

See discussions, stats, and author profiles for this publication at: <https://www.researchgate.net/publication/228064861>

# On the Organocatalytic Activity of N-Heterocyclic Carbenes: Role of Sulfur in Thiamine

ARTICLE *in* THE JOURNAL OF ORGANIC CHEMISTRY · JUNE 2012

Impact Factor: 4.72 · DOI: 10.1021/jo300745e · Source: PubMed

---

CITATIONS

31

---

READS

53

3 AUTHORS, INCLUDING:



Oldamur Holloczki

University of Bonn

36 PUBLICATIONS 473 CITATIONS

SEE PROFILE

# On the Organocatalytic Activity of N-Heterocyclic Carbenes: Role of Sulfur in Thiamine

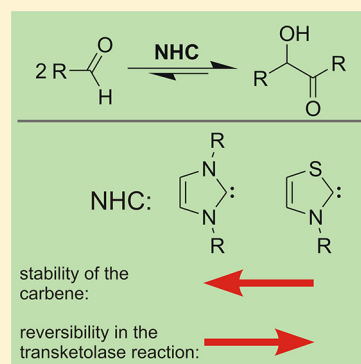
Oldamur Hollóczki,<sup>\*,†,‡</sup> Zsolt Kelemen,<sup>†</sup> and László Nyulászi<sup>\*,†</sup>

<sup>†</sup>Department of Inorganic and Analytical Chemistry, Budapest University of Technology and Economics, Szt. Gellért tér 4., Budapest, H-1111, Hungary

<sup>‡</sup>Wilhelm-Ostwald-Institut für Physikalische und Theoretische Chemie, Universität Leipzig, Linnéstrasse 2, D-04103 Leipzig, Germany

## S Supporting Information

**ABSTRACT:** The reaction energy profiles of the benzoin condensation from three aldehydes catalyzed by imidazol-2-ylidene, triazol-3-ylidene, and thiazol-2-ylidene have been investigated computationally. The barriers for all steps of all investigated reactions have been found to be low enough to indicate the viability of the mechanism proposed by Breslow in the 1950s. The most remarkable difference in the catalytic cycles has been the increased stability of the Breslow intermediate in case of thiazol-2-ylidene (by ca. 10 kcal/mol) compared to the other two carbenes, which results in lower energy for the coupling of the second aldehyde molecule, thus, increasing the reversibility of the reaction. Since the analogous transketolase reaction, being involved in the carbohydrate metabolism of many organisms, requires an initial decoupling—a reverse benzoin condensation—this difference provides a reasonable explanation for the presence of a thiazolium ring in thiamine instead of the otherwise generally more available imidazole derivatives. The “resting intermediate” found by Berkessel and co-workers for a triazole-based catalyst was found more stable than the Breslow intermediate for all of the systems investigated. The (gas phase) proton affinities of several carbenes were compared, the relative trends being in agreement with the available (in aqueous solution) data. The hydrolytic ring-opening reaction of the thiazole-based carbene was shown to be different from that of imidazole-2-ylidenes.



## ■ INTRODUCTION

The organocatalytic activity of N-heterocyclic carbenes (NHCs)<sup>1</sup> is of great current interest in synthetic chemistry, providing efficient routes among others for highly important C–C coupling reactions, such as benzoin condensation (Figure 1).<sup>1</sup> This reaction can be considered “biomimetic”,<sup>1a</sup> imitating a biochemical reaction catalyzed by vitamin B1 (thiamine, Figure 2) within the transketolase enzyme.<sup>2</sup> The corresponding enzymatic reaction, the transketolase reaction (TK, Figure 3) is involved in the carbohydrate metabolism of many organisms, catalyzing the transfer of a two-carbon unit from one carbohydrate to another one.<sup>2</sup>

By analogy with the cyanide-catalyzed process,<sup>3</sup> and considering the observed H/D exchange at position 2 of the thiazolium cation, Breslow introduced a mechanism for the NHC-catalyzed benzoin condensation in the 1950s (this can be seen with some modifications in Figure 1),<sup>4</sup> and given that thiamine itself also catalyzes this reaction,<sup>5</sup> he assumed that an analogous mechanism also holds for the TK reaction, possessing structurally similar products (Figure 3).<sup>4</sup> The first step of both reactions is the formation of the NHC (called “carbanion” by Breslow) from its salt precatalyst via deprotonation. This might be performed by an appropriate external base (amine or carbonate)<sup>1</sup> or by the counteranion of the azolium cation,<sup>6</sup> while in the biochemical reaction the deprotonating agent is the

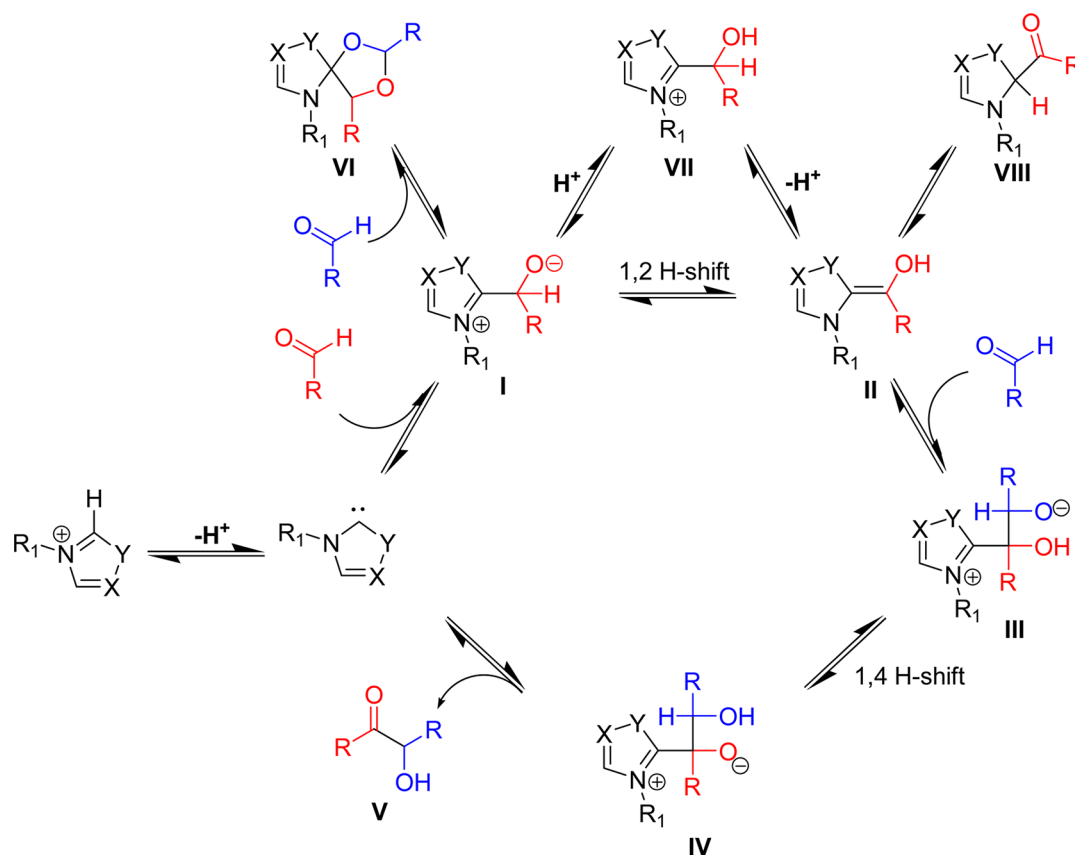
pyrimidine moiety of thiamine itself.<sup>7</sup> The reaction of the NHC with the substrate aldehyde yields pentafulvene II, which is often called the Breslow intermediate (Figure 1). The formation of this structure allows the polarity inversion of the carbonyl carbon atom (“umpolung”), making the coupling with another substrate (aldehyde) feasible, yielding eventually product V. However, interestingly, the substrate of the TK reaction does not possess any formyl groups, but an  $\alpha$ -hydroxy ketone unit, thus, can also be rationalized as a *product* of a benzoin condensation.<sup>2</sup> Hence, the overall reaction necessitates an initial reverse benzoin condensation (highlighted by a frame in Figure 3), yielding an aldose and the Breslow intermediate, which then can be coupled with another aldose. It is worthy to note in this respect that we have used benzoin as synthetic equivalent of benzaldehyde using an imidazolium-based catalyst,<sup>6c</sup> and Bode has reported an elegant synthesis utilizing an  $\alpha$ -hydroxy ketone as a synthetic equivalent of  $\alpha,\beta$ -unsaturated aldehydes using a triazolium based catalyst,<sup>8</sup> showing the feasibility of the reverse reactions under different conditions and with different NHC catalysts.

Although the above-described mechanistic scheme is well-accepted, it is interesting to note that the Breslow intermediate itself could not yet be isolated nor detected by any spectroscopic

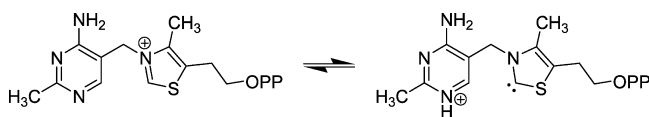
Received: April 11, 2012

Published: June 25, 2012

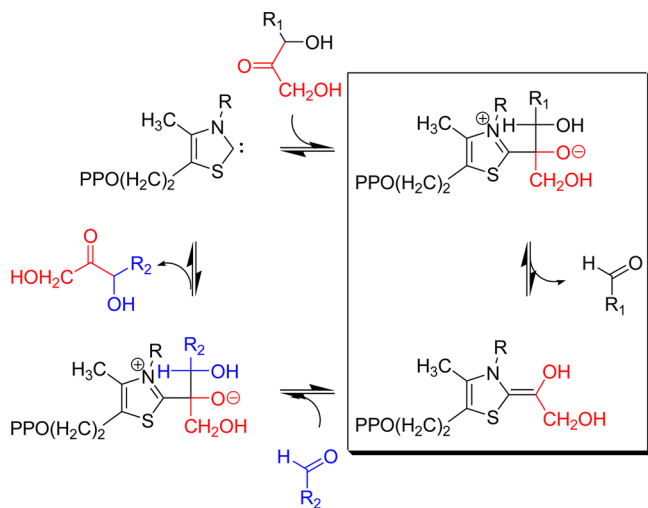




**Figure 1.** Mechanistic scheme on the benzoin condensation catalyzed by N-heterocyclic carbenes ( $X = C-H$ ,  $Y = S$ ;  $X = N$ ,  $Y = N-R$ ;  $X = C-H$ ,  $Y = N-R$ ).



**Figure 2.** Structure of vitamin B1 (thiamine) and its isomerization to its active carbene isomer.

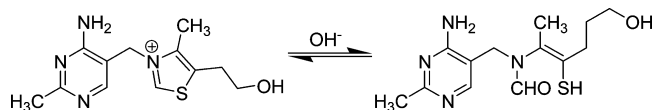


**Figure 3.** Mechanism of the transketolase (TK) reaction, including the initial formation of the Breslow intermediate by a reverse benzoin condensation (highlighted by a frame).

methods, only the protonated VII (Figure 1).<sup>6b,9,10</sup> Moreover, very recently VIII, an isomer of II, has been detected in the case

of triazol-3-ylidene catalysis by Berkessel and co-workers.<sup>10a</sup> This structure has been shown to be more stable than the corresponding II and has been indicated together with VI to be a “resting state” of the reaction (Figure 1).<sup>10a</sup>

In the light of this close relationship between the benzoin condensation and the TK reaction, it is interesting that while in the benzoin condensation thiazol-2-ylidenes, triazol-5-ylidenes, and imidazol-2-ylidenes can all be applied as catalyst<sup>1</sup> although with a different activity,<sup>11</sup> the TK reaction only utilizes the thiazolium-containing thiamine as catalyst.<sup>2</sup> This is strange, since thiazole-based derivatives are otherwise relatively rare in biological systems, while many structures, such as histidine and histamine, contain an imidazole ring. Hence, an apparent question is raised: what is the unique and desirable feature of thiazol-2-ylidene that makes biological systems use exclusively thiamine for such biocatalysis? Clearly, the higher acidity of thiazolium salts ( $pK_a = 19.5$  for methylthiazol-2-ylidene vs  $pK_a = 21.6$  for 1,3-dimethylimidazol-2-ylidene)<sup>12a</sup> is of importance, resulting in easier access to the catalytically active carbene, precipitating in enhanced rates for the overall reaction.<sup>12b</sup> Furthermore, unlike the imidazolium derivatives,<sup>13</sup> thiazolium salts have been shown by an early NMR study to undergo a facile and reversible ring-opening (Figure 4.) in aqueous solutions even at physiological pH,<sup>13c</sup> which has been tentatively suggested to



**Figure 4.** Ring opening of thiamine.

allow easier transport through the lipophilic lipid double layer of cell membranes due to the loss of charge.<sup>13c</sup>

Although these arguments indeed provide some explanation for the preference of thiazoles in biocatalysis over NHCs of other kinds, the view on the role of the structure of thiamine cannot be complete without considering the effect of the heteroatoms on the reaction itself. The importance of this issue is indicated by the fact that the transketolase reaction is built upon the delicate equilibrium between several possible benzoin condensations and the corresponding reverse reactions;<sup>2</sup> therefore the slightest change in catalytic properties may alter the carbohydrate metabolism. Moreover, considering that the suppression or facilitation of the transketolase reaction have been shown to have desirable effects on tumor cells<sup>14</sup> and on diabetic complications,<sup>15</sup> respectively, having a more detailed insight into the parameters influencing the reaction may eventually lead to pharmaceutical applications.

Since it has been shown that even the substituents at the nitrogens of the NHC have significant effect on the catalytic properties<sup>16</sup> and considering that selective catalysis could be achieved even in the case of several competing reactions<sup>11</sup> it is important to study comparatively the effect of the different NHCs on the benzoin condensation. It is interesting in this respect that while there are some limited comparative studies on the benzoin condensation about the different catalytic activities of some NHCs considering yields, rates, and (stereo)-selectivities,<sup>1,17</sup> to our knowledge no comprehensive mechanistic study considering the energetic viewpoint has been performed yet. The results of these investigations should be useful to predict the catalytic activity of the NHC in these reactions and design the catalyst for the desired synthetic approach.

In this computational study, an in depth comparison of the catalytic activities of different carbenes (including several NHCs) in the benzoin condensation is addressed, aiming toward the better understanding of this process and, accordingly, to account for the reasons of the closely related structural conservation of thiamine in living organisms. For the sake of completeness, proton affinities of carbenes and the hydrolytic ring-opening process for thiazol-2-ylidenes will also be discussed.

## MODELS AND METHODS

To provide comprehensive data regarding the effects of the ring heteroatoms on the catalytic properties of NHCs, carbenes 1–24 have been investigated (Figure 5), including the generally used carbene catalysts (7, 9, 13) as well as some more exotic species, which, however, contribute to obtain a complete picture on the matter. Since the effect of the substituents attached to the nitrogen atoms of the NHC has recently been reported,<sup>16</sup> this issue has not been addressed here; thus, at those positions methyl groups have been introduced in all cases. All the intermediates and transition states of the condensation of formaldehyde, acetaldehyde and benzaldehyde have been optimized with the synthetically most important NHCs 7, 9, and 13 according to the mechanism proposed by Breslow.<sup>1,4</sup> The energetically most determining intermediates have been calculated for the rest of the carbenes as well with acetaldehyde. It should be noted that although in the TK reaction sugars are involved, the electronic effects of the carbohydrate chain on the moieties being directly involved in the reaction can be considered similar to those in case of acetaldehyde, which, therefore, is a reasonable model system for the reaction of carbohydrates.

All structures involved in the catalytic cycle have been fully optimized at the B3LYP/6-311+G\*\* level using the Gaussian

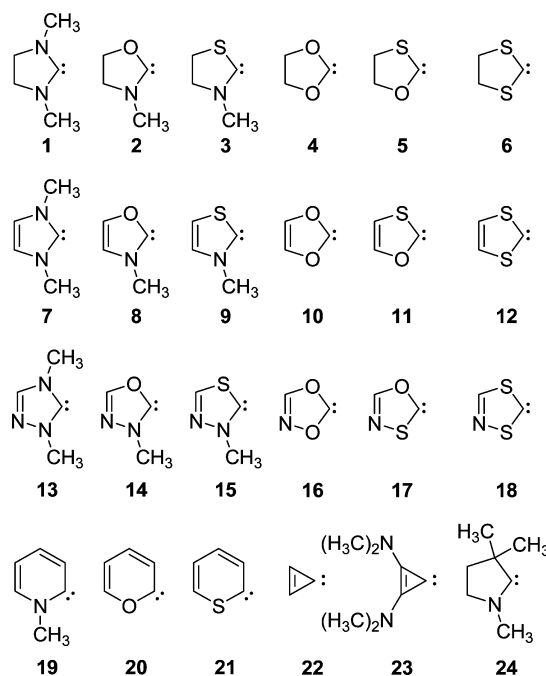


Figure 5. Carbenes investigated in the present study.

03<sup>18</sup> program package (unless otherwise noted), followed by the subsequent calculation of the eigenvalues of the Hessian at the same level, to characterize the nature of the stationary point obtained. For transition states IRC calculations have been performed to locate the corresponding minima. To check the reliability of the B3LYP functional,  $\omega$ B97X-D, PBEh, TPSSH, M05-2X, M06-2X, BMK, and MP2 calculations have been performed on the energy profile of the reaction of formaldehyde and NHCs 7 and 9 with the 6-311+G\*\* basis set by using the Gaussian 09<sup>19</sup> program package.

Since the reaction involves the association of three molecules, entropy surely has significant effect on the reaction. However, considering that quantifying the entropy of solutes accurately is of great challenge,<sup>20</sup> and that our goal has been the comparison of the catalytic properties of different carbene catalysts in basically the same process, we believe that the information being necessary to draw the consequences of this study can be extracted from the energy values as well. Nonetheless, to avoid the mismatch of entropy contribution in the most interesting II  $\rightarrow$  III coupling step, we introduced structure II' into the catalytic cycle, which consists of II bound to the reacting aldehyde with a H-bond.

In the investigation of the hydrolytic ring opening, we followed the same strategy that has been found applicable for 7 in our previous study.<sup>13a</sup> Thus, first the reaction with one to three water molecules has been calculated to gain information regarding the behavior of 9 against traces of water in a predominantly nonpolar solution. Studying the aqueous solution has been performed by applying a microsolvation approach, thus, by building up the first solvate shell (consisting of 30 water molecules in this case) around the carbene and the reacting water molecule, and a similar water cage around the intermediates and products of the reaction. Optimizing such "solvated" structures to model aqueous reactions has previously been found to provide significantly better results than implicit models<sup>21</sup> and has shown good accordance with experimental findings for the hydrolytic reaction of 7.<sup>13a</sup> It should be noted here that for the

reaction of **7** with 1–3 and 31 water molecules the calculation of the reaction has been performed by a series of different DFT functionals (B3PW91, PW91PW91, B97-1, MPW1K, MPWB1K, BMK, M05-2X, TPSSH, RI-B97-D,  $\omega$ B97X-D) and other methods (MP2, CCSD(T), RI-MP2, MOS( $\omega$ 600)-RI-MP2), which, together with the experiments, fully confirmed the reasonable quality of the B3LYP/6-311+G\*\* and B3LYP/6-311+G\*\*//B3LYP/6-31+G\* level calculations.<sup>13a</sup> Thus, in this study B3LYP/6-311+G\*\* level calculations have been performed for the reaction of **9** with one to three water molecules, while B3LYP/6-311+G\*\*//B3LYP/6-31+G\* level calculations for the solvated system, providing reasonably good results being directly comparable with those obtained previously.

## RESULTS AND DISCUSSION

**Proton Affinities.** The reaction necessitates the formation of the NHC catalyst from its salt by deprotonation, therefore, the basicity of the carbene (the acidity of its salt) has significant effect on the catalytic activity in terms of rates. Although there are many experimental<sup>12a,22a–g</sup> and calculated<sup>6a,22g–k</sup> data in literature regarding the proton affinity and basicity of carbenes, the effect of the NHCs' structure on their basicity has not yet been investigated systematically for as wide spectrum of different compounds as **1–24**; thus, first the protonation energies of these structures have been calculated. The data obtained are compiled together in Table 1.

**Table 1. Proton Affinities (in kcal/mol Units) of Carbenes 1–18 and the Corresponding II (R = Me) Derivatives**

carbene	PA <sub>carbene</sub>	PA <sub>II</sub>	carbene	PA <sub>carbene</sub>	PA <sub>II</sub>
1	+268.9	+262.2	13	+255.6	+266.5
2	+256.3	+249.3	14	+238.1	+244.4
3	+257.8	+246.5	15	+244.6	+245.1
4	+236.8	+229.7	16	+209.3	+214.3
5	+244.3	+224.9	17	+226.9	+218.8
6	+244.8	+223.2	18	+229.3	+221.2
7	+267.8	+273.9	19	+278.1	+262.4
8	+251.9	+251.8	20	+267.2	+237.3
9	+254.2	+254.2	21	+264.3	+238.8
10	+229.1	+229.2	22	+234.5	+229.7
11	+240.8	+229.4	23	+226.6	+268.8
12	+243.8	+230.4	24	+271.4	+251.1

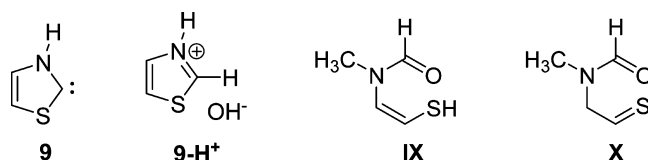
In agreement with the known strong basicity of carbenes,<sup>12,22</sup> the proton affinities are high values and are in reasonable agreement with the published data.<sup>22</sup> The basicity of the five-membered carbenes **1–12** is generally decreasing in the N > S > O order; thus, those possessing two nitrogen atoms are the most basic, while the exchange of one and two nitrogens to chalcogens decreases the proton affinity by ca. 10 and 20–30 kcal/mol, respectively. Replacing one of the electronegative nitrogens of **1** by a saturated carbon, results in **24**. This structure has a slightly increased proton affinity, since the electron donating carbon substituent stabilizes the cation. Likewise, pyridin-2-ylidene (**19**) has a larger proton affinity than the diaminocarbenes (e.g., **7**).<sup>23</sup>

The introduction of a double bond at the backbone of the ring decreases the proton affinities by a few kcal/mol, and the effect is more pronounced in case of carbenes containing only chalcogen atoms. NHCs **13–18** have lower proton affinities compared to the analogous **7–12** because of the electron-withdrawing effect of the extra ring nitrogen that destabilizes the corresponding cation.

Carbene **22**, possessing a three-membered ring has a relatively low proton affinity, which is further decreased by the amino substituents of **23** at the backbone, similar to NHCs **13–18**.

The trends above fit to the reported pK<sub>a</sub> values of carbenes **7**, **8**, and **9**, measured in aqueous solutions (23.0, 16.9, and 19.5, respectively).<sup>12a</sup> The differences in proton affinities between **7** and **13** are also in good qualitative agreement with the kinetic acidities of the salts of analogous derivatives, measured in terms of the rate constant of the H/D exchange ( $2.0 \times 10^2 \text{ M}^{-1} \text{ s}^{-1}$  for 1,3-dimethylimidazolium iodide,<sup>22e</sup> and  $8.6 \times 10^7 \text{ M}^{-1} \text{ s}^{-1}$  for 1-ethyl-4-phenyl-1,2,4-triazolium chloride<sup>22f</sup>).

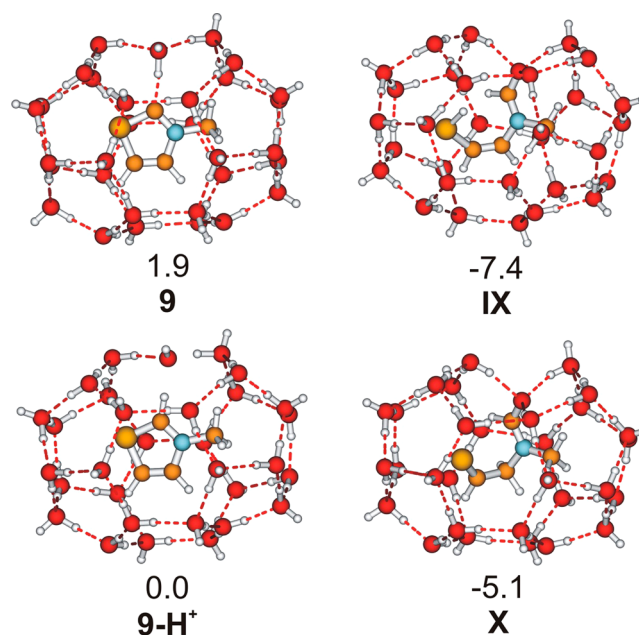
**Hydrolytic Ring Opening of 9.** First, the reaction of **9** with one to three water molecules has been investigated. Interestingly, the reaction energy profiles (see the Supporting Information) are similar to those for the previously studied,<sup>7,13a</sup> despite the difference in the stability of these two carbenes; most importantly, both open chain hydrolysis products (Figure 6)



**Figure 6.** Structures involved in the hydrolysis of **9**.

are significantly more stable than the corresponding carbene. Accordingly, these two compounds should behave similarly against traces of water in a predominantly nonpolar media; viz. under such circumstances a slow, irreversible ring-opening should occur in both reactions.

However, using the microsolvation approach by inserting the carbene into a water cluster (see Figures 6 and 7), the integrity of the two five membered rings becomes highly different. While for **7** the two feasible open-chain products in the cage “built” from 31 water molecules are 4.7 and 5.4 kcal/mol higher in energy



**Figure 7.** B3LYP/6-311+G\*\*//B3LYP/6-31+G\* level optimized structures and relative energies (in kcal/mol units) of **9**, **9-H+**, **IX**, and **X**. For the Lewis structures, see Figure 6.



compared to the microsolvated imidazolium hydroxide,<sup>13a</sup> in the case of **9** the relative energy of the corresponding structures (depicted in Figure 6) are  $-7.4$  (**IX**) and  $-5.1$  kcal/mol (**X**), respectively, compared to the microsolvated thiazolium-hydroxide. In agreement with the slight difference in the stability of **IX** and **X**, a structure analogous to **IX** has been observed in the NMR experiments.<sup>13c</sup> Accordingly, by dissolving either **9** in water (or its salt in a basic aqueous solution) will result in the opening of the thiazole ring, similarly to **1**,<sup>13a</sup> and in contrast with **7**.<sup>13a</sup> Thus, it is reasonable to suggest a more facile ring-opening of the thiazolium cation in neutral pH conditions as well, in agreement with the experiments.<sup>13c</sup>

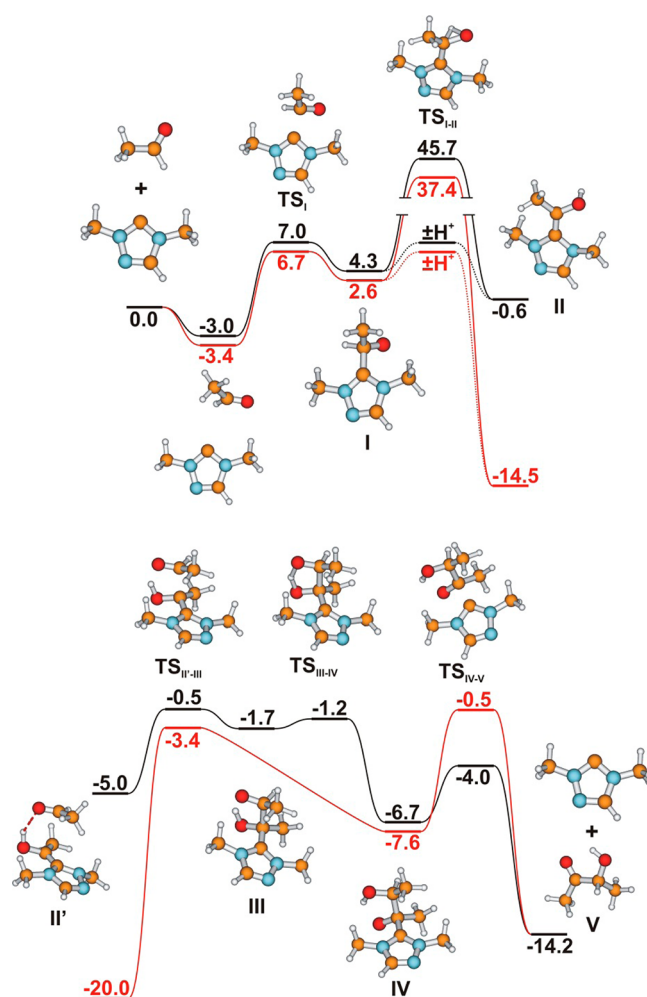
Beyond the differences in the energetics of the ring opening, it is interesting to observe that the relative energy of the solvated carbene compared to the solvated thiazolium hydroxide is much lower (1.9 kcal/mol) than in case of **7** (6.1 kcal/mol at the same level),<sup>13a</sup> in agreement with the lower basicity<sup>12a</sup> and protonation energy of thiazolium based carbene, as discussed above.

**Benzoin Condensation.** As expected, the reaction is exothermic for all three aldehydes, with decreasing reaction energy in the order of  $H > Me > Ph$  substituents. The small exothermicity for benzaldehyde (note that the entropy contribution favoring dissociation is not accounted for here) is in good agreement with the known reversibility of the reaction for aromatic aldehydes,<sup>6c,25</sup> while for the aliphatic aldehydes the reverse benzoin reaction is thermodynamically less favored.

The mechanism of the benzoin condensation has been calculated according to the original suggestion of Breslow,<sup>4</sup> considering also the “resting states” suggested by Berkessel et al.<sup>10a</sup> (shown in Figure 1). The structures (with energies) involved in the reaction of acetaldehyde with **13** are depicted in Figure 8, together with the corresponding energy values of the reaction of **9** (red) with the same aldehyde. The energies for the stationary points of the reactions between formaldehyde, acetaldehyde and benzaldehyde with NHCs **7**, **9**, and **13** are presented in Table 2. The reaction energy profiles and the trends in the stabilities of the intermediates and transition states for the different reactions has been found qualitatively similar by all DFT functionals applied and also by the MP2 method (see the Supporting Information), suggesting the applicability of B3LYP for the investigation of this reaction.

The first step of the reaction is the attachment of the carbene to the carbonyl carbon atom, which proceeds via a low barrier. The conversion of adduct **I** to the Breslow intermediate **II** by a 1,2-hydrogen shift is apparently kinetically hindered by a sizable gap in the gas phase. Nevertheless, in solution this high barrier can presumably easily be overcome by an alternative protonation–deprotonation mechanism via **VII**, similarly to related isomerization processes.<sup>21,26</sup> In this respect, it is worth to note that the protonation energies of **I** and **II** are comparable to that of carbenes (Table 1), indicating that they exist in the reaction mixture in protonated form, as **VII**. Accordingly, as mentioned above, **VII** (but not **I** or **II**) has been characterized by NMR spectroscopy,<sup>6b,9,10</sup> in the reaction of triazolylidenes with benzaldehyde and alkyl-aldehydes,<sup>9</sup> and also for imidazol-2-ylidenes<sup>6b</sup> and thiazol-2-ylidenes<sup>10</sup> with benzaldehyde. In the case of the asymmetrically substituted NHCs (**9** and **13**), two rotamers are conceivable for **II** by the rotation around the exocyclic  $C=C$  bond. The energy difference between these isomers, however, is within 1–2 kcal/mol in all cases (see the Supporting Information).

The attachment of the second reacting aldehyde molecule requires the presence of the “unpoled” **II**. Several possible



**Figure 8.** Reaction energy profile of the reaction of **13** and **9** (with red) with acetaldehyde at the B3LYP/6-311+G\*\* level (relative energies in kcal/mol units).

transition states are conceivable for this step, differing from one another by the rotamer of **II** involved, and by the orientation of the (second) aldehyde with respect to the Breslow intermediate. The most stable structure **III** is shown in Figure 8, stabilized by the  $OH\cdots H$  hydrogen bond (at B3LYP/6-311+G\*\* it is by 7.3 kcal/mol more stable than the most stable alternative not possessing this H-bond). Accordingly, we assumed for each type **III** structure and **II**'→**III** transition state the analogous hydrogen-bonded arrangement.

Compounds **7** and **13** generally exhibit barriers of a few kcal/mol for the **II**'→**III** step, hence indicating a facile coupling, and in case of the reaction of formaldehyde and **7**, the addition of a formaldehyde to **II** proceeds even without any barrier resulting in **III** (marked by an arrow in Table 2). For **9**, however, these barriers are much higher, but they are still below 25 kcal/mol with all aldehydes. By the low barrier migration of the proton within the  $O\cdots H-O$  hydrogen bond in **III**, the adduct of the carbene with the product (**IV**) can be formed, which recovers the carbene catalyst and the product **V** by dissociation. It is worth to note, that we were not able to locate type **III** structures on the potential energy surface for each investigated case. For the reaction of **9** with any aldehyde and in case of **13** and benzaldehyde the addition of the second aldehyde to **II** is followed by the subsequent 1,4-proton shift in a single step, forming directly **IV** (see arrows in Table 2).

Table 2. B3LYP/6-311+G\*\* Relative Energies of the Intermediates and Transition States of the Benzoin Condensation of Different Aldehydes with Carbenes 7, 9, and 13 (in kcal/mol Units)

	H <sub>2</sub> C=O			Me-CHO			Ph-CHO		
	7	9	13	7	9	13	7	9	13
TS <sub>I</sub>	-4.1	-2.8	-3.5	0.8	-3.4	-3.0	-3.1	-3.7	-2.8
I	-0.1	4.6	2.5	9.1	6.7	7.0	8.2	8.5	10.8
TS <sub>I-II</sub>	-6.0	-1.8	-1.8	5.0	2.6	4.3	4.6	4.7	8.6
II	33.8	29.7	36.1	47.3	37.4	45.7	44.2	41.6	47.4
VIII	-12.2	-23.5	-12.2	-0.3	-14.5	-0.6	-2.1	-13.5	-1.1
II'	-13.4	-26.0	-13.6	-10.9	-23.1	-11.1	-7.0	-18.7	-7.2
II'	↓	-28.7	-18.5	-4.7	-20.0	-5.0	-9.8	-18.9	-9.5
TS <sub>II-III</sub>		-18.0	-17.4	-1.8	-3.4	-0.5	4.2	2.5	6.8
III	-24.0	↓	-18.4	-2.9	↓	-1.7	3.9	↓	↓
TS <sub>III-IV</sub>	-23.4		-17.8	-2.8		-1.2	4.0		
IV	-29.1	-23.9	-24.4	-9.1	-7.6	-6.7	0.5	0.2	3.0
TS <sub>IV-V</sub>	-21.7	-15.3	-19.3	-5.0	-0.5	-4.0	4.8	5.1	6.6
V	-23.3	-23.3	-23.3	-14.2	-14.2	-14.2	-5.8	-5.8	-5.8
VI	-29.6	-40.0	-31.0	-18.6	-29.2	-20.3	-6.6	-16.9	-8.6

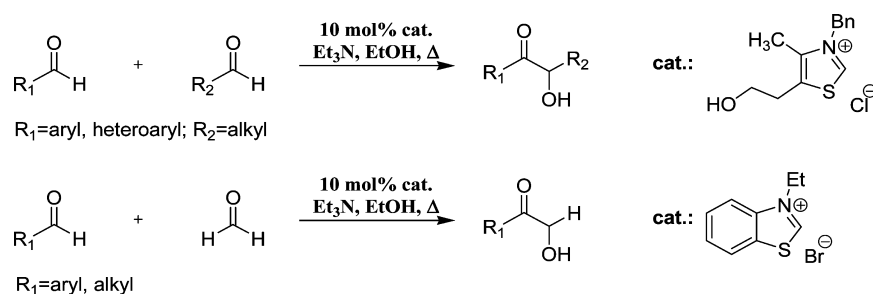


Figure 9. Selective cross-benzoin condensations, catalyzed by different thiazolium salts.

The relative energies of the intermediates are influenced by the substituents at the aldehyde and by the carbene catalyst as well. Interestingly, the “resting state” VIII shows significant stabilities for *all* carbenes and aldehydes with respect to II. It should be noted again that in Table 2 the energies and not the Gibbs free energies are given. Since in II' and VI an additional aldehyde is involved, the entropy factor contributes here significantly and while their energy can directly be compared, for their comparison to VIII and II further considerations are needed. From this respect it is worthy to note that in case of benzaldehyde II' is more stable than VI for all carbenes, while for the other aldehydes the stability of VI is significantly larger.

For a given aldehyde, the relative energies of III and IV are similar for each investigated carbene, the stability of II (and its tautomer VIII) depends significantly on the carbene. This is of crucial importance for the reaction, determining the energy benefit of the catalytically most important coupling step. Most notably, while for 7 and 13 type II (and VIII) structures exhibit similar relative energies with respect to the starting materials (or product), for the sulfur-containing 9 these intermediates are by ca. 10 kcal/mol more stable.

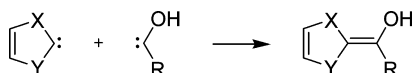
This immense stability of II in the catalytic cycles of 9 should affect the reaction significantly. For a better understanding of the nature of this effect, it is advantageous to compare the relative energies of II and V, which are both composed of two molecular units, therefore, the role of the entropy factor in the II→V rearrangement is presumably small. Comparing the energy of these two species for the different carbenes and aldehydes reveals that while for 7 and 13 the II→V transformation is exothermic in all cases, for 9 it is about thermoneutral in case of formaldehyde and acetaldehyde, and even endothermic in case of benzalde-

hyde. This stability of II (II') in case of 9 results in higher barriers of the II'→IV steps than for the other carbenes, resulting in a prolonged lifetime of II'. Accordingly, with 9 those aldehydes can be selected for II', which form the most stable V, while for the other carbenes the fast decomposition to the products allows a less effective selection; thus, statistics should play a bigger role in the product distribution. In this respect, it is worth to mention that in some cases of the so-called cross-benzoin condensation (Figure 9,) significant selectivities (up to even 100%) could be achieved,<sup>27</sup> preferring mostly one product out of the possible four. Most notably, all in these selective cases thiazol-2-ylidenes have been applied, while to our knowledge no such selectivity has been reported with other NHCs. These experimentally observed selectivities may be explained by the above-discussed stability of II in case of thiazole-based 9 type carbenes.

The differences in the stability of II derived from different NHCs should also affect the catalytic cycle of the transketolase reaction. Most importantly as has been shown above, the TK reaction is initiated by a reverse benzoin condensation;<sup>2</sup> thus, the reversibility of the coupling is the essence of this process (step marked by a frame in Figure 3). Since with acetaldehyde (this models the transketolase reaction) the benzoin product is rather stable, it is difficult to start the reverse reaction, unless by the help of 9 the stable II' (and then II) can be obtained. The situation is completely different for benzaldehyde, where in accordance with previous experimental<sup>16c,16</sup> and computational<sup>25</sup> data the reaction is reversible. It should also be noted that the above-mentioned increased selectivity in the presence of multiple possible (sugar) substrates (as described above) can also be a valuable property in a biochemical process, determining the concentration of different

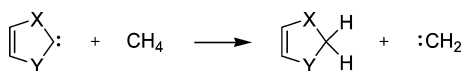
sugars, although in this respect the enzymatic environment should also be of great influence.

As has been shown above, the relative energy of the Breslow intermediate has significant effects on the reaction energy profile of the benzoin condensation and of the analogous TK reaction; thus, it is essential to understand the structural effects stabilizing **II**. The structure of **II** is analogous to that of carbene dimers, thus, it can also be rationalized as the carbene catalyst coupled to a hydroxycarbene (Figure 10). According to this description, the



**Figure 10.** Description of the Breslow intermediate's formation as a carbene–hydroxycarbene coupling.

stability of **II** might be influenced by the same effects as the dimerization energy of the corresponding carbenes. Due to its prominent role in the stability of free carbenes, the dimerization itself has thoroughly been investigated, and its energy ( $\Delta E_{\text{carbene}}$ ) has been found to be in good correlation with that of the isodesmic reaction depicted in Figure 11,<sup>24</sup> which, hence, can be



**Figure 11.** Isodesmic reaction, of which energy ( $\Delta E_{\text{carbene}}$ ) can be defined as a measure of the stability of carbenes.

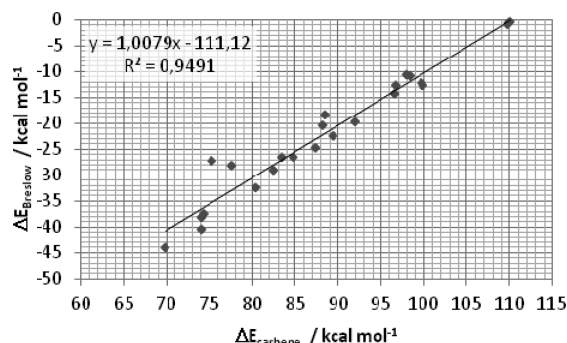
defined as a measure of stability of carbenes. To gain a general picture on the relationship between the relative energy of **II** ( $R = \text{Me}$ ) structures and the stability of the carbenes, these two sets of data have been calculated for compounds 1–24 (Table 3.).

**Table 3. Stabilization Energies of Carbenes 1–24 ( $\Delta E_{\text{carbene}}$ ) According to the Reaction in Figure 10 ( $\Delta E_{\text{carbene}}$ ) and the Energy of the “Carbene + MeCHO  $\rightarrow$  **II**” Reaction ( $\Delta E_{\text{II}}$  in kcal/mol Units)**

carbene	$\Delta E_{\text{carbene}}$	$\Delta E_{\text{II}}$	carbene	$\Delta E_{\text{carbene}}$	$\Delta E_{\text{II}}$
1	98.4	−10.8	13	109.7	−0.6
2	92.0	−19.6	14	98.7	−12.2
3	87.3	−24.8	15	96.7	−12.7
4	84.7	−26.6	16	88.4	−18.3
5	74.0	−38.2	17	78.4	−32.0
6	74.3	−37.4	18	83.4	−26.5
7	110.1	−0.3	19	89.4	−22.4
8	99.8	−12.6	20	69.8	−44.0
9	96.6	−14.5	21	74.0	−40.3
10	88.2	−20.3	22	75.3	−28.2
11	80.4	−32.4	23	98.0	−10.6
12	82.5	−29.0	24	77.5	−28.2

$\Delta E_{\text{carbene}}$ , as expected,<sup>24</sup> is the largest for nitrogen-substituted hypovalent centers. Thus, while for NHC 7 and 13 the stability is similar (about 110 kcal/mol), for thiazol-2-ylidene 9 it is about 13 kcal/mol lower. Apparently, aromaticity has an impact on the stability, as revealed by comparing  $\Delta E_{\text{carbene}}$  for 1–6 and 7–12, respectively.<sup>28</sup> It is worth noting here that this difference in aromaticity has recently been shown to have an effect also on the catalytic activity, explaining why **1** is significantly less effective in umpolung catalysis than **7**.<sup>29</sup>

In agreement with the aforementioned analogy between carbene dimers and **II**-type structures, their relative energy in the benzoin condensation correlates well with  $\Delta E_{\text{carbene}}$  for carbenes 1–24 (Figure 12.). Thus, the more stable is the carbene, the



**Figure 12.** Correlation between the Stabilization energies of carbenes 1–24 according to the reaction in Figure 10, and the energy of the carbene + MeCHO  $\rightarrow$  **II** reaction.

smaller is the energy benefit of the formation of the Breslow intermediate. Accordingly, the balance in the equilibrium between **II** and **V** in the benzoin condensation is predominantly determined by the stability of the carbene catalyst itself, which, as discussed above, may determine reversibility and selectivity in both biochemical processes and synthetic applications. Hence, it is reasonable to assume that the biochemical preference of the thiazole ring over imidazoles in thiamine is due to the lower stability of the corresponding carbene, which stabilizes the Breslow intermediate, resulting in a more facile decoupling of the aliphatic aldehydes in the first step of the TK reaction.

## CONCLUSION

The influence of the structure of carbene catalysts on their catalytic properties has been examined by DFT calculations, motivated by the fact that in biological systems the transketolase reaction is catalyzed exclusively by thiamine (possessing a thiazole ring), while in synthetic approaches imidazole and triazole derivatives can also be used.

First, we focused on the proton affinities of the different carbenes, which is related to the first step of most of the NHC organocatalytic processes, namely the formation of the catalyst from its salt. The protonation energies exhibited significant substituent effects according to the atoms attached to the hypovalent carbon. In case of the synthetically most important five-membered rings the obtained high proton affinity decreases in the order of  $N > S > O$ . These high values, however, can be slightly decreased by the introduction of a double bond at the backbone, or even more by the replacement of a backbone carbon to nitrogen.

Interestingly, according to the DFT calculations, with traces of water in nonpolar media thiazol-2-ylidenes and imidazol-2-ylidenes react similarly, despite the significant differences in their stability, and a slow, irreversible ring-opening should occur. Nonetheless, in accordance with previous experimental findings, with large excesses of water (modeled by using a microsolvation approach) the ring opening of thiazole is feasible, unlike in case of imidazole derivatives.

The structure of both the aldehyde and the carbene affects the energy of the reaction intermediates and transition states. Most remarkably, the Breslow intermediate **II** has been found to be by 10 kcal/mol more stable for thiazol-2-ylidene **9** than for **7** and **13**.



Because of the stabilization of **II** the formation of **IV** (by the addition of the second aldehyde molecule to **II**) exhibits less energetic benefit and a somewhat increased barrier; thus, eventually effects the lifetime of **II** in the reaction mixture, increasing the reversibility of the reaction, and also its selectivity, when different aldehydes are present.

Considering the differences that sulfur makes to the catalytic process and to the ring-opening with water, a complete explanation of the exquisite structure of the corresponding biocatalyst thiamine can be compiled. Together with the relatively high acidity of thiazolium salts that increase the carbene concentration, and the facile and reversible ring-opening with an excess of water that may provide better transport through cell membranes, the lower stability of thiazol-2-ylidene results in the increased stability of the Breslow intermediate. This facilitates the reversible decoupling step within the transketolase reaction, where the substrates (sugars) are benzoin condensed products from *aliphatic* aldehydes being stabilized with respect to their aromatic counterparts. Thus, with thiamine catalyst the Breslow intermediate becomes available in the otherwise irreversible (*aliphatic*) benzoin condensation, making the transketolase reaction possible. These results indicate the possibility of tuning the rate of the transketolase reaction via the development of thiamine analogues, being less/more prone either to isomerize to the active (carbene) isomer within the enzyme, or to catalyze the initial decoupling step of the reaction as potential targets of (anticancer or antidiabetic) drug design.

## ■ ASSOCIATED CONTENT

### ■ Supporting Information

XYZ coordinates and total energies of all optimized structures, schemes on the energy profile of the hydrolysis of **9** in the presence of one to three water molecules, detailed discussion of the validation of the applied method, and structures of the different isomers of **II** derivatives. This material is available free of charge via the Internet at <http://pubs.acs.org/>.

## ■ AUTHOR INFORMATION

### Corresponding Author

\*E-mail: [holloczki@gmail.com](mailto:holloczki@gmail.com), [nyulaszi@mail.bme.hu](mailto:nyulaszi@mail.bme.hu).

### Notes

The authors declare no competing financial interest.

## ■ ACKNOWLEDGMENTS

Financial support from New Széchenyi Plan TAMOP-4.2.2/B-10/1-2010-0009 is gratefully acknowledged.

## ■ REFERENCES

- (1) (a) Enders, D.; Balensiefer, T. *Acc. Chem. Res.* **2004**, *37*, 534. (b) Enders, D.; Niemeier, O.; Henseler, A. *Chem. Rev.* **2007**, *107*, 5606. (c) Marion, N.; Díez-González, S.; Nolan, S. P. *Angew. Chem., Int. Ed.* **2007**, *46*, 2988.
- (2) (a) Stryer, L. *Biochemistry*, 4th ed.; Freedman and Co.: New York, 1995. (b) *Thiamine: Catalytic Mechanisms in Normal and Disease States*; Jordan, F., Patel, M. S., Eds.; Marcel Dekker Inc.: New York, 2004.
- (3) (a) Wöhler, F.; Liebig, J. *J. Ann. Pharm.* **1832**, *3*, 249. (b) Lapworth, A. *J. Chem. Soc.* **1903**, *83*, 995.
- (4) Breslow, R. *J. Am. Chem. Soc.* **1958**, *80*, 3719.
- (5) Ugai, T.; Tanaka, S.; Dokawa, S. *J. Pharm. Soc. Jpn.* **1943**, *63*, 269.
- (6) (a) Hollóczki, O.; Gerhard, D.; Massone, K.; Szarvas, L.; Németh, B.; Veszprémi, T.; Nyulászi, L. *New J. Chem.* **2010**, *34*, 3004. (b) Rodríguez, H.; Gurau, G.; Holbrey, J. D.; Rogers, R. D. *Chem. Commun.* **2011**, *47*, 3222. (c) Kelemen, Z.; Hollóczki, O.; Nagy, J.; Nyulászi, L. *Org. Biomol. Chem.* **2011**, *9*, 5362. (d) Fevre, M.; Pinaud, J.

Leteneur, A.; Gnanou, Y.; Vignolle, J.; Taton, D.; Miqueu, K.; Sotiropoulos, J.-M. *J. Am. Chem. Soc.* **2012**, *134*, 6776–84.

(7) (a) Kern, D.; Kern, G.; Neef, H.; Tittmann, K.; Killenberg-Jabs, M.; Winker, C.; Schneider, G.; Hübner, G. *Science* **1997**, *275*, 67. (b) Kluger, R.; Tittmann, K. *Chem. Rev.* **2008**, *108*, 1797.

(8) Chiang, P.-C.; Rommel, M.; Bode, J. W. *J. Am. Chem. Soc.* **2009**, *131*, 8714.

(9) White, M. J.; Leeper, F. J. *J. Org. Chem.* **2001**, *66*, 5124.

(10) (a) Berkessel, A.; Elfert, S.; Etzenbach-Effers, K.; Teles, J. H. *Angew. Chem., Int. Ed.* **2010**, *49*, 7120. (b) It should be noted that recently a few structural (enamine) analogues of the Breslow intermediate have been isolated; see: DiRocco, D. A.; Oberg, K. M.; Rovis, T. *J. Am. Chem. Soc.* **2012**, *134*, 6143.

(11) It has been shown that lactones could be synthesized via selective homoenolate production in the presence of benzaldehyde using imidazolium-based catalysts, while with the apparently more active thiazolium-based catalysts benzoin condensation was observed. (a) Burstein, C.; Glorius, F. *Angew. Chem., Int. Ed.* **2004**, *43*, 6205. (b) Sohn, S. S.; Rosen, E. L.; Bode, J. W. *J. Am. Chem. Soc.* **2004**, *126*, 14370. (c) Nair, V.; Vellalath, S.; Poonoth, M.; Mohan, R.; Suresh, E. *Org. Lett.* **2006**, *8*, 507.

(12) (a) Amyes, T. L.; Diver, S. T.; Richard, J. P.; Rivas, F. M.; Tóth, K. *J. Am. Chem. Soc.* **2004**, *126*, 4366. (b) Teles, J. H.; Melder, J.-P.; Ebel, K.; Schneider, R.; Gehrer, E.; Harder, W.; Brode, S.; Enders, D.; Breuer, K.; Raabe, G. *Helv. Chim. Act.* **1996**, *79*, 61.

(13) (a) Hollóczki, O.; Terleczy, P.; Szieberth, D.; Mourgas, G.; Gudat, D.; Nyulászi, L. *J. Am. Chem. Soc.* **2011**, *133*, 780. (b) Denk, K. D.; Rodezno, J. M.; Gupta, S.; Lough, A. J. *Organomet. Chem.* **2001**, *617–618*, 242. (c) Duclos, J. M.; Haake, P. *Biochemistry* **1974**, *13*, 5358.

(14) (a) Boros, L. G.; Torday, J. S.; Bassilian, S.; Cascante, M.; Lee, W.-N. P. *Cancer Res.* **2000**, *60*, 1183. (b) Zhao, J.; Zhong, C.-J. *Neurosci. Bull.* **2009**, *25*, 94. (c) Rais, B.; Comin, B.; Puigjaner, J.; Brandes, J. L.; Creppy, E.; Saboreau, D.; Ennamany, R.; Lee, W.-N.; Boros, L. G.; Cascante, M. *FEBS Lett.* **1999**, *456*, 113. (d) Gyuris, J.; O'Hagan, R. C.; Han, M.; Robinson, M.; Weiler, S. WO 2005-US9758 20050323.

(15) (a) Thornalley, P. J. *Curr. Diabetes Rev.* **2005**, *1*, 287. (b) Beltramo, E.; Berrone, E.; Tarallo, S.; Porta, M. *Acta Diabetol.* **2008**, *45*, 131. (c) Babaei-Jadidi, R.; Karachalias, N.; Ahmed, N.; Battach, S.; Thornalley, P. J. *Diabetes* **2003**, *42*, 2120.

(16) Mahatthananchai, J.; Bode, J. W. *Chem. Sci.* **2012**, *3*, 192.

(17) (a) Cheong, P. H.-Y.; Legault, C. Y.; Um, J. M.; Celebi-Olcum, N.; Houk, K. N. *Chem. Rev.* **2011**, *111*, 5042. (b) Dudding, T.; Houk, K. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 5770.

(18) Gaussian 03, Revision C.02: Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Montgomery, J. A., Jr.; Vreven, T.; Kudin, K. N.; Burant, J. C.; Millam, J. M.; Iyengar, S. S.; Tomasi, J.; Barone, V.; Mennucci, B.; Cossi, M.; Scalmani, G.; Rega, N.; Petersson, G. A.; Nakatsuji, H.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Klene, M.; Li, X.; Knox, J. E.; Hratchian, H. P.; Cross, J. B.; Bakken, V.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Yazyev, O.; Austin, A. J.; Cammi, R.; Pomelli, C.; Ochterski, J. W.; Ayala, P. Y.; Morokuma, K.; Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Zakrzewski, V. G.; Dapprich, S.; Daniels, A. D.; Strain, M. C.; Farkas, O.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Ortiz, J. V.; Cui, Q.; Baboul, A. G.; Clifford, S.; Cioslowski, J.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Challacombe, M.; Gill, P. M. W.; Johnson, B.; Chen, W.; Wong, M. W.; Gonzalez, C.; Pople, J. A. Gaussian, Inc., Wallingford CT, 2004.

(19) Gaussian 09, Revision A.1: Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Scalmani, G.; Barone, V.; Mennucci, B.; Petersson, G. A.; Nakatsuji, H.; Caricato, M.; Li, X.; Hratchian, H. P.; Izmaylov, A. F.; Bloino, J.; Zheng, G.; Sonnenberg, J. L.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Vreven, T.; Montgomery, J. A., Jr.; Peralta, J. E.; Ogliaro, F.; Bearpark, M.; Heyd, J. J.; Brothers, E.; Kudin, K. N.; Staroverov, V. N.; Kobayashi, R.; Normand, J.; Raghavachari, K.; Rendell, A.; Burant, J. C.; Iyengar, S.

S.; Tomasi, J.; Cossi, M.; Rega, N.; Millam, N. J.; Klene, M.; Knox, J. E.; Cross, J. B.; Bakken, V.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Yazyev, O.; Austin, A. J.; Cammi, R.; Pomelli, C.; Ochterski, J. W.; Martin, R. L.; Morokuma, K.; Zakrzewski, V. G.; Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Dapprich, S.; Daniels, A. D.; Farkas, Ö.; Foresman, J. B.; Ortiz, J. V.; Cioslowski, J.; Fox, D. J. Gaussian, Inc., Wallingford CT, 2009.

(20) Lau, J. K.C.; Deubel, D. V. J. *Chem. Theory Comput.* **2006**, *2*, 103.

(21) Terleczy, P.; Nyulászi, L. *J. Phys. Chem. A* **2009**, *113*, 1096.

(22) (a) Alder, R. W.; Allen, P. R.; Williams, S. J. *J. Chem. Soc., Chem. Commun.* **1995**, *12*, 1267. (b) Kim, Y.-J.; Streitwieser, A. *J. Am. Chem. Soc.* **2002**, *124*, 5757. (c) Chen, H.; Justes, D. R.; Cooks, R. G. *Org. Lett.* **2005**, *7*, 3949. (d) Chu, Y.; Deng, H.; Cheng, J.-P. *J. Org. Chem.* **2007**, *72*, 7790. (e) Schroeder, M. A.; Makino, R. C. *Tetrahedron* **1973**, *29*, 3469. (f) Kemp, D. S.; O'Brien, J. T. *J. Am. Chem. Soc.* **1970**, *92*, 2554. (g) Liu, M.; Yang, I.; Buckley, B.; Lee, J. K. *Org. Lett.* **2010**, *12*, 4764. (h) Graham, D. C.; Cavell, K. J.; Yates, B. F. *J. Phys. Org. Chem.* **2005**, *18*, 298. (i) Magill, A. M.; Cavell, K. J.; Yates, B. F. *J. Am. Chem. Soc.* **2004**, *126*, 8717. (j) Alder, R. W.; Blake, M. E.; Oliva, J. M. *J. Phys. Chem. A* **1999**, *103*, 11200. (k) Kassaei, M. Z.; Shakib, F. A.; Momeni, M. R.; Ghambarian, M.; Musavi, S. M. *J. Org. Chem.* **2010**, *75*, 2539. (l) Maji, B.; Breugst, M.; Mayr, H. *Angew. Chem., Int. Ed.* **2011**, *50*, 6915–6919.

(23) Hollóczki, O.; Nyulászi, L. *Org. Biomol. Chem.* **2011**, *9*, 2634.

(24) Forró, A.; Veszprémi, T.; Nyulászi, L. *Phys. Chem. Chem. Phys.* **2000**, *3*, 3127.

(25) The reversibility of the benzaldehyde benzoin condensation was shown for the cyanide-catalyzed reaction experimentally: (a) Kuebrich, J. P.; Schowen, R. L.; Wang, M.; Lupes. *J. Am. Chem. Soc.* **1971**, *93*, 1214. It was also shown computationally: (b) M., E.; Yamabe, S.; Yamazaki, S. *Org. Biomol. Chem.* **2009**, *7*, 951–961.

(26) (a) Kuo, J.; Ciobanu, C. V.; Ojamäe, L.; Shavitt, I.; Singer, S. J. *J. Chem. Phys.* **2003**, *118*, 3583. (b) Cypryk, M.; Apeloig, Y. *Organometallics* **2002**, *21*, 2165. (c) Orregeno, J. F.; Cano, H.; Restrepo, A. *J. Phys. Chem. A* **2009**, *113*, 6517. (d) Cramer, C. J.; Truhlar, D. G. *Chem. Rev.* **1999**, *99*, 2161.

(27) (a) Stetter, H.; Dämbkes, G. *Synthesis* **1977**, 403. (b) Stetter, H.; Dämbkes, G. *Synthesis* **1980**, 309. (c) Heck, R.; Henderson, A. P.; Köhler, B.; Rétey, J.; Golding, B. T. *Eur. J. Org. Chem.* **2001**, 2623. (d) Matsumoto, T.; Ohishi, M.; Inoue, S. *J. Org. Chem.* **1985**, *50*, 603. (e) Piel, I.; Pawelczyk, M. D.; Hirano, K.; Fröhlich, R.; Glorius, F. *Eur. J. Org. Chem.* **2011**, 5475.

(28) For the aromaticity of imidazol-2-ylidenes, see: (a) Boehme, C.; Frenking, G. *J. Am. Chem. Soc.* **1996**, *118*, 2039. (b) Heinemann, C.; Müller, T.; Apeloig, Y.; Schwartz, H. *J. Am. Chem. Soc.* **1996**, *118*, 2023. (c) Cheng, M.-J.; Hu, C.-H. *Chem. Phys. Lett.* **2001**, *349*, 477. (d) Hollóczki, O.; Nyulászi, L. *J. Org. Chem.* **2008**, *73*, 4794. (e) Guha, A. K.; Sarmah, S.; Phukan, A. K. *Dalton Trans.* **2010**, *39*, 7374–7383. (f) Gronert, S.; Keeffe, J. R.; More O'Ferrall, R. A. *J. Am. Chem. Soc.* **2011**, *133*, 3381–3389. (g) Gronert, S.; Keeffe, J. R.; More O'Ferrall, R. A. *J. Am. Chem. Soc.* **2011**, *133*, 11817–11818. (h) A more detailed discussion of this aspect will be discussed elsewhere : Kelemen, Z.; Hollóczki, O.; Oláh, J.; Nyulászi, L. To be submitted.

(29) Maji, B.; Horn, M.; Mayr, H. *Angew. Chem., Int. Ed.* **2012**, *51*, 6231–6235.