts as catalyst in the benzoin condensation. However, further experimental studies reported by Breslow and Schmuck[14] indicated that the reaction is first order in thiazolium ion thus excluding the participation of anions as **17**.

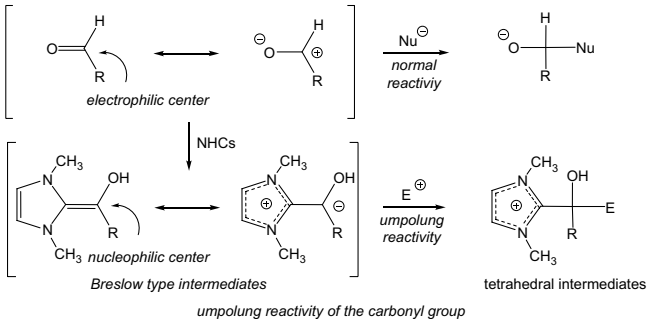
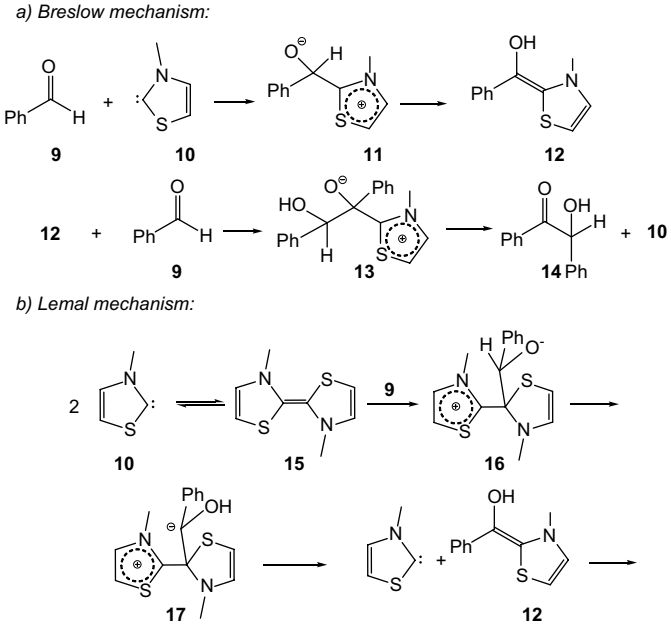


Chart 1.

The NHC catalyzed benzoin condensation has been theoretically studied firstly by Bofill et al.[15] at the AM1 semiempirical level and more recently by Goldfuss and Schumacher[16] using density functional theory (DFT) methods at the B3LYP/6-31G* level. Formation of the Breslow intermediate **12**, which is involved in most of the NHC *umpolung* catalyzed reactions of aldehydes, comprises two steps (see Scheme 4). The first one is the nucleophilic attack of the thiazol-2-yliden carbene **10** to benzaldehyde **9** to yield the alkoxy intermediate **11**, which by a proton-transfer process yields in the second step the Breslow intermediate **12**. Although formation of the intermediates **11** and **12** were slightly exothermic, −1.3 and −5.4 kcal/mol, respectively, the activation energy associated with the proton-transfer process was very high, 38.1 kcal/mol. This unfavorable activation energy was closer to that obtained by Bofill at the AM1 level, 33.2 kcal/mol.[15] The Lemal mechanism was also studied by Bofill et al.[15] at the AM1 semiempirical level. They found that the formation of the alkoxide **16** is endothermic in 18.8 kcal/mol, being the barrier for the proton-transfer process of 64.6 kcal/mol.



Scheme 4.

Our interest in the organocatalysis[17] has prompted us to carry out a series of theoretical investigations about the mechanisms of the NHC catalyzed reactions of aldehydes. In this first study, we would investigate NHC catalyzed ring-expansion of 4-formyl-β-lactams to succinimide derivatives using DFT methods at the well-established B3LYP/6-31G** level. For this propose the

ring-expansion of *N*-methyl-4-formyl-β-lactam **27** catalyzed by *N*,*N*-dimethyl-imidazol-2-ylidene **19** was selected as a computational reaction model (see Scheme 6). We have investigated the transition state structures (TSs) for the Breslow intermediate formation, as well as the lactam ring-cleavage and succinimide ring-formation steps.

2. Computational methods

DFT calculations were carried out using the B3LYP[18] exchange-correlation functionals, together with the standard 6-31G** basis set.[19] The optimizations were carried out using the Berny analytical gradient optimization method.[20] The stationary points were characterized by frequency calculations in order to verify that the TSs have one and only one imaginary frequency. The intrinsic reaction coordinate (IRC)[21] path was traced in order to check the energy profiles connecting each TS to the two associated minima of the proposed mechanism by using the second order González–Schlegel integration method.[22] The electronic structures of stationary points were analyzed by the NBO method.[23] All calculations were carried out with the Gaussian 03 suite of programs.[24]

Solvent effects have been considered by B3LYP/6-31G** full geometry optimization of the gas-phase structures using a self-consistent reaction field (SCRF)[25] based on the polarizable continuum model (PCM) of the Tomasi's group.[26] Since these reactions are carried out in dichloromethane (DCM), we have selected its dielectric constant at 298.0 K, ε=8.93. Values of free energies in DCM were calculated with the standard statistical thermodynamics at 298.15 K.[19] Thermodynamic calculations were scaled by a factor of 0.96. The gas-phase standard states at 1 atm, denoted by the superscript ^{0}, were converted to 1 mol/L, denoted by the superscript *.[27] The relationship between these two standard states is

$$\Delta G^{*} = \Delta G^{0} - \Delta G^{0\rightarrow *}$$

where

$$\Delta G^{0\rightarrow *} = RT\ln\left(Q^{0}/Q^{*}\right)$$

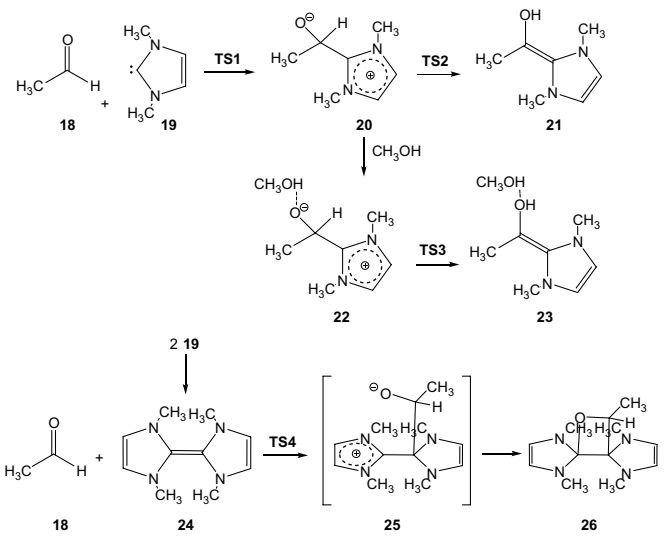
For A+B→C reaction, at 298 K $\Delta G^{0\rightarrow *}$ equals 1.9 kcal/mol.

The global electrophilicity index,[28] ω, which measures the energy stabilization when the system acquires an additional electronic charge ΔN from the environment, has been given by the following simple expression, $\omega=(\mu^2/2\eta)$, in terms of the electronic chemical potential μ and the chemical hardness η. These quantities may be approached in terms of the energies of the frontier molecular orbital HOMO and LUMO, ε_H and ε_L, as $\mu\approx(\varepsilon_H+\varepsilon_L)/2$ and $\eta\approx(\varepsilon_L-\varepsilon_H)$, respectively.[29] Recently, we have introduced an empirical (relative) nucleophilicity index, *N*,[30] based on the HOMO energies obtained within the Kohn–Sham scheme, and defined as $N=\varepsilon_{HOMO\ (Nu)}-\varepsilon_{HOMO\ (TCE)}$, where tetracyanoethylene (TCE) is chosen as reference. On the other hand, recently we have shown that the local nucleophilicity of simple substituted aromatic systems are well described on a quantitative basis by using a condensed-to-atoms nucleophilicity index N_k,[31] which is given by the equation $N_k=Nf_k^-$, were f_k^- is the nucleophilic Fukui function.[32]

3. Results and discussion

3.1. Study of the formation of the Breslow intermediate 21

Due to the relevance of the Breslow intermediates on the *umpolung* reactivity of aldehydes, we studied firstly the formation of the enoldiamine **21** from the reaction of acetaldehyde **18** with the NHC **19** as a reduced reaction model (see Scheme 5). Formation of **21** involves two consecutive steps: (i) the nucleophilic attack of the NHC **19** to the carbonyl carbon of acetaldehyde **18** to yield the zwitterionic intermediate **20**, and (ii) a proton-transfer process to afford the Breslow intermediate **21**.



Scheme 5.

The activation barrier associated with the nucleophilic attack of the NHC **19** to acetaldehyde **18** via **TS1** has a very low value, 1.3 (1.3) kcal/mol; formation of the zwitterionic intermediate **20** is slightly exothermic, −6.9 (−1.6) kcal/mol (values in parenthesis correspond to the gas-phase energies) (see Table 1). However, the activation barrier associated with the intramolecular proton-transfer process via **TS2** has very large value, 48.0 (42.0) kcal/mol. Formation of the Breslow intermediate **21** is exothermic by −0.8 (−4.1) kcal/mol. Therefore, the proton-transfer process is the rate-determining step of the formation of the Breslow intermediate **21**. The energetic difference between the gas-phase and DCM are mainly due to the large stabilization of the zwitterionic intermediate **20** in DCM. This energetic result are closer to those obtained by Goldfuss et al. for the proton-transfer step of the addition of the *N*-methylthiazol-2-ylidene **10** to acetaldehyde in THF, 38.1 kcal/mol.[16b]

An important part of the large activation barrier associated with the formation of **TS2** can be related to the strain associated with the three-membered TS.[33] Because these reactions are initialized by a proton abstraction of the azolium salt by bases as KO^{t}Bu, NEt$_3$ or DBU, it is expected that the presence of Brønsted acid species BH$^+$ could catalyze the proton-transfer process via formation of hydrogen bond to the alkoxy oxygen of **20**, which could favor the proton-transfer process via a lesser strained five-membered TS (see Scheme 5). Thus, the activation barrier for the proton transfer via the methanol hydrogen-bonded **TS3** is reduced to 22.9 (23.7) kcal/mol.

Finally, in order to assess the Lemal mechanism via dimer carbenes, the addition of the dimer **24** to acetaldehyde **18** to yield the zwitterionic intermediate **25** was also studied (see Scheme 5). Formation of the dimer **24** is slightly endothermic 0.9 (−6.6) kcal/mol. This unlike result with the gas-phase is a consequence of the larger solvation of the NHC **19** than the dimer **24**. On the other hand, the activation barrier for the nucleophilic attack of the dimer **24** to acetaldehyde **18** presents a very large value, 22.8 (28.7) kcal/mol. Note that the activation barrier associated with the attack of monomer **19** to **18** was only of 1.3 kcal/mol. In addition, all attempts to obtain the intermediate **25** in gas-phase and in DCM as a stationary point were unsuccessful, because the zwitterionic structure **25** becomes the oxetane **26**. Formation of this new intermediate is kinetically and thermodynamically unfavorable (see Table 1).

Table 1
Total (E, in au) and relative (ΔE, in kcal/mol) energies, in gas phase and in dichloromethane, and total (G, in au) and relative (ΔG^0 (1 atm), ΔG^* (1 M), in kcal/mol) free energies, in dichloromethane of the stationary points involved on the formation of the Breslow intermediate **21**

	E	ΔE	E_{sol}	ΔE_{sol}	G_{sol}	ΔG^0_{sol}	ΔG^*_{sol}
18	−153.835730		−153.841196		−153.812955		
19	−304.803845		−304.812771		−304.722559		
TS1	−458.637483	1.3[a]	−458.651920	1.3[a]	−458.512481	14.5[a]	12.6[a]
20	−458.642202	−1.6[a]	−458.665008	−6.9[a]	−458.522140	8.4[a]	6.5[a]
TS2	−458.575271	40.4[a]	−458.588521	41.1[a]	−458.448993	54.3[a]	52.4[a]
21	−458.646059	−4.1[a]	−458.655252	−0.8[a]	−458.514886	12.9[a]	11.0[a]
22	−574.400513		−574.418168		−574.228870		
TS3	−574.362671	23.7[b]	−574.381676	22.9[b]	−574.196723	20.2[b]	20.2[b]
23	−574.383782	10.5[b]	−574.391295	16.9[b]	−574.206466	14.1[b]	14.1[b]
24	−609.618177	−6.6[c]	−609.624083	0.9[c]	−609.416952	17.7[c]	15.8[c]
TS4	−763.408172	28.7[d]	−763.428930	22.8[d]	−763.169614	37.8[d]	35.9[d]
26	−763.450598	2.1[d]	−763.457040	5.2[d]	−763.196426	21.0[d]	19.1[d]

[a] Relative to **18**+**19**.
[b] Relative to **22**.
[c] Relative to **19**.
[d] Relative to **18**+**24**.

Because the two reaction steps involved in the formation of the Breslow intermediate **21** comprise chemical processes of different molecularity, the total and relative free energies associated with the stationary points of this reaction were computed at the reaction conditions (25 °C and in DCM).[8b] The energy data are collected in Table 1. With the inclusion of the thermal corrections and the entropy, the activation free energy associated with the nucleophilic attack of NHC **19** to acetaldehyde **18** arises to 12.6 kcal/mol; formation of the intermediate zwitterionic is endergonic in 6.5 kcal/mol. These results are a consequence of the bimolecular nature of the addition step. The activation free energy associated with the intramolecular proton-transfer process presents a very large value, 45.9 kcal/mol. For the Brønsted acid catalyzed process the activation free energy decreases to 20.2 kcal/mol. Finally, the Breslow intermediate **21** is located in the free energy surface 11.0 kcal/mol above the reagents. The unfavorable entropy of formation is responsive of the endergonic character of the process.

The free energy of formation of the dimer **24** arises to 15.8 kcal/mol. In addition, the activation free energy associated with the nucleophilic attack of the dimer **24** to acetaldehyde **18** presents a very large value, 35.9 kcal/mol. These unfavorable energies allow us to discard the Lemal mechanism for the formation of the Breslow intermediate **21**.

The geometries of the TSs involved in the formation of the Breslow intermediate **21** are given in Figure 1. A comparison of the length of the forming and breaking bonds at the TSs obtained in gas-phase and in DCM indicates that there are not significant differences. So, only the gas-phase results will be discussed. At **TS1** the length of the C–C forming bond is 1.958 Å. The perpendicular arrangement of NHC **19** relative to acetaldehyde **18** accounts for the nucleophilic attack of the lone pair of the NHC **19**, which is located in a sp^2 orbital, to the carbonyl sp^2 carbon of acetaldehyde **18**. At **TS2** the lengths of C–H breaking and O–H forming bonds are 1.192 and 1.297 Å, respectively. The O–C–H bond angle, 57.5°, points to

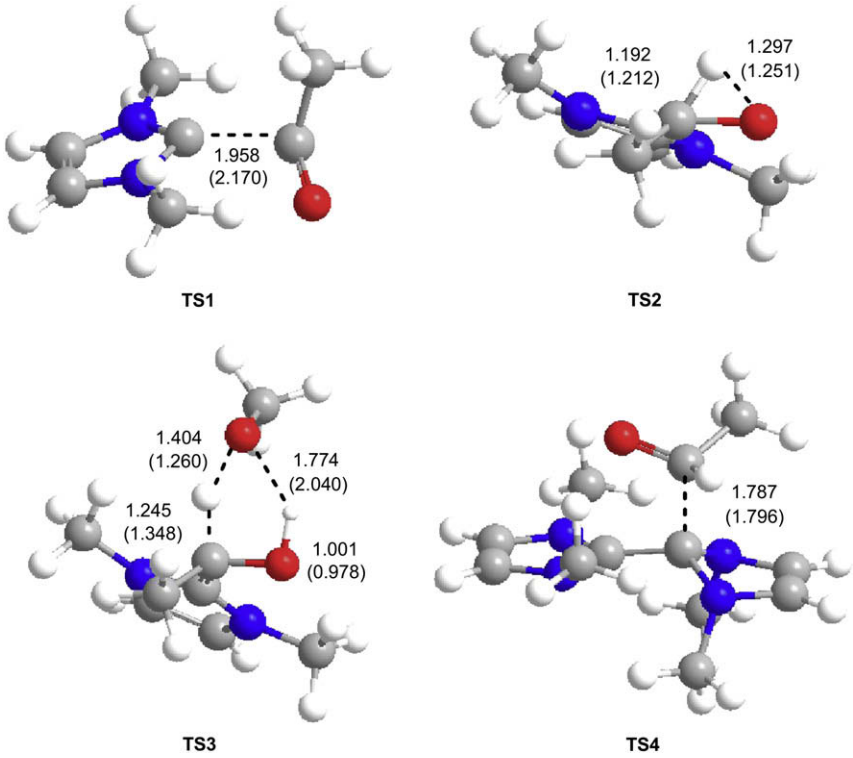
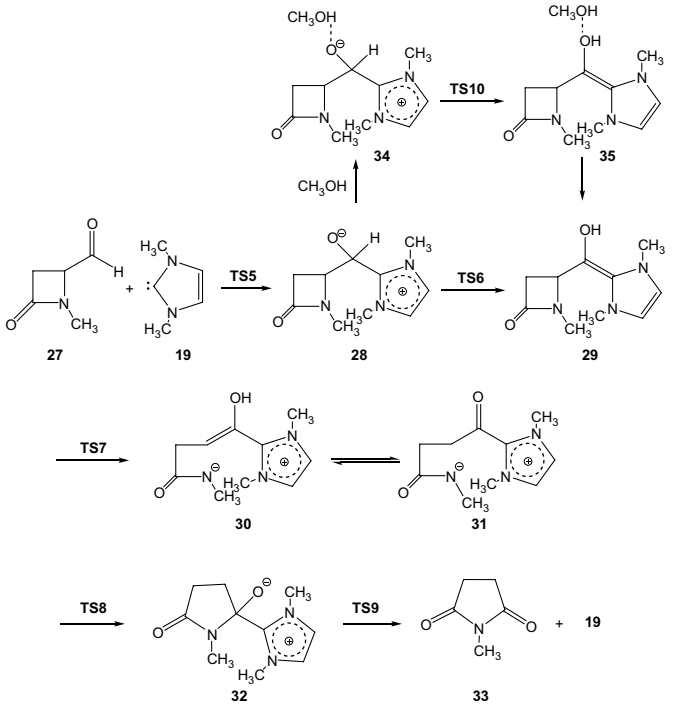


Figure 1. Transition structures associated with the formation of the Breslow intermediate 21. In parenthesis are the distances in DCM. The distances are given in Å.



Scheme 6.

the large strain associated with this intramolecular process. Note that this bond angle at the intermediate **20** is 115.0°. At **TS3** the lengths of breaking and forming bonds associated with the double proton transfer indicate that the proton transfer from methanol to the alkoxy oxygen is more advanced than that from carbon to the oxygen of methanol (see Fig. 1). The C–H breaking and O–H forming bonds at the later process are 1.245 and 1.404 Å, respectively. At this TS, the O–C–H bond angle is 96.0°. Finally, at **TS4** the length of the C–C forming bond is 1.787 Å.

The extent of bond-formation along a reaction pathway is provided by the concept of bond order (BO).[34] At **TS1** the BO value of the C–C forming bond is 0.48. At **TS2** the BO values of C–H breaking and O–H forming bonds are 0.49 and 0.24, respectively. At **TS3** the BO values of breaking and forming bonds associated with the double proton transfer, 0.58 and 0.24 for the C–H–O, and 0.10 and 0.62 for the O–H–O, respectively, indicate that proton transfer from methanol to alkoxy oxygen is more advanced than that from carbon to the oxygen of methanol. Finally, at **TS4** the BO value of the C–C forming bond is 0.69. This BO value, which is larger than that at **TS1**, points out the very advanced character of this TS, and it is in agreement with high activation barrier and the endothermic character of the addition step.[35] Both energies, geometries and BO values rule out the Lemal mechanism for the formation of the Breslow intermediates via dimerization of the NHCs.

3.2. Study of the NHC catalyzed ring-expansion on the *N*-methyl-4-formyl-β-lactam 27 to *N*-methysuccinimide 33

The NHC catalyzed ring-expansion on the 4-formyl-β-lactam **27** to the succinimide **33** comprises several elementary steps (see Scheme 6). The first step is the nucleophilic attack of the imidazol-2-ylidene **19** to the 4-formyl-β-lactam **27** to yield the zwitterionic intermediate **28**, which by a proton-transfer process affords the Breslow intermediate **29**. The N–C breaking bond in **29** yields the amidate **30**, which by a keto–enol type equilibrium becomes the ketone form **31**. The subsequent ring-closure on **31** achieved by the nucleophilic attack of the amidate anion to carbonyl carbon atom present in **31** allows the formation of the zwitterionic intermediate **32**, which by elimination of NHC **19** affords the succinimide **33**. The energy data are collected in the Table 2.

The **TS5**, associated with the nucleophilic attack of the NHC **19** to the 4-formyl-β-lactam **27**, and the corresponding zwitterionic intermediate **28** are located below reagents: −1.4 (−2.3) and −11.1 (−6.8) kcal/mol, respectively. That is, the nucleophilic attack of **19** to **27** has not any appreciable barrier. The subsequent intermolecular proton transfer via **TS6** presents also a very high activation barrier, 46.4 (41.9) kcal/mol; formation of the Breslow intermediate **29** is exothermic by −7.3 (−9.7) kcal/mol. For the Brønsted acid/base catalyzed proton-transfer process the activation barrier associated with **TS10** is 20.4 (18.1) kcal/mol. These results are similar to those obtained for the addition of the NHC **19** to acetaldehyde **18**. Therefore, it is expected that the proton-transfer process from **28** to **29** takes place also by a Brønsted acid/base catalyzed process.

The N–C breaking bond in the Breslow intermediate **29** via **TS7** has an activation barrier of 9.1 (11.4) kcal/mol. Formation of the amidate **30** is exothermic by −4.7 (8.1) kcal/mol. The amidate **30** by a keto–enol type equilibrium can be irreversibly transformed into the ketone-amidate **31**, which is −15.6 (−8.7) kcal/mol more stable than the Breslow intermediate **29**.

In gas-phase, the subsequent intramolecular nucleophilic attack of the amidate to the carbonyl carbon of **31** has not any appreciable activation barrier. Geometrical optimization in DCM allowed to find the TS associated with the ring-closure process. In DCM **TS8** was

Table 2
Total (E, in au) and relative[a] (ΔE, in kcal/mol) energies, in gas phase and in dichloromethane, and total (G, in au) and relative[a] (ΔG^0 (1 atm), ΔG^* (1 M), in kcal/mol) free energies, in dichloromethane of the stationary points involved in the NHC catalyzed ring-expansion on the *N*-methyl-4-formyl-β-lactam **27**

	E	ΔE	E_{sol}	ΔE_{sol}	G_{sol}	ΔG^0_{sol}	ΔG^*_{sol}
27	−399.925271		−399.937814		−399.858330		
TS5	−704.732833	−2.3	−704.752868	−1.4	−704.562570	11.5	9.6
28	−704.739969	−6.8	−704.768205	−11.1	−704.572867	5.1	3.2
TS6	−704.673193	35.1	−704.694356	35.3	−704.502724	49.1	47.2
29	−704.744651	−9.7	−704.762265	−7.3	−704.569332	7.3	5.4
TS7	−704.726377	1.7	−704.747671	1.8	−704.555427	16.0	14.1
30	−704.731612	−1.6	−704.769632	−12.0	−704.578123	1.8	−0.1
31	−704.758486	−18.4	−704.787106	−22.9	−704.591794	−6.8	−8.7
TS8			−704.787002	−22.9	−704.590275	−5.9	−7.8
32	−704.782310	−33.4	−704.806549	−35.1	−704.609204	−17.7	−19.6
TS9	−704.780065	−32.0	−704.798855	−30.3	−704.603744	−14.3	−16.2
33	−399.992731		−400.002981		−399.921288		
34	−820.490768		−820.519166		−820.279542		
TS10	−820.461959	18.1[b]	−820.486578	20.4[b]	−820.248743	19.3[b]	19.3[b]

[a] Relative to **27**+**19**.
[b] Relative to **34**.

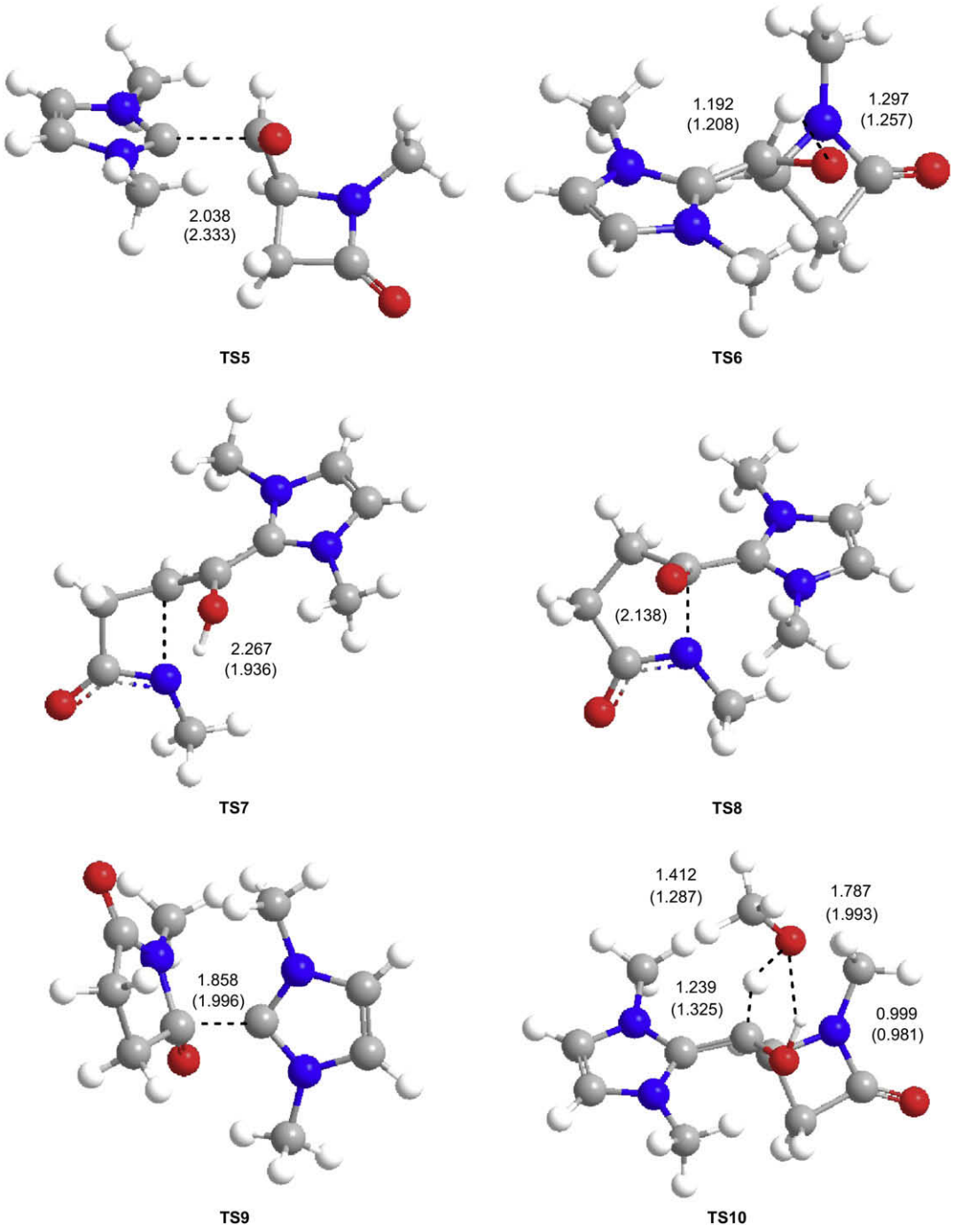


Figure 2. Transition structures associated with the NHC catalyzed ring-expansion on the N-methyl-4-formyl-β-lactam 27. In parenthesis are the distances in DCM. The distances are given in Å.

only 0.07 kcal/mol more energetic than the ketoamidate **31**. Formation of the intermediate **32** is exothermic by −12.2 (−15.0) kcal/mol. Finally, the intermediate **32** with a very low activation barrier, 4.8 (1.4) kcal/mol, loses the NHC catalyst via **TS9** to yield the succinimide derivative **33**. This last step of the reaction is also exothermic by −5.8 (−9.0) kcal/mol. The NHC catalyzed ring-expansion of the 4-formyl-β-lactam **27** is strongly exothermic by −40.9 (−42.3) kcal/mol.

The free energies of the stationary points involved in the NHC catalyzed ring-expansion reaction of 4-formyl-β-lactam **27** were computed at the reaction conditions (25 °C and in DCM).[8b] The energy data are collected in Table 2. With the inclusion of the thermal corrections and the entropy, the activation free energy associated with the nucleophilic attack of NHC **19** to the aldehyde **27** arises to 9.6 kcal/mol; formation of the intermediate zwitterionic is endergonic in 3.2 kcal/mol. The activation free energy associated with the intramolecular proton-transfer process presents also a very large value, 44.0 kcal/mol. For the Brønsted acid/base catalyzed process, the activation free energy decreases to 19.3 kcal/mol. Finally, the Breslow intermediate **29** is located in the free energy surface 5.4 kcal/mol above the reagents. These energies are slightly lower than those found for the reaction of the NHC **19** with acetaldehyde.

The activation free energy associated with the N–C breaking bond at the Breslow intermediate **29** via **TS7** is 8.7 kcal/mol; formation of the amidate **30** is exergonic by −5.5 kcal/mol. From the Breslow intermediate **29**, formation of the ketone form **31** is strongly exergonic, −14.1 kcal/mol. Therefore, formation of the ketoamidate **31** via the ring-aperture of the Breslow intermediate **29** can be considered irreversible. The amidate **31**, with a very low activation free energy, 0.9 kcal/mol, is converted into the succinimide derivative **32**. This step is also exergonic by −10.9 kcal/mol. Finally, the intermediate **32** with a very low activation free energy, 3.4 kcal/mol, loses the NHC catalyst to yield the succinimide derivative **33**. This last step is also strongly exergonic, −21.7 kcal/mol, as a consequence of the increase of the reaction entropy associated with the extrusion of the NHC catalyst. The NHC catalyzed ring-expansion on the 4-formyl-β-lactam **27** is exergonic by −39.5 kcal/mol. These energetic results indicate that the NHC catalyzed ring-expansion is kinetically and thermodynamically very favorable.

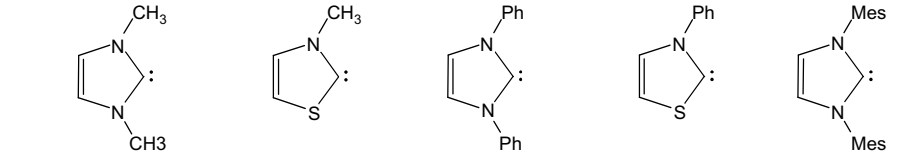
The geometries of the TSs involved in the NHC catalyzed ring-expansion of the *N*-methyl-4-formyl-β-lactam **27** are given in Figure 2. At **TS5**, associated with the nucleophilic attack of the NHC **19** of the carbonyl carbon atom of the formyl derivative **27**, the length of the C–C forming bond is 2.038 Å. As at **TS1**, the perpendicular arrangement of NHC **19** relative to carbonyl group of **26** is in agreement with the nucleophilic attack of the singlet carbene lone pair of **19** to the carbonyl sp^2 carbon of the aldehyde **27**. At **TS6**, associated with the intramolecular proton-transfer process, the lengths of C–H breaking and O–H forming bonds are 1.192 and 1.297 Å, respectively. At this TS, the O–C–H bond angle, 57.6°, points to the large strain associated with the intermolecular process. These geometrical parameters as identical to those found at **TS2**. At **TS7**, associated with the lactam ring-cleavage, the length of the C–N breaking bond is 2.267 Å, while at **TS8**, associated with the succinimide ring-formation, the length of the C–N forming bond is 2.138 Å. Note that this TS was obtained only in DCM. At **TS9**, associated with the elimination of the NHC **19**, the length of the C–C breaking bond is 1.858 Å. Finally, at **TS10** the lengths of breaking and forming bonds associated with the double proton transfer indicate that the proton transfer from methanol to the alkoxy oxygen is more advanced than that from the carbon to the oxygen of methanol (see Fig. 2). The C–H breaking and O–H forming bonds at the later process are 1.239 and 1.412 Å, respectively. These values are closer to those found at **TS3**.

The BO value of the C–C forming bond at **TS5** is 0.48. At **TS6**, the BO values of C–H breaking and O–H forming bonds are 0.49 and 0.23, respectively. The C–H breaking bond is more advanced than the O–H forming bond. At **TS7** the BO value of the C–N breaking bond is 0.40, while at **TS8** the BO value of the C–N forming bond is 0.29 (in DCM). At **TS9** the BO value of the C–C breaking bond is 0.63. Finally, at **TS10** the BO values of breaking and forming bonds associated with the double proton transfer, 0.58 and 0.24 for the C–H–O, and 0.10 and 0.62 for the O–H–O, respectively, indicate that proton transfer from methanol to alkoxy oxygen is more advanced than that from carbon to the oxygen of methanol.

3.3. Analysis of the reactivity indices of the NHCs and Breslow intermediates

Finally, due to the relevance of the nucleophilicity on the *umpolung* reactivity of the carbonyl compounds, the nucleophilic behaviors of the some NHC and Breslow intermediates have been studied analyzing the global[27] and local[28] nucleophilicity indices. Since singlet carbenes could have some electrophilic behavior,[36] the corresponding electrophilicity indices have also been

Table 3
HOMO and LUMO energies, and global electrophilicity, ω, and nucleophilicity, N, of NHCs and Breslow intermediates



	HOMO (au)	LUMO (au)	ω (eV)	N (eV)
24	−0.1317	0.0380	0.18	5.54
41	−0.1342	0.0019	0.44	5.47
21	−0.1387	0.0390	0.19	5.35
42	−0.1436	−0.0213	0.76	5.21
12	−0.1658	−0.0208	0.82	4.61
40	−0.1687	0.0089	0.49	4.53
43	−0.1873	−0.0738	2.04	4.02
19	−0.1963	0.0425	0.34	3.78
39	−0.2008	−0.0018	0.70	3.66
37	−0.2113	−0.0170	0.91	3.37
36	−0.2164	−0.0053	0.79	3.23
38	−0.2197	−0.0255	1.05	3.14

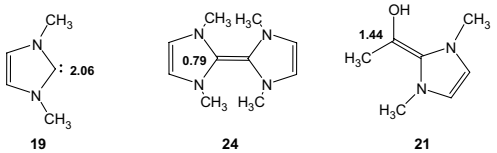
calculated. The global electrophilicity and nucleophilicity of the NHC and Breslow intermediates are given in Table 3.

Regarding the electrophilicity of the simplest carbene CH_2 **43**, ω=2.04 eV, the series of NHCs presents low electrophilicity powers, ω ranges from 0.34 to 1.05 eV. These low electrophilicity values are a consequence of the presence of the two α nitrogen or sulfur atoms able to delocalize theirs lone pair on the carbene carbon atom.

For the selected series of NHC, the global nucleophilicity N ranges from 3.14 to 3.78 eV, they being classified as strong nucleophiles.[37] These values are slightly lower than that for the simplest carbene **43**, N=4.02 eV. Some correlation can be obtained from the structure of these NHC and the nucleophilicity. The nucleophilicity of the imidazole carbenes **19**, N=3.78 eV, and **37**, N=3.37 eV, is slightly larger than that for the thiazole carbenes **36**, N=3.23 eV, and **38**, N=3.14 eV, respectively, in clear agreement with the large electron-releasing character of the nitrogen than the sulfur atom. On the other hand, substitution of the methyl group by a phenyl group decreases the nucleophilicity of the corresponding carbene; see **37** and **38** respect to **19** and **36**, respectively. The mesityl imidazole carbene **39**, N=3.66 eV, presents a large nucleophilicity than the phenyl imidazole carbene **37**, N=3.37 eV, as a consequence of the presence of the electron-releasing methyl groups on **39**. The dimer **24** presents the largest nucleophilicity, N=5.54 eV. However, the symmetry present in this molecule can be responsible for the poor efficacy as nucleophile (see later).

The Breslow intermediates present larger nucleophilicity values, N ranges from 4.53 to 5.47 eV, than that for the corresponding NHCs. The nucleophilicity of the imidazole intermediates **21**, N=5.35 eV, and **41**, N=5.47 eV, is slightly larger than that for the thiazole intermediates **40**, N=4.53 eV, and **12**, N=4.61 eV, respectively. This trend is similar to that observed at the corresponding carbenes.

A recent study about the reactivity of the cyano ethylene series as electrophiles in polar Diels–Alder reaction has shown that the symmetric substitution of the 1,2-dicyanoethylenes produces a poor electrophilic activation on the ethylene relative to that at the asymmetric 1,1-dicyanoethylenes.[38] Analysis of the local electrophilicity index ω_k at the ethylenic positions of these cyano derivatives accounted for the loss of reactivity on the symmetric substituted ethylenes. Therefore, the local nucleophilicity index N_k of the species involved in the formation of the Breslow intermediate **21** was analyzed (see Scheme 7).



Scheme 7.

The NHC **19** has the largest nucleophilic activation at the carbene carbon center, N_k=2.06 eV. Note that this carbon supports ca. the 55% of the nucleophilicity of **19**, N=3.78 eV. This result is a consequence of the large location of the carbene lone par on a sp^2 hybrid that is located in the molecular plane. Unlike, the dimer **24** presents a low local nucleophilic activation at the two symmetric ethylene carbons, N_k=0.79 eV, in spite of the large global nucleophilicity of **24**, N=5.54 eV. Note that each one of these carbons supports only 14% of the nucleophilicity of **24**. In this case, the large delocalization of the ethylenic π system of **24** on the dimeric structure together with the symmetry of the molecule is responsible for the poor local nucleophilic activation. Finally, analysis of the local nucleophilicity indices at the Breslow intermediate **21** indicates that the *umpolung* carbonyl carbon atom of acetaldehyde presents the largest nucleophilic activation, N_k=1.44 eV. Note that this value is ca. twice the value on the symmetric dimer **24**.

4. Conclusions

The mechanism of the *N*-heterocyclic carbene-catalyzed ring-expansion of 4-formyl-β-lactams to succinimide derivatives has been studies using DFT methods at the B3LYP/6-31G** computational level. This NHC catalyzed ring-expansion comprises several elementary steps. The first step is the nucleophilic attack of the imidazol-2-ylidene **19** to the 4-formyl-β-lactam **27** to yield the zwitterionic intermediate **28**, which by a proton-transfer process affords the Breslow intermediate **29**. Due to the large energy associated with the intramolecular process, this step requires a Brønsted acid catalyst. The N–C breaking bond in the Breslow intermediate yields the amidate intermediate **30**, which by a keto–enol type equilibrium becomes the ketone form **31**. The subsequent ring-closure on **31** achieved by the nucleophilic attack of the amidate to the carbonyl carbon atom present in **31** allows the formation of the zwitterionic intermediate **32**, which by elimination of NHC **19** affords the succinimide **33**. Analysis of the free activation energies associated to each elementary step indicates that they present low values, allowing to explain the catalytic effect of NHC. In addition, the overall catalyzed process is thermodynamically very favorable.

Due to the relevance of the Breslow intermediates on the *umpolung* reactivity of aldehydes, the formation of the corresponding intermediate from the reaction of NHC **19** with acetaldehyde has been also studied. This study allowed us to discard the formation of the Breslow intermediates by the nucleophilic attacks of NHC dimers as was proposed by Lemal.

Finally, analysis of the global and local nucleophilicity indices allows to explain the nucleophilicity behaviors of the NHCs, the NHC dimer, and the Breslow intermediates in the *umpolung* reactivity of aldehydes. Thus, the analysis of the local nucleophilicity index, N_k, at the NHC dimer allows to explain the poor reactivity of this species as nucleophiles, in clear agreement with the large free activation energy associated with addition reaction.

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