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Keto–Enol Thermodynamics of Breslow Intermediates

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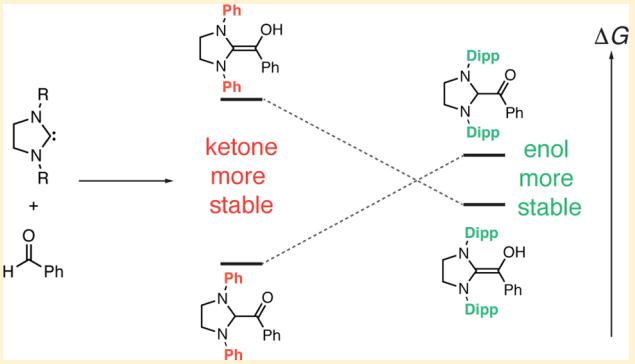
Supporting Information

ABSTRACT: Breslow intermediates, first postulated in 1958, are pivotal intermediates in carbene-catalyzed umpolung. Attempts to isolate and characterize these fleeting amino enol species first met with success in 2012 when we found that saturated bis-Dipp/Mes imidazolidinylidenes readily form isolable, though reactive diamino enols with aldehydes and enals. In contrast, triazolylidenes, upon stoichiometric reaction with aldehydes, gave exclusively the keto tautomer, and no isolable enol. Herein, we present the synthesis of the "missing" keto tautomers of imidazolidinylidene-derived diamino enols, and computational thermodynamic data for 15 enol–ketone pairs derived from various carbenes/aldehydes. Electron-withdrawing substituents on the aldehyde favor enol formation, the same holds for *N*,*N*′-Dipp [2,6-di(2-propyl)phenyl] and *N*,*N*′-Mes [2,4,6-trimethylphenyl] substitution on the carbene component. The latter effect rests on stabilization of the diamino enol tautomer by Dipp substitution, and could be attributed to dispersive interaction of the 2-propyl groups with the enol moiety. For three enol–ketone pairs, equilibration of the thermodynamically disfavored tautomer was attempted with acids and bases but could not be effected, indicating kinetic inhibition of proton transfer.

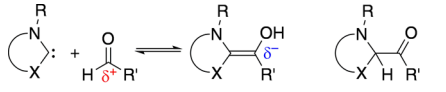


1. INTRODUCTION

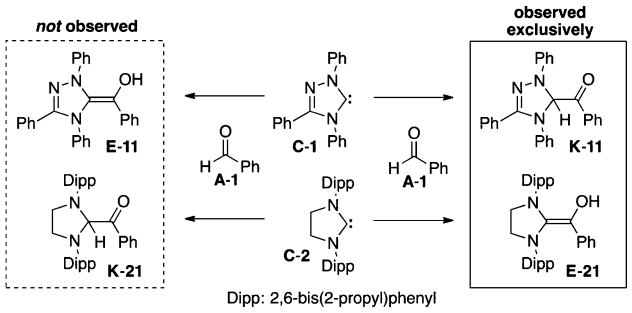
Both in vitamin-B1-dependent enzymes and in organocatalytic umpolung, catalysis by N-heterocyclic carbenes (NHCs) hinges on the formation of the so-called Breslow intermediates[1,2] [chemically: (di)amino enols] **E** (Scheme 1) in which the genuine polarity of, for example, an aldehyde substrate is inverted from electrophilic to nucleophilic. Attack of the nucleophilic amino enol **E** on various electrophiles gives rise to benzoin condensation, Stetter reaction, and other well-known NHC-catalyzed umpolung reactions. The Breslow intermediate was first postulated in 1958 for thiamine-catalyzed transformations (X = S, Scheme 1).[1,2] The first successful generation of diamino enols **E** (X = NR) from aldehydes and imidazolidinylidenes, and their characterization by in situ NMR, was reported by us in 2012, followed by isolation and X-ray characterization in 2013.[3,4]

The keto tautomer **K** (Scheme 1) of the Breslow intermediate has received considerably less attention than the amino enol **E**. In our study on the stoichiometric interaction of the 1,2,4-triphenyltriazolylidene carbene **C-1** with various aldehydes [e.g., benzaldehyde (**A-1**), Scheme 2], we observed rapid and exclusive formation of the ketone **K-11**, and no corresponding enol (*E* or *Z*) **E-11** (Scheme 2).[5,6] The ketone **K-11** was shown to be catalytically incompetent, indicating that its formation from benzaldehyde (**A-1**) and carbene **C-1** is irreversible.[5] It is worthy of note that in 2012, the first keto form of a thiamine-derived Breslow intermediate was identified

Scheme 1. Breslow Intermediate as Enol (E) and Keto (K) Tautomer



Scheme 2. Comparison of the Reaction of Benzaldehyde (A-1) with the Triazolylidene C-1 and with the Imidazolidinylidene C-2



Received: December 18, 2015
Published: February 14, 2016

DOI: 10.1021/jacs.5b13236
J. Am. Chem. Soc. 2016, 138, 5044–5051

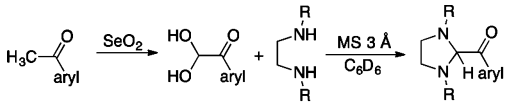
in pyruvate oxidase.[7] In this enzyme, acetyl thiamine serves as an intermediate en route to acetyl phosphate. As pyruvate decarboxylation first affords the enol, the interconversion with its keto form must be feasible in the enzyme.

As briefly summarized in Scheme 2, the reactions of imidazolidinylidenes (such as **C-2**, SIPr) with aldehydes have thus far led exclusively to diamino enols **E**, and no ketones **K** have been observed.[3] In contrast, the ketones **K** were the only observable products in the reaction of triazolylidenes (such as **C-1**) with aldehydes, and no enols could be isolated or traced spectroscopically.[5] We decided to embark on a joint experimental/computational approach to elucidate the reasons (thermodynamics/kinetics) underlying this divergent behavior. Here we disclose a combined experimental and computational study which (i) by synthesis proves the existence and stability of the "missing ketones" of the saturated carbene/aldehyde combination and (ii) analyzes [DFT calculations using M06-2X-D3/def2-TZVPP/IEFPCM(THF)//M06-L-D3/6-31+G(d,p)] the thermodynamics of the enol−keto system for both saturated and unsaturated NHCs in combination with various aldehydes.

2. RESULTS

2.1. Synthesis and Characterization of the "Missing Ketones" Derived from Imidazolidinylidenes. Our synthetic approach to the ketones **K-21**−**K-26**, **K-31**, and **K-41** is shown in Scheme 3. In the first step, aryl ethanones were converted to glyoxyl hydrates by SeO_2 oxidation, as described by Sutherland et al.[8] For *p*-bromophenyl glyoxal hydrate, we were able to obtain the first X-ray crystal structure of its monomeric *gem*-diol form (see Supporting Information). Subsequent condensation with *N,N′*-disubstituted ethylenediamines in the presence of molecular sieves afforded the desired ketones (see Supporting Information for experimental details), a method originally described by Schönberg et al.[9] Note that ketone **K-31** had already been obtained in 1961 by Wanzlick and Schikora, by reacting the "Wanzlick dimer" with benzaldehyde at elevated temperature.[10]

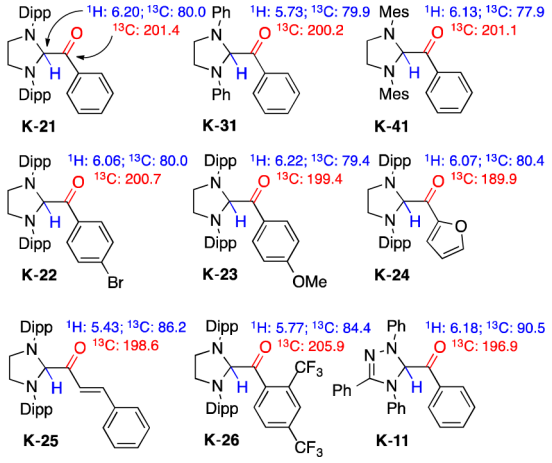
Scheme 3. Preparation of Aryl Glyoxyl Hydrates and Condensation with Ethylenediamines



K-21-26, 31, 41

Figure 1 summarizes the ketones thus prepared, together with characteristic NMR data. As mentioned already, ketone **K-11** also results from the stoichiometric interaction of the triazolylidene carbene **C-1** with benzaldehyde (**A-1**), and its NMR data in THF-d_8 were published before.[5] In the case of ketone **K-31**, we were able to obtain crystals suitable for X-ray crystallography, whereas all other ketones prepared in this study were viscous liquids. The molecular structure of ketone **K-31** is shown in Figure 2.

As a most important structural feature, the crystal structure of ketone **K-31** revealed a syn-periplanar arrangement of the aminal C2−H bond and the carbonyl C−O bond [H−C−C−O = 2.9°]. Additionally, the phenyl rings at N1 and N3 are more or less coplanar with the imidazolidine ring. Of the latter, the ring puckering places C4 somewhat below the plane defined by the other four imidazolidine ring atoms. NMR spectra of



Dipp: 2,6-bis(2-propyl)phenyl; Mes: 2,4,6-trimethylphenyl

Figure 1. Ketones prepared in this study, together with characteristic $^1H/^{13}C$ shifts [ppm (298 K, C_6D_6)].

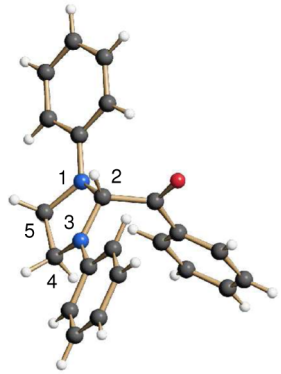


Figure 2. X-ray crystal structure of the ketone **K-31**.

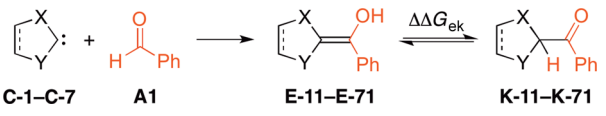
ketone **K-31** were already reported by Schönberg et al. and interpreted in terms of the five-ring dynamics in **K-31**.[9] Our own NMR investigation of **K-31** and of the other ketones in this study revealed that in addition to the syn-periplanar arrangement of the aminal C−H and the carbonyl C−O bond (as seen in the crystal), in solution also the anti-periplanar conformer is present. Both conformers readily equilibrate at room temperature (see NOESY data in the Supporting Information, exemplified for **K-21**). Additionally, rapid rotation of the Dipp substituents is evident through the exchange signals of the 2-propyl groups in the NOESY spectra (see Supporting Information).[11] In summary, we were able to prepare and characterize, in addition to the "Wanzlick ketone" **K-31**, the "missing keto tautomers" of all diamino enols previously reported by us.[3]

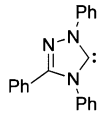
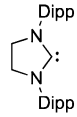
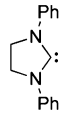
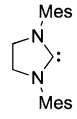
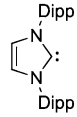
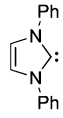
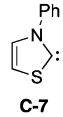
2.2. Computational Studies. *Influence of the Carbene Component on the Keto−Enol Thermodynamics.* Having established that both the keto and the enol tautomers exist for quite a number of **C-2** (SIPr) or **C-4** (SIMes) combinations with aldehydes, this part of our study aimed at calculating the thermodynamic relation of the corresponding enol−ketone pairs. We furthermore aimed at elucidating how the structural and electronic features of the carbene and the aldehyde influence the keto−enol thermodynamics.

Within the different classes of N-heterocyclic carbenes, we first computationally analyzed the combination of different triazole- (**C-1**), imidazolidine- (**C-2**, **C-3**, **C-4**), imidazole- (**C-**

DOI: 10.1021/jacs.5b13236
J. Am. Chem. Soc. 2016, 138, 5044−5051

Table 1. Reaction Free Energies for the Formation of the Breslow Intermediates [ΔG_{enol}] and the Corresponding Ketones [ΔG_{ketone}] from the Free Carbenes and Benzaldehyde, as well as the Keto−Enol Difference [$\Delta\Delta G_{KE}$][a]



Entry	Carbene	ΔG_{enol}	ΔG_{ketone}	$\Delta\Delta G_{ek}$
1	 **C-1**	+3.6 (*E*-**E-11**) +3.5 (*Z*-**E-11**)	−3.5 (**K-11**)	−7.0
2	 **C-2**	−9.6 (**E-21**)	−7.2 (**K-21**)	+2.5
3	 **C-3**	−4.9 (**E-31**)	−13.5 (**K-31**)	−8.7
4	 **C-4**	−10.4 (**E-41**)	−5.4 (**K-41**)	+5.0
5	 **C-5**	+0.1 (**E-51**)	+3.6 (**K-51**)	+3.4
6	 **C-6**	+2.4 (**E-61**)	−3.1 (**K-61**)	−5.6
7	 **C-7**	−7.5 (*E*-**E-71**) −9.1 (*Z*-**E-71**)	−14.2 (**K-71**)	−5.2

[a]All in kcal mol^{-1}, M06-2X-D3/def2-TZVPP/IEFPCM(THF)//M06-L-D3/6-31+G(d,p).

5, **C-6**), and thiazole-derived (**C-7**) carbenes with benzaldehyde (**A-1**). Table 1 presents the reaction free energies for the formation of the Breslow intermediates (amino enols) and the tautomeric ketones as well as the keto−enol energy difference $\Delta\Delta G_{KE}$. While all structures are depicted in the Supporting Information, selected optimized structures are shown in Figure 3. In the lowest energy conformers of all Breslow intermediates obtained from **C-1**−**C-7** and benzaldehyde (**A-1**), the O−H proton is not hydrogen bonded to an azole nitrogen atom but is pointing away from the heterocyclic ring (cf. Figure 3, Supporting Information, and X-ray crystal structures in refs 3). In the corresponding ketones, both the syn- and the anti-orientation of the H−C−C−O dihedral angle could be located

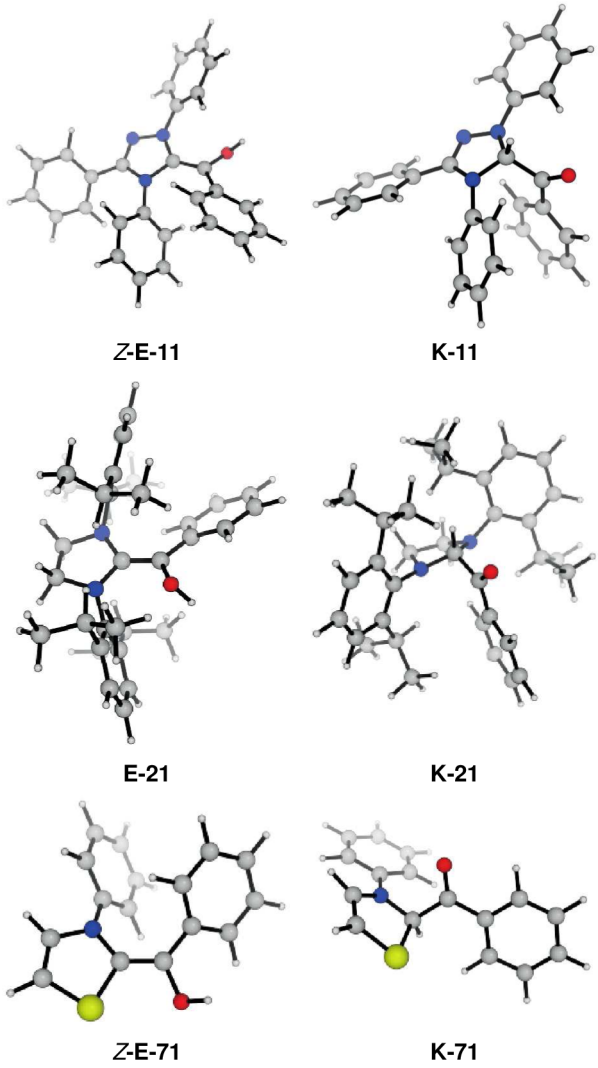


Figure 3. Lowest energy structures for the enol−ketone pairs **E-11**/**K-11**, **E-21**/**K-21**, and **E-71**/**K-71**.

with the syn being preferred in most cases ($\Delta\Delta G_{syn/anti}$ **K-11**: +2.8, **K-21**: +1.0, **K-31**: +2.5, **K-41**: +0.1, **K-51**: −0.4, **K-61**: +3.8, **K-71**: −0.7 kcal mol^{-1}, respectively).

In line with previous investigations,[12] our computational study again shows that sterically demanding N-substituents, e.g., Dipp in the bis-Dipp carbene **C-2** (SIPr), or Mes in **C-4** (SIMes), induce larger interplanar angles, i.e., an almost perpendicular orientation compared to smaller substituents (Figure 3 and Supporting Information).

Within the phenyl-substituted series (i.e., carbenes **C-1**, **C-3**, **C-6**, and **C-7**), the reactions of the thiazole-derived carbene **C-7** are most exergonic (ΔG_{enol} = −9.1 kcal mol^{-1} and ΔG_{ketone} = −14.2 kcal mol^{-1}; Table 1, entry 7) followed by the saturated "Wanzlick carbene" **C-3** (ΔG_{enol} = −4.9 kcal mol^{-1} and ΔG_{ketone} = −13.5 kcal mol^{-1}; Table 1, entry 3). For both unsaturated carbenes **C-1** and **C-6**, the formation of the Breslow intermediate is endergonic (ΔG_{enol} = +3.5 and +2.4 kcal mol^{-1}) while the tautomeric ketone was calculated to be thermodynamically more stable than the reactants (ΔG_{ketone} = −3.5 and −3.1 kcal mol^{-1}). Enol and ketone formation are thermoneutral/endergonic for the combination of the unsaturated Dipp-substituted carbene **C-5** (IPr) and benzaldehyde (**A-1**; Table 1, entry 5). Almost identical reaction free energies

DOI: 10.1021/jacs.5b13236
J. Am. Chem. Soc. 2016, 138, 5044−5051

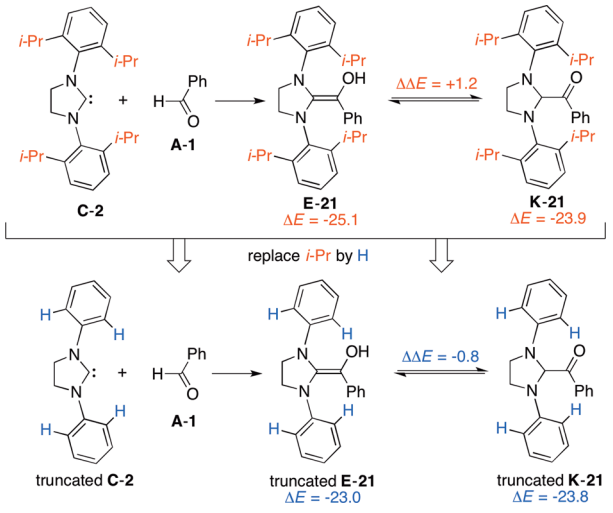
were calculated for the formation of the *E*- and *Z*-enol **E-11** derived from the triazolylidene **C-1** and benzaldehyde (**A-1**; Table 1, entry 1), indicating that the additional phenyl group at C3 has no significant effect on the stabilities of the two diastereomers. In contrast, a significant preference for the *Z*- over the *E*-configuration was calculated for the Breslow intermediate **E-71** formed from the thiazolylidene **C-7** and benzaldehyde (**A-1**; Table 1, entry 7). The unfavorable steric interaction of the two phenyl groups in the *Z*-orientation is obviously compensated by a stabilizing $\pi-\pi$-interaction between the aromatic groups (Figure 3). Within the series of phenyl-substituted carbenes, the ketones are thermodynamically preferred over the corresponding enols (Table 1, entries 1, 3, 6, 7). However, the nature of the carbene **C-1**, **-3**, **-6**, **-7** has only a small effect, as evidenced by the relatively narrow range of 3.5 kcal mol^{-1} in which all keto−enol differences are found ($-8.7 < \Delta\Delta G_{KE} < -5.2$ kcal mol^{-1}).

The most striking feature revealed by our study is the influence of the substituents at the carbene nitrogen atoms on the keto−enol energy difference. When the phenyl substituents in **C-3** (the "Wanzlick carbene") were exchanged for 2,6-di(2-propyl)phenyl (**C-2**, SIPr) or mesityl (**C-4**, SIMes), the formation of both Breslow intermediates and their corresponding ketones remained exergonic (Table 1, entries 2, 3, 4). Closer inspection of the reactions involving the carbenes **C-2** and **C-3** reveals, however, that the reaction free energy for the formation of the enols (**E-21** vs **E-31**) is 4.7 kcal mol^{-1} more favorable for **E-21** (Table 1, entries 2, 3). In contrast, **K-31** is formed in a more exergonic reaction ($\Delta\Delta G$ = 6.3 kcal mol^{-1}) than **K-21**. The same trend, i.e., stabilization of the enol and destabilization of the ketone, was found for the (saturated) imidazolidinylidene pair **C-3**/**C-4** (Table 1, entries 3, 4), and for the (unsaturated) imidazolylidene pair **C-5**/**C-6** (Table 1, entries 5, 6).

An explanation for the remarkable influence of the 2,6-di(2-propyl)phenyl groups on the keto−enol energy difference may be seen in stabilizing dispersive interactions between the 2-propyl groups and the enol substructure within the Breslow intermediates.[13] To assess dispersive effects caused by the 2-propyl groups, we employed a truncated model system. In the latter, we replaced the 2-propyl groups of the carbene **C-2** (SIPr), the enol **E-21**, and the ketone **K-21** by hydrogen atoms (Scheme 4). All atoms present in the starting "full" system were frozen for the optimization of the "truncated" model system, and only the hydrogen atoms added were allowed to relax during the optimizations. As expected, the relative keto−enol energy differences in the presence and absence of 2-propyl groups are not identical. Closer inspection reveals that the reaction energy for ketone formation is virtually unaffected by the truncation (−23.9 kcal mol^{-1} for **K-21** vs −23.8 kcal mol^{-1} for truncated **K-21**). However, for enol formation, the reaction energy in the presence of the 2-propyl groups is ca. 2 kcal mol^{-1} more negative (−25.1 kcal mol^{-1} for **E-21** vs −23.0 kcal mol^{-1} for truncated **E-21**). The calculated change in the keto−enol energy therefore results exclusively from the energy change of the enol. As the reaction energy for **E-21** is 2 kcal mol^{-1} more exothermic, we have to conclude that there is an attractive, dispersive stabilization caused by the 2-propyl groups.

2.3. Computational Studies. *Influence of the Aldehyde on the Keto−Enol Thermodynamics.* We further studied how a variation of the aldehyde influences the keto−enol thermodynamics. For that purpose, we chose the carbene system **C-2** as our model system. As this system had the keto−enol difference which was closest to zero (Table 1, entry 2), this system lends itself best as the starting point. The calculated reaction free energies for the formation of the Breslow intermediates and the corresponding tautomeric ketones from different aldehydes are summarized in Table 2, and selected structures are depicted in Figure 4.

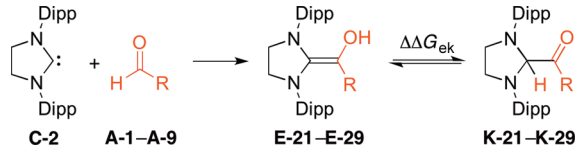
Scheme 4. Influence of the 2-Propyl Groups on the Keto−Enol Energy Difference (all values in kcal mol^{-1})

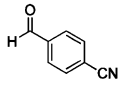
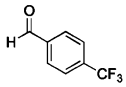
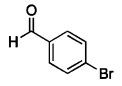
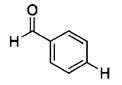
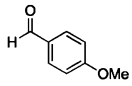
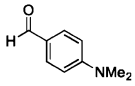
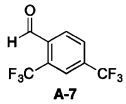


All reactions were found to be exergonic with the exception of the formation of the keto-adduct **K-27** derived from 2,4-bis(trifluoromethyl)benzaldehyde (**A-7**; entry 7, Table 2). In the latter case, the additional *o*-CF_3 substituent destabilizes the ketone due to unfavorable steric interactions with the 2,6-di(2-propyl)phenyl groups (Table 2, compare entries 2 and 7). When steric effects can be neglected, e.g., within a series of *para*-monosubstituted benzaldehydes (entries 1−6 in Table 2), the substituents still have a substantial effect on the thermodynamic stabilities of the Breslow intermediates ($-12.5 < \Delta G < -3.2$ kcal mol^{-1}). In contrast, the corresponding ketones are significantly less affected by a change in substituents ($-7.8 < \Delta G < -6.4$ kcal mol^{-1}). This can be rationalized by the direct interaction of the aromatic substituent and the diamino enol C−C double bond within the Breslow intermediates, which is not present in the tautomeric ketones. Electron-withdrawing substituents such as CN or CF_3 stabilize the diamino enol significantly, while electron-donating groups such as OMe or NMe_2 cause a small destabilization. This effect can also be deduced from the correlation between the substituent constants σ_p[14] and the calculated reaction free energies for the formation of the Breslow intermediates. As a consequence of the relative insensitivity of the ketone stabilities toward substituent effects, the free energies for the keto−enol tautomerism ($\Delta\Delta G_{KE}$) vary between −3.2 and +4.7 kcal mol^{-1} for *para*-substituted benzaldehydes. Again, a good correlation exists between the calculated differences in free energies and the substituent constants σ_p (Figure 5, r^2 = 0.94; see Supporting Information for the additional correlations of ΔG_{ketone} vs σ_p, ΔG_{enol} vs σ_p, and $d_{C=C}$ vs σ_p). The substituents' influence on the stability of the Breslow intermediates is also reflected in the positive slope in Figure 5 which again indicates that electron-withdrawing substituents stabilize the enol tautomer. Entry 9 of Table 2 shows that the formation of the diamino dienol **E-29**, derived from cinnamic aldehyde (**A-9**) and SIPr (**C-2**) is the most exergonic of all the calculated systems (−15.4 kcal mol^{-1}).

DOI: 10.1021/jacs.5b13236
J. Am. Chem. Soc. 2016, 138, 5044−5051

Table 2. Reaction Free Energies for the Formation of the Breslow Intermediates [ΔG_{enol}] and the Corresponding Ketones [ΔG_{ketone}] from SIPr (C-2) and Various Aldehydes, Together with the Keto–Enol Difference [$\Delta\Delta G_{KE}$][a]



Entry	Aldehyde	ΔG_{enol}	ΔG_{ketone}	$\Delta\Delta G_{ek}$
1	 A-2	−12.5 (**E-22**)	−7.8 (**K-22**)	+4.7
2	 A-3	−10.7 (**E-23**)	−7.4 (**K-23**)	+3.3
3	 A-4	−9.6 (**E-24**)	−7.6 (**K-24**)	+2.0
4	 A-1	−9.6 (**E-21**)	−7.2 (**K-21**)	+2.5
5	 A-5	−6.0 (**E-25**)	−6.8 (**K-25**)	−0.8
6	 A-6	−3.2 (**E-26**)	−6.4 (**K-26**)	−3.2
7	 A-7	−12.6 (**E-27**)	+1.9 (**K-27**)	+14.5
8	 A-8	−10.0 (**E-28**)	−8.6 (**K-28**)	+1.4
9	 A-9	−15.4 (**E-29**)	−6.6 (**K-29**)	+8.8

[a]All in kcal mol^{-1}, M06-2X-D3/def2-TZVPP/IEFPCM(THF)//M06-L-D3/6-31+G(d,p).

This can be explained by the elongation of the π-system, while at the same time unfavorable steric interactions become less when compared with the system derived from benzaldehyde (**E-21**, entry 4, Table 2).

3. DISCUSSION

3.1. Enol–Keto Systems Derived from the Saturated Imidazolidinylidenes C-2, C-3, and C-4. As mentioned in the Introduction, Breslow intermediates are formed smoothly and quantitatively when the bis-Dipp- and bis-Mes-substituted imidazolidinylidenes **C-2** (SIPr) and **C-4** (SIMes) are reacted with aldehydes.[3] As shown in entries 2 and 4 of Table 1, this experimental result is in perfect agreement with the reaction thermodynamics: for both carbenes, enol and ketone formation

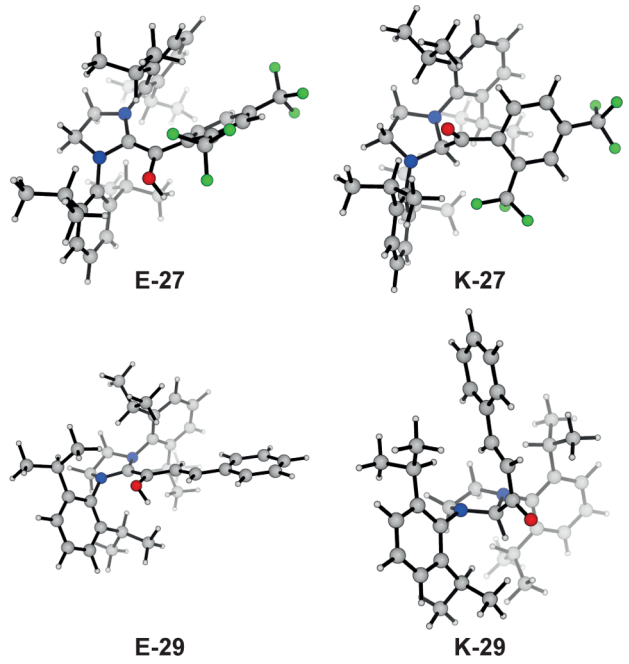


Figure 4. Lowest energy structures for the enol–ketone pairs **E-27**/**K-27** and **E-29**/**K-29**.

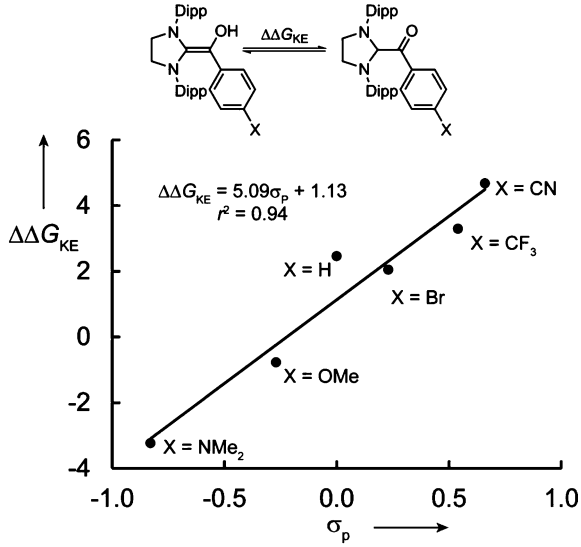


Figure 5. Correlation of the $\Delta\Delta G_{KE}$ and the corresponding substituent constant σ_p[14] [in kcal mol^{-1}, M06-2X-D3/def2-TZVPP/IEFPCM(THF)//M06-L-D3/6-31+G(d,p)].

are significantly exergonic, but again for both carbenes, the enol is the energetically more favorable product tautomer. For the enol–ketone pair **E-41**/**K-41**, $\Delta\Delta G_{KE}$ amounts to 5 kcal mol^{-1}, meaning basically exclusive enol tautomer in equilibrium at room temperature. For the enol–ketone pair **E-21**/**K-21**, $\Delta\Delta G_{KE}$ amounts to 2.5 kcal mol^{-1}, translating to there being ca. 98% of the enol in equilibrium at room temperature. According to our analysis, the favorable energetics of enol formation are mostly due to stabilizing intramolecular dispersive interactions in the enol, between the 2,6-di(2-propyl) groups (or analogously the 2,6-methyl groups) and the enol substructure. For nonheteroatom-substituted enols, the stabilizing effect of the Dipp and Mes substitution, for example, has been recognized and experimentally quantified previ-

DOI: 10.1021/jacs.5b13236
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ously.[4,15] Both conjugative and steric effects have been discussed as the sources of stabilization. In view of our computational assessment of intramolecular dispersive interaction (vide supra), it appears reasonable to assume that this hitherto neglected aspect also contributes to the enol stabilization observed previously, e.g., for Dipp substituents.[4,15]

The fact that the (themodynamically unfavorable) ketones **K-41** and **K-21** can be prepared in pure form (Scheme 3, Figure 1) raised our suspicion that their keto−enol tautomerization may be extremely slow, i.e., kinetically inhibited. In fact, preliminary experiments (see Supporting Information) revealed that the addition of neither acid nor base effects any conversion of **K-41**/**K-21** to **E-41**/**E-21**. Even for the enol−ketone pair **K-27**/**E-27** with the highest $\Delta\Delta G_{KE}$ (−14.5 kcal mol^{-1}; Table 2, entry 7), no ketone-to-enol tautomerization occurred. For keto−enol tautomerization to occur, a proton needs to be added to or removed from the carbon atom flanked by the N atoms, i.e., the former carbene center. We attribute the kinetic inhibition to the extreme shielding of this carbon atom by the N-substituents' 2,4,6-trimethylphenyl or 2,6-di(2-propyl)phenyl groups (see Figure 3 for the **E-21**−**K-21** pair). In fact, treatment of ketone **K-21** with equimolar acetic acid-d_1 did not result in H/D-exchange at the ketone's α-carbon atom over 3 days (see Supporting Information). The assumption of kinetically inhibited keto−enol tautomerization is further supported by the system composed of **C-2** (SIPr) and *p*-methoxybenzaldehyde (**A-5**): As shown in Table 2, entry 5, the formation of both **K-25** and **E-25** from carbene and aldehyde is exergonic by 6−7 kcal mol^{-1}. The ketone is favored by 0.8 kcal mol^{-1}, corresponding to a ca. 80/20 ketone−enol equilibrium mixture at room temperature. The experiment, however, affords the pure diamino enol **E-25** and no ketone **K-25**.[3] This observation can be explained by initial, i.e., kinetically favored, formation of the enol **E-25**, and kinetically inhibited subsequent tautomerization to **K-25**. An even more clear-cut preference for ketone formation should be expected for the system **C-2** (SIPr) plus *p*-dimethylamino benzaldehyde (**A-6**), with $\Delta\Delta G_{KE}$ amounting to −3.2 kcal mol^{-1} (Table 2, entry 6). Unfortunately, for this extremely electron-rich benzaldehyde derivative, the reaction with the carbene **C-2** was very slow and led to the formation of a multitude of products. An unambiguous assignment of the newly emerging resonances to the enol **E-26** or the ketone **K-26** was not possible.

As already reported by Wanzlick and Schikora in 1961, heating of the dimer of **C-3** (the "Wanzlick dimer") with benzaldehyde (**A-1**) cleanly affords the ketone **K-31**.[10] This result is in perfect agreement with the large negative ΔG_{ketone} found for this system (−13.5 kcal mol^{-1}; Table 1, entry 3), as compared to its ΔG_{enol} (−4.9 kcal mol^{-1}). It is tempting to assume that, in this system, generation of the Breslow intermediate may in fact precede the formation of the ketone; the unsubstituted *N*-phenyl substituents should not impede enol-to-ketone tautomerization. Unfortunately, the experimental (NMR) approach to answering this question is barred by the nonexistence of monomeric Wanzlick carbene (**C-3**). In contrast, repetition of the Wanzlick/Schikora experiment with SIPr (**C-2**) as the carbene component led to the formation of benzoin in high yield, but the ketone **K-21** could not be detected (see Supporting Information). The benzoin condensation is indicative for the formation of the Breslow intermediate **E-21**, and the ketone **K-21**, according to our study, is thermodynamically disfavored.

3.2. Enol−Ketone Systems Derived from the Unsaturated Triazolylidene C-1, Imidazolylidenes C-5, C-6, and the Thiazolylidene C-7.

Triazolylidene C-1. For this carbene, we experimentally observed ketone formation when exposed to benzaldehyde (**A-1**) in a stoichiometric fashion.[5] This earlier finding is in good agreement with the calculated $\Delta\Delta G_{KE}$ of −7.0 kcal mol^{-1} (Table 1, entry 1). It is interesting to note that for this highly active carbene catalyst, the formation of the Breslow intermediate is in fact endergonic. The ΔG_{enol} of +3.5 kcal mol^{-1} explains why all efforts to detect Breslow intermediates derived from **C-1** have thus far met with frustration. The thermodynamic data shown in Table 1, entry 1, furthermore explain why for slow catalytic processes (e.g., benzoin condensations), ketone formation may occur as a competing catalyst deactivation pathway.

Imidazolylidenes C-5 (IPr), C-6. For the bis-Dipp imidazolylidene **C-5**, ketone formation with benzaldehyde (**A-1**) is endergonic by +3.6 kcal mol^{-1}, and the driving force for enol formation is almost zero, resulting in an overall preference for enol formation ($\Delta\Delta G_{KE}$ = +3.4 kcal mol^{-1}; Table 1, entry 5). As may be expected from the thermodynamic data of the **C-5**/**A-1** system, NMR monitoring of the carbene's interaction with benzaldehyde (**A-1**) did not point to the accumulation of either **E-51** or **K-51**. Instead, the conversion of the benzaldehyde to benzoin was observed. The enol-stabilizing and ketone-destabilizing effect of the Dipp substituents in **C-5** (IPr) becomes apparent again when the thermodynamic data of the **C-5** plus benzaldehyde (**A-1**) system are compared with those of the *N*,*N*′-diphenylimidazolylidene **C-6**. For the latter, the formation of ketone **K-61** is exergonic by −3.1 kcal mol^{-1}, while the formation of the enol **E-61** becomes significantly endergonic (+2.4 kcal mol^{-1}), resulting in an overall preference for ketone formation ($\Delta\Delta G_{KE}$ = −5.6 kcal mol^{-1}; Table 1, entry 6). Unfortunately, the experimental assessment of this prediction is thus far frustrated by the nonavailability of the monomeric carbene **C-6**.

Thiazolylidene C-7. Within the series of phenyl-substituted carbenes studied, both enol and ketone formation are most exergonic when the *N*-phenylthiazolylidene **C-7** acts as carbene component. For benzaldehyde (**A-1**) as the aldehyde component, ketone formation is preferred by ca. 5 kcal mol^{-1}, well in line with the other *N*-phenyl-substituted carbenes **C-1** (triazolylidene), **C-3** (imidazolidinylidene), and **C-6** (imidazolylidene).

4. CONCLUSIONS

Our analysis of reaction free energies for the formation of various Breslow intermediates and their keto tautomers provides rationalization for previously unexplained experimental observations:

4.1. Ketone Formation from Triphenyltriazolylidene (C-1) and Aldehydes. The failure to observe Breslow intermediate **E-11** when reacting triphenyltriazolylidene (**C-1**) with benzaldehyde (**A-1**) can be explained by the 7.0 kcal mol^{-1} thermodynamic preference for ketone formation. Once at the ketone stage, the concentration of enol **E-11** will be much too low to be detected.

4.2. Formation of Breslow Intermediates from the Imidazolidinylidenes C-2 (SIPr), C-4 (SIMes) and Aldehydes. The introduction of *N*-Mes and *N*-Dipp substituents at the carbene significantly stabilizes the enol form, and destabilizes the ketone. The synergism of these effects makes the enol the thermodynamically favored tautomer for both the

DOI: 10.1021/jacs.5b13236
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saturated [imidazolidinylidenes **C-2** (SIPr) and **C-4** (SIMes)] and the unsaturated [imidazolylidene **C-5** (IPr)] carbenes studied. The enol-stabilizing effect of the Dipp substituents could be attributed to intramolecular dispersive interactions between the 2-propyl groups and the enol moiety. In other words, for all carbene applications where fostering of enol formation is desired, resorting to *N*-Dipp and/or *N*-Mes substitution is advisible. Note that the beneficial effect of mesityl substitution, for triazolylidene catalytic reactions where the formation of Breslow intermediates is crucial, has been reported previously by Bode et al.[16]

We furthermore discovered a remarkable case of kinetic inhibition of proton translocation: For the carbene/aldehyde combinations for which the Breslow intermediate is the thermodynamically favored tautomer, and for which the Breslow intermediates have been characterized experimentally, the keto tautomers were prepared by an alternative synthetic route. With these materials in hand, the ketone-to-enol tautomerization was attempted, both in the presence and absence of acid and base additives. Thus far, no ketone−enol interconversion could be effected. This kinetic inhibition of proton transfer is attributed to the steric shielding of the ketone's α-/enol's β-carbon atom by the 2,6-di(2-propyl)-phenyl or 2,4,6-trimethylphenyl substituents on the carbene's N-atoms.[17]

5. EXPERIMENTAL SECTION

Details of the preparation and characterization of the ketones **K-11**, **K-21-26**, **K-31**, and **K-41** are summarized in the Supporting Information.

6. COMPUTATIONAL METHODS

First, the conformational space of all structures was explored using the OPLS-2005 force field[18] and a modified Monte Carlo search routine implemented in MacroModel 10.2.[19] An energy cutoff of 20 kcal mol^{-1} was used during the conformational analysis, and structures with a heavy atom root-mean-square deviation (RMSD) less than 1−2 Å after the initial force field optimization were considered to be the same conformer. All remaining structures were then optimized in the gas phase, employing the local meta-GGA functional M06-L[20] with Grimme's dispersion-correction D3[21] and the double-ζ split-valence basis set 6-31+G(d,p) as well as density fitting. Furthermore, we included geometries obtained from previously determined crystal structures as additional starting points for the geometry optimization. Subsequent vibrational analysis verified that each structure was a minimum. Thermal corrections were calculated from unscaled harmonic vibrational frequencies at the same level of theory for a standard state of 1 mol L^{-1} and 298.15 K. The entropic contributions to the reported free energies were derived from partition functions evaluated using Truhlar's quasiharmonic correction.[22] This method uses the same approximations as the usual harmonic oscillator except that all vibrational frequencies lower than 100 cm^{-1} are set equal to 100 cm^{-1} to correct for the breakdown of the harmonic oscillator approximation for low frequencies. Electronic energies were subsequently obtained from single-point calculations of the M06-L geometries employing the meta-hybrid M06-2X functional,[23] Grimme's dispersion-correction D3 (zero damping),[21] and the large triple-ζ def2-TZVPP basis set,[24] a level which is expected to result in accurate energies.[25] Solvation by tetrahydrofuran, a solvent frequently used in carbene-catalyzed reactions, was taken into account by using the integral equation formalism polarizable continuum model (IEFPCM)[26] during the single point calculations. In general, solvation effects were found to be rather small as demonstrated for the relative stabilities of **E-21** and **K-21** in the Supporting Information (Table S1, p S8). Throughout this investigation, an ultrafine grid corresponding to 99 radial shells and 590 angular points was used for the numerical integration of the density.[27] All density functional theory calculations were performed with Gaussian 09.[28]

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.5b13236.

X-ray data of *p*-bromophenyl glyoxal hydrate[29] (CIF)
X-ray data of ketone **K-31**[29] (CIF)
Cartesian coordinates and energies of all calculated structures, graphical visualization of lowest-energy conformers, and details of computational methods (PDF)
Experimental details of the preparation and characterization of the ketones **K-11**, **K-21−26**, **K-31**, and **K-41** (PDF)

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§J.-M.N.: x-ray crystallography.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work was supported by the Deutsche Forschungsgemeinschaft (DFG), Priority Program "Control of London Dispersion Interactions in Molecular Chemistry" (SPP 1087, grant no. BE 998/14-1) and by the Fonds der Chemischen Industrie (Liebig Fellowship to M.B.). Computations were performed on the DFG-funded Cologne High Efficiency Operating Platform for Sciences (CHEOPS).

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DOI: 10.1021/jacs.5b13236
J. Am. Chem. Soc. 2016, 138, 5044−5051