Organocatalysis

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Are There Carbenes in N-Heterocyclic Carbene Organocatalysis?

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Abstract: *Azolium cations are widely employed in organocatalysis to catalyse highly valuable synthetic processes in the presence of a base. These reactions are called "N-heterocyclic carbene catalysis", based on the assumption that they are initiated by the formation of a free carbene through deprotonation, which can then react with the substrates and thereby affect their reactivity to obtain the desired products. However, we herein provide evidence that an electrophilic aromatic substitution mechanism is energetically more favourable, in which the azolium cation reacts directly with the substrate, avoiding the formation of the free carbene in solution.*

Reactions catalysed by metal-free N-heterocyclic carbenes (NHCs)[1] are of great interest in both chemistry[2–8] and biochemistry.[4,9,10] While these organocatalytic[11] processes enable synthetically valuable reactions, the analogous biochemistry of vitamin B1 (thiamine) plays a role in metabolism.[9] One of the key steps in these reactions is the formation of a bond between the NHC catalyst and the substrate as this covalent interaction is essential for the catalysis to take place. In a typical reaction, the NHC is not employed as the free carbene, but in its protonated form as an azolium salt, together with a suitable base.[2–6] According to the generally accepted reaction mechanism,[2,12] a proton is removed from the azolium ring by the base, creating a certain concentration of the free NHC in solution, which reacts with the substrate. The identified intermediates[2,13] and resting states[13,14] of the reaction and H/D exchange experiments[2] indicate that one of the ring protons can indeed be exchanged for a deuteron or an electrophile, suggesting a certain mobility for this proton. However, apart from this indirect evidence, there is no direct proof for the involvement of an NHC in the reaction as a free intermediate, and the detection of free carbenes in such reactive environments is restricted to a special case, in which the carbene is confined within an enzyme.[10]

In fact, carbenes are very basic, some with a pK_a value for the conjugated acid of greater than 20[15] (e.g., pK_a = 23.0 for 1,3-dimethylimidazol-2-ylidene in water),[16a] while some of the bases that are used in such processes are significantly weaker (e.g., pK_a = 10.65 for triethylamine in water).[16b] Therefore, it seems unlikely for such a proton transfer to occur frequently enough that reasonable catalytic effects could be expected. This contradiction becomes particularly intriguing if one considers some recently reported NHC catalytic processes that were conducted successfully in acidic media,[17,18] where the deprotonation of the very weakly acidic azolium cation is questionable. Moreover, persistent carbenes,[1] which are resistant to decomposition, are usually decorated with significantly bulkier substituents than those employed in carbene catalysis, suggesting the possibility of decomposition if deprotonation would occur.

Motivated by these highly contradictive interpretations and observations, we computationally explored the thus far unconsidered direct reaction between azolium cations and possible simple substrates. We selected the three NHC variants that are used most commonly in such processes (Figure 1), and although many modern NHC catalysts have larger substituents to introduce stereoselectivity, structures with similarly small functional groups at the nitrogen atoms have also been identified as active catalysts.[2–8] We chose trimethylamine as the base and formaldehyde, acetaldehyde, and benzaldehyde as the substrates to cover most of the possible electronic effects on the reaction.

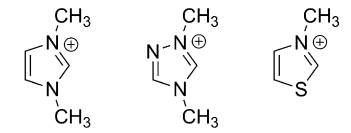

Figure 1. The three catalysts investigated here.

First, we investigated the "classic", dissociative reaction mechanism, where the process is initiated by proton transfer from the azolium cation precatalyst to the amine base. The first step of this pathway is the slightly exergonic formation of a hydrogen bond between the base and the azolium cation (structure **I**; Figure 2). The proton transfer and subsequent dissociation into carbene **II** and the ammonium cation have a large Gibbs free energy demand of 22–23 kcal mol^{-1} for the triazolium and thiazolium derivatives, and of even 35 kcal mol^{-1} for the imidazolium species, in clear agreement with the basicity trends of the corresponding carbenes.[15]

The free carbene reacts through $\mathbf{TS_{II\rightarrow III}}$ to form the catalyst–substrate bond in **III** (Figure 2). The highest-energy point in this mechanism is $\mathbf{TS_{II\rightarrow III}}$, rendering its relative Gibbs free energy with respect to **I** the activation Gibbs free energy of this pathway. The height of this barrier is sizeable in all cases, amounting to 35–51 kcal mol^{-1} (Figure 3). As adduct **III** is less stable than the hydrogen-bonded assembly **I**, a final proton transfer from the protonated base is necessary to

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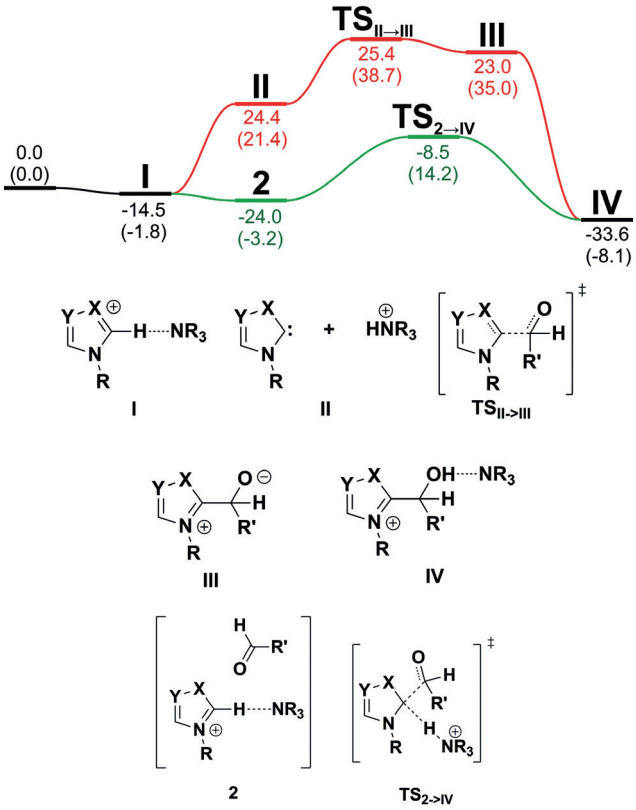

Figure 2. Energy profiles of the dissociative (red) and associative (green) reaction mechanisms for the binding of the azolium catalyst to the aldehyde substrate. The relative enthalpies and Gibbs free energies (in parentheses) for the exemplary reaction between the triazolium cation and acetaldehyde are given. Lewis formulae of the structures involved are shown below (X = NMe, S; Y = CH, N; R = Me; R′ = H, Me, Ph); ball-and-stick representations are shown in the Supporting Information. For the barriers of all investigated systems, see Figure 3 and the Supporting Information.

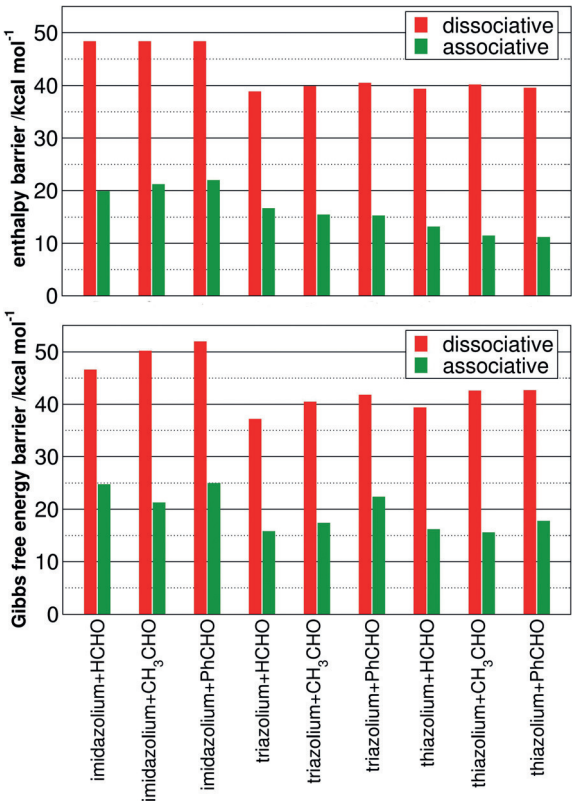

Figure 3. Comparison of the CCSD(T)/CBS enthalpy (top) and Gibbs free energy (bottom) barriers of the dissociative (ΔH and ΔG of **I** and $\mathbf{TS}_{II\rightarrow III}$; red bars) and associative (ΔH and ΔG of **2** and $\mathbf{TS}_{2\rightarrow IV}$; green bars) pathways for the binding of the catalyst to the substrate (see Figure 2). The detailed energetics of the two mechanisms, including solvent effects and electronic energies, are included in the Supporting Information.

stabilize the product as structure **IV** and to provide a driving force for the reaction. The sizable barrier of this pathway suggests that the reaction should be sluggish even at elevated temperatures, in contrast to the experimental observations.

Recently, we found that a carbene centre can form two hydrogen bonds at a time (e.g., in **A**; Figure 4).[19] In the present study, we successfully located transition states that are analogous to **A**, where instead of two hydrogen bonds, two reacting moieties interact with the carbene, similarly to other systems.[20,21] These transition states (e.g., **B** in Figure 4) allow the deprotonation of the azolium cation and the formation of the substrate–catalyst C–C bond to proceed in a simultaneous fashion, in a concerted, associative reaction mechanism.

According to this associative mechanism, **I** first forms the non-covalent complex **2** (Figure 2) with the substrate. Complex **2** and **I** exhibit similar Gibbs free energies. As **2** is a highly ordered complex of three molecules, entropic effects have a great impact on its accessibility. Indeed, the formation enthalpy of **2** is significantly more negative than the corresponding Gibbs free energy values (see the Supporting Information). It should be noted that the calculations applied here have been shown to provide a significant (50–100%) overestimation of the entropy compared to the values for the

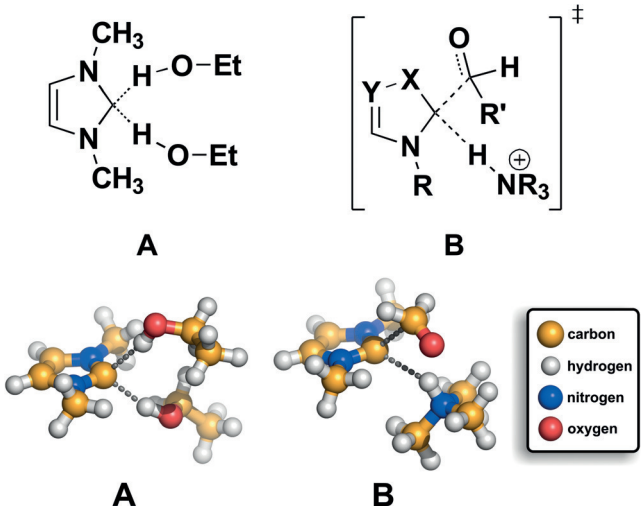

Figure 4. The transient doubly hydrogen-bonded structure of an NHC (**A**) from molecular dynamics simulations,[19] and one of the optimized structures of $\mathbf{TS}_{2\rightarrow IV}$ (**B**), the key transition state of the associative mechanism (R = Me; R′ = H, Me, Ph).

liquid phase.[22] This error results in higher Gibbs free energies for associated states, such as **2**. The observation that the Gibbs

free energy of **2** is nonetheless similar to that of **I** shows that the formation of **2** is preferred in the reaction.

To arrive at **IV**, the proton must shift from the azolium cation to the base, and the aldehyde must bind to the ring. Apparently, the two steps occur in a concerted asynchronous manner,[23] that is, through a single elementary reaction step via transition state $\mathbf{TS_{2\rightarrow IV}}$. $\mathbf{TS_{2\rightarrow IV}}$ has the highest Gibbs free energy in the associative reaction mechanism in all cases; however, it is still lower in Gibbs free energy than $\mathbf{TS_{II\rightarrow III}}$ by a remarkable 19–29 kcal mol^{-1} (Figure 3). Thus the obtained barriers show a clear preference for this novel associative reaction mechanism in all cases. As the association of the molecules involved in the associative pathway has already occurred once **2** has been formed, entropic effects on the barriers themselves are negligible, and the activation enthalpies are similar to the activation Gibbs free energies (see the Supporting Information).

It has been shown for diphenylcarbene, which is structurally very different from NHCs, that solvation can have a strong effect on its reactivity.[24] Thus we performed a series of calculations with an implicit conductor-like polarizable continuum model of toluene, THF, and DMSO, which are perhaps the most commonly used solvents in carbene catalysis and cover a wide range of polarities. The preference for the associative mechanism was, however, not influenced at all by these solvents (see the Supporting Information), suggesting that the polarity of the solvent is qualitatively unimportant for the present reaction mechanisms.

Although our associative mechanism is more favourable in all cases, the question can be raised how the dissociative pathway could be used to describe trends in the reactivity of catalysts with, for example, different basicity in previous studies for the last 50 years. Interestingly, upon correlating the dissociative and associative barriers with each other, a clear common trend is visible, showing that the higher activation energy for the dissociative mechanism will likely result in a higher barrier for the associative reaction pathway as well (Figure 5). This explains how using the model involving carbene formation provides information on the trends of the actual mechanism, even if the applied mechanistic picture in the free NHC model might not represent the real physical process.

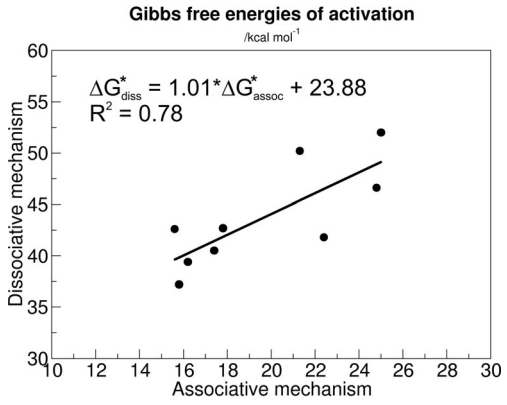

Figure 5. Correlation of the barriers of the two mechanisms (see Figure 3) for each system.

This important finding also indicates a possible way to observe the present reaction mechanism experimentally. By varying the steric properties of the base, catalyst, and substrate, which affect $\mathbf{TS_{2\rightarrow IV}}$ and $\mathbf{TS_{II\rightarrow III}}$ differently, one should find outliers from the common trend. In agreement, the most significant outlier in this study was the reaction of the triazolium cation with bulky PhCHO, where the barrier of 23.4 kcal mol^{-1} for the associative mechanism appears to be too high compared to the general trend. In such cases, kinetic measurements, in combination with calculated activation energies, could help identifying which mechanism is operating. Surely, the complicated multistep nature of the corresponding catalytic process is another obstacle in such measurements. However, simple model reactions where the primary adduct **IV** cannot react further (for example, with benzophenone as the substrate) may enable reducing this complicated process into a single step for a detailed characterization of the process in question.

The cornerstone of this curious reaction pathway is transition state $\mathbf{TS_{2\rightarrow IV}}$, which directly connects the product **IV** and the starting cluster **2**. In light of the structure of $\mathbf{TS_{2\rightarrow IV}}$, the process itself is very similar to an electrophilic aromatic substitution (EAS), exchanging a proton at an aromatic ring for an electrophilic group. EAS reactions proceed through a structure that is very similar to $\mathbf{TS_{2\rightarrow IV}}$, where the leaving proton and the electron-deficient group are both bound to the same carbon atom at the substitution site (see structures **B** in Figure 4 and **C** in Figure 6). Furthermore, some EAS reactions[25] follow a concerted pathway, similarly to the presented associative mechanism. As azolium cations are also known to be aromatic,[26,27] it is reasonable to describe the present associative mechanism as an electrophilic aromatic substitution reaction.

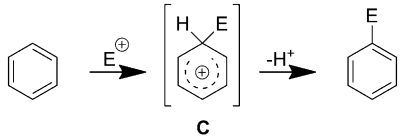

Figure 6. The mechanism of electrophilic aromatic substitution reactions.

Thus, instead of the generally accepted mechanism of the so-called NHC catalysis, which involves the deprotonation of an azolium salt to liberate the free NHC, an alternative reaction pathway could be identified. In this process, the proton transfer and the binding of the substrate to the catalyst occur simultaneously in a single elementary reaction step, without the involvement of an explicit carbene molecule. This process was calculated to have a low barrier, as opposed to the hindered formation of the free carbene. This finding explains various discrepancies in carbene organocatalysis, such as the absence of catalyst decomposition despite the occasionally very small substituents on the ring and the fact that reactions also take place for large pK_a differences between carbene and base or even in acidic media. In ongoing follow-up studies, we are investigating the effect of solvents, substrates, catalysts,

steric effects, and bases on such reactions to gain in-depth insight into this curious reaction mechanism.

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Conflict of interest

The authors declare no conflict of interest.

Keywords: carbenes · computational chemistry · electrophilic substitution · organocatalysis · reaction mechanisms

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[1] M. N. Hopkinson, C. Richter, M. Schedler, F. Glorius, *Nature* **2014**, *510*, 485–496.
[2] R. Breslow, *J. Am. Chem. Soc.* **1958**, *80*, 3719–3726.
[3] D. Enders, T. Balensiefer, *Acc. Chem. Res.* **2004**, *37*, 534–541.
[4] D. Enders, O. Niemeier, A. Henseler, *Chem. Rev.* **2007**, *107*, 5606–5655.
[5] N. Marion, S. Díez-González, S. Nolan, *Angew. Chem. Int. Ed.* **2007**, *46*, 2988–3000; *Angew. Chem.* **2007**, *119*, 3046–3058.
[6] "Carbene Catalysts": J. L. Moore, T. Rovis in *Asymmetric Organocatalysis*, *Vol. 291* of *Top. Curr. Chem.*, Springer, Berlin, **2009**.
[7] B.-S. Li et al., *Nat. Commun.* **2016**, *7*, 12933.
[8] Z. Fu, J. Xu, T. Zhu, W. W. Y. Leong, Y. R. Chi, *Nat. Chem.* **2013**, *5*, 835–839.
[9] L. Stryer, *Biochemistry*, 4th ed., Freedman, New York, **1995**.
[10] D. Meyer, P. Neumann, R. Ficner, K. Tittmann, *Nat. Chem. Biol.* **2013**, *9*, 488–490.
[11] D. W. MacMillan, *Nature* **2008**, *455*, 304–308.
[12] O. Hollóczki, Z. Kelemen, L. Nyulászi, *J. Org. Chem.* **2012**, *77*, 6014–6022.
[13] a) A. Berkessel, S. Elfert, K. Etzenbach-Effers, J. H. Teles, *Angew. Chem. Int. Ed.* **2010**, *49*, 7120–7124; *Angew. Chem.* **2010**, *122*, 7275–7279; b) A. Berkessel, V. R. Yatham, S. Elfert, J.-M. Neudörfl, *Angew. Chem. Int. Ed.* **2013**, *52*, 11158–11162; *Angew. Chem.* **2013**, *125*, 11364–11369.
[14] J. Mahatthananchai, J. W. Bode, *Acc. Chem. Res.* **2014**, *47*, 696–707.
[15] a) Y.-J. Kim, A. Streitwieser, *J. Am. Chem. Soc.* **2002**, *124*, 5757–5761; b) A. M. Magill, K. J. Cavell, B. F. Yates, *J. Am. Chem. Soc.* **2004**, *126*, 8717–8724; c) R. S. Massey, C. J. Collet, A. G. Lindsay, A. D. Smith, A. C. O'Donoghue, *J. Am. Chem. Soc.* **2012**, *134*, 20421–20432.
[16] a) T. L. Amyes, S. T. Diver, J. P. Richard, F. M. Rivas, K. Toth, *J. Am. Chem. Soc.* **2004**, *126*, 4366–4374; b) H. K. Hall, Jr., *J. Am. Chem. Soc.* **1957**, *79*, 5441–5444.
[17] X. Zhao, D. A. DiRocco, T. Rovis, *J. Am. Chem. Soc.* **2011**, *133*, 12466–12469.
[18] R. De Vreese, M. D'hooghe, *Beilstein J. Org. Chem.* **2012**, *8*, 398–402.
[19] O. Hollóczki, *Phys. Chem. Chem. Phys.* **2016**, *18*, 126–140.
[20] Z. Kelemen et al., *Chem. Eur. J.* **2014**, *20*, 13002–13008.
[21] F. Yan, N. R. Dhumal, H. J. Kim, *Phys. Chem. Chem. Phys.* **2017**, *19*, 1361–1368.
[22] a) S. Tobisch, T. Ziegler, *J. Am. Chem. Soc.* **2004**, *126*, 9059–9071; b) H. Zhu, T. Ziegler, *J. Organomet. Chem.* **2006**, *691*, 4486–4497; c) D. H. Wertz, *J. Am. Chem. Soc.* **1980**, *102*, 5316–5322.
[23] For an example, see: D. H. Nouri, D. J. Tantillo, *J. Org. Chem.* **2006**, *71*, 3686–3695.
[24] J. Knorr, P. Sokkar, S. Schott, P. Costa, W. Thiel, W. Sander, E. Sanchez-Garcia, P. Nuernberger, *Nat. Commun.* **2016**, *7*, 12968.
[25] B. Galabov et al., *Acc. Chem. Res.* **2016**, *49*, 1191–1199.
[26] Z. Kelemen, O. Hollóczki, J. Oláh, L. Nyulászi, *RSC Adv.* **2013**, *3*, 7970–7978.
[27] O. Hollóczki, L. Nyulászi, *J. Org. Chem.* **2008**, *73*, 4794–4799.

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