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Keto-Enol Thermodynamics of Breslow Intermediates

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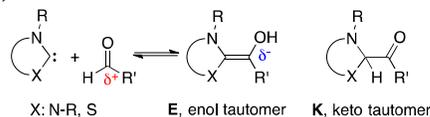
KEYWORDS: Carbenes; Umpolung; keto-enol tautomerization; DFT calculations; NMR spectroscopy

ABSTRACT: Breslow intermediates, first postulated in 1958, are pivotal intermediates in carbene-catalyzed Umpolung. Attempts to isolate and characterize these fleeting amino enol species have first met with success in 2012 when we found that saturated bis-Dipp/Mes imidazolidinylienes 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. With one exception, the experimentally observed enol-ketone preferences correspond to the calculated thermodynamics of the enol-ketone pairs. 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.

I. 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 e.g. an aldehyde substrate is inverted from electrophilic to nucleophilic. Attack of the nucleophilic aminoenol **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 imidazolidinylienes, and their characterization by *in situ* NMR, was reported by us in 2012, followed by isolation and X-ray characterization in 2013.^{3,4}

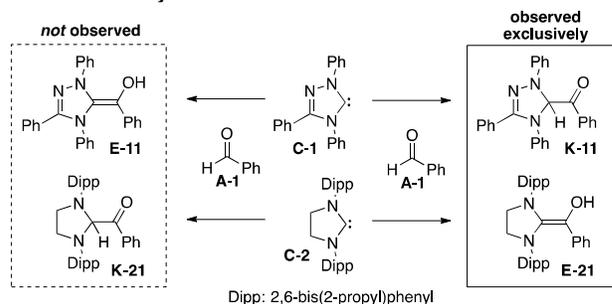
Scheme 1. The Breslow Intermediate as Enol (E) and Keto (K) Tautomer.



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 has been identified 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.

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



As briefly summarized in Scheme 2, the reactions of imidazolidinylienes (such as **C-2**, SIPr) with aldehydes have

thus far led exclusively to diamino enols **E**, and no ketones **K** were observed.^{3,4,6} 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. In 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 Mo6-2X-D3/def2-TZVPP/IEFPCM(THF)//Mo6-L-D3/631+G(d,p)] the thermodynamics of the enol/keto system for both saturated and unsaturated NHCs in combination with various aldehydes.

II. RESULTS

II.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 SeO₂ oxidation, as described by Sutherland *et al.*⁸ For the *para*-bromophenyl glyoxal hydrate, we were able to obtain the first X-ray crystal structure of its monomeric *gem*-diol form (see SI). Subsequent condensation with *N,N'*-disubstituted ethylenediamines in the presence of molecular sieves afforded the desired ketones (see SI 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

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

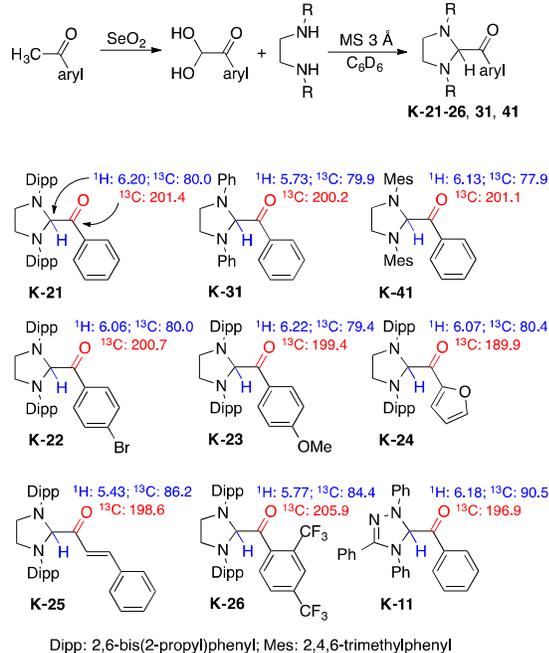


Figure 1. Ketones prepared in this study, together with characteristic ¹H/¹³C shifts [ppm (298 K, C₆D₆)].

"Wanzlick dimer" with benzaldehyde at elevated temperature.¹⁰

Figure 1 summarizes the ketones thus prepared, together with characteristic NMR data. As mentioned already, ketone **K-11** results from the stoichiometric interaction of the triazolylidene carbene **C-1** with benzaldehyde (**A-1**), and its published NMR data⁵ are included in Figure 1 for completeness. 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.

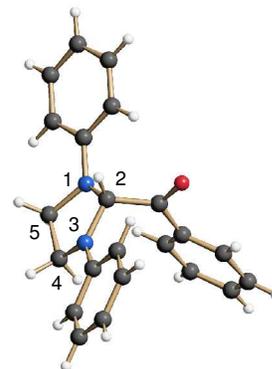


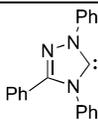
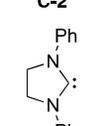
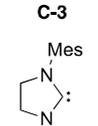
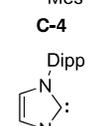
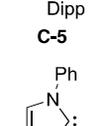
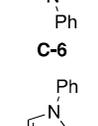
Figure 2: X-Ray crystal structure of the ketone **K-31**.

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 ketone **K-31** were already reported by Schönberg *et al.*, and interpreted in terms of the 5-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 Breslow diaminoenols previously reported by us.^{3,4}

II.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 ketone-enol pairs. We furthermore aimed at elucidating how the structural and electronic

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 [$\Delta\Delta G_{\text{KE}}$]^a

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

^aall in kcal mol⁻¹, Mo6-2XD3/def2-TZVPP/IEFPCM(THF)//Mo6-L-D3/6-31+G(d,p).

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-5, C-6), and thiazole-derived (C-7) carbenes with benzaldehyde (A-1). Table 1 collects the reaction free energies for the formation of the Breslow intermediates (aminoenols) and the tautomeric ketones as well as the keto-enol energy difference $\Delta\Delta G_{\text{KE}}$. 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 2, Supporting Information, and X-ray crystal structures in refs. 3,4). In the corresponding ketones, both the *syn*- and the *anti*-orientation of the H-C-C-O dihedral could be located with the *syn* being preferred in most cases ($\Delta\Delta G_{\text{syn/anti}}$ 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).

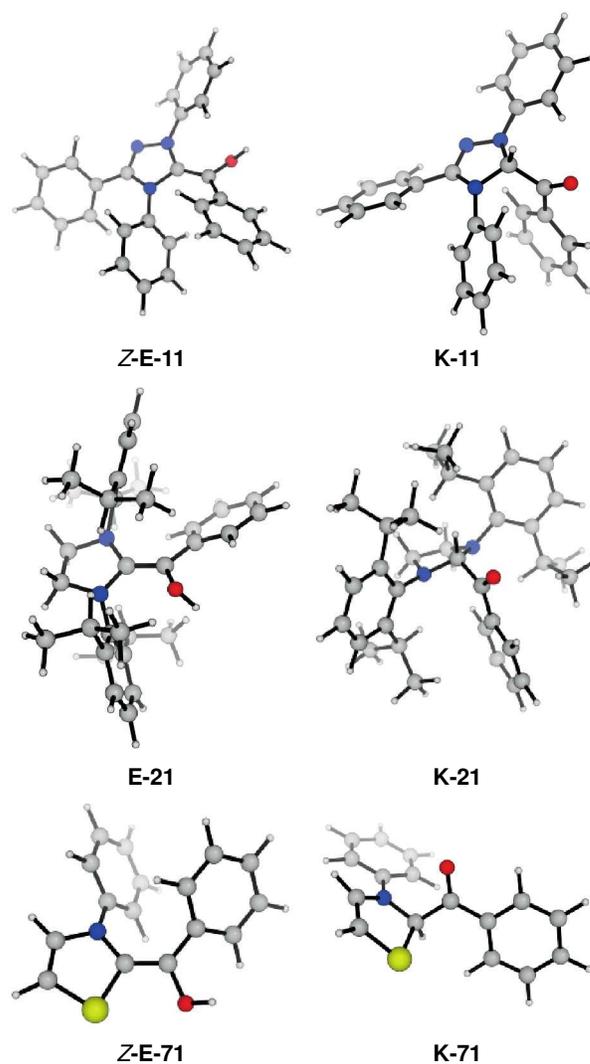


Figure 3: Lowest energy structures for the enol-ketone pairs E-11/K-11, E-21/K-21, and E-71/K-71.

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).

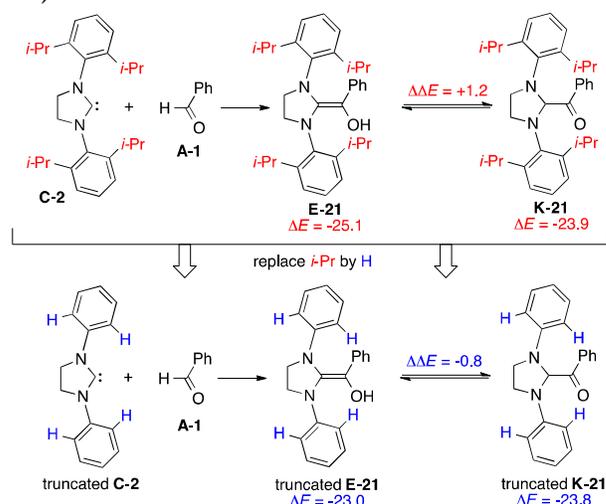
Within the phenyl-substituted series (i.e., carbenes C-1, C-3, C-6, and C-7), the reactions of the thiazole derived carbene C-7 are most exergonic ($\Delta G_{\text{Enol}} = -9.1$ kcal mol⁻¹

and $\Delta G_{\text{Ketone}} -14.2 \text{ kcal mol}^{-1}$; Table 1, entry 7) followed by the saturated "Wanzlick carbene" **C-3** ($\Delta G_{\text{Enol}} = -4.9 \text{ kcal mol}^{-1}$ and $\Delta G_{\text{Ketone}} = -13.5 \text{ kcal mol}^{-1}$; Table 1, entry 3). For both unsaturated carbenes **C-1** and **C-6**, the formation of the Breslow intermediate is endergonic ($\Delta G_{\text{Enol}} = +3.5$ and $+2.4 \text{ kcal mol}^{-1}$) while the tautomeric ketone was calculated to be thermodynamically more stable than the reactants ($\Delta G_{\text{Ketone}} = -3.5$ and $-3.1 \text{ kcal mol}^{-1}$). 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 were calculated for the formation of the *E*- and *Z*-enol **E-11** derived from the triazole carbene **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 ne carbene **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 π - π -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 $3.5 \text{ kcal mol}^{-1}$ in which all keto-enol-differences are found ($-8.7 < \Delta\Delta G_{\text{KE}} < -5.2 \text{ kcal mol}^{-1}$).

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 $4.7 \text{ kcal mol}^{-1}$ more favorable for **E-21** (Table 1, entries 2,3). In contrast, **K-31** is formed in a more exergonic reaction ($\Delta\Delta G = 6.3 \text{ kcal mol}^{-1}$) 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) imidazolyliidene 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

Scheme 4: Influence of the 2-Propyl Groups on the Keto-Enol Energy Difference (all Values in kcal mol⁻¹).



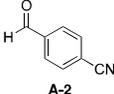
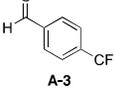
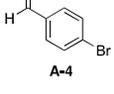
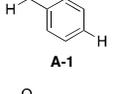
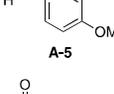
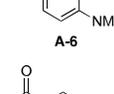
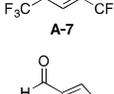
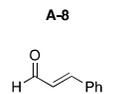
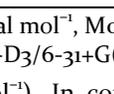
the hydrogen atoms added were allowed to relax during the optimizations. As expected, the relative keto-enol energy differences in the presence and absence of 2-propyl groups are not identical. Closer inspection reveals that the reaction energy for ketone formation is virtually unaffected by the truncation ($-23.9 \text{ kcal mol}^{-1}$ for **K-21**, vs. $-23.8 \text{ kcal mol}^{-1}$ for truncated **K-21**). However, for enol formation, the reaction energy in the presence of the 2-propyl groups is by ca. 2 kcal mol^{-1} more negative ($-25.1 \text{ kcal mol}^{-1}$ for **E-21** vs. $-23.0 \text{ kcal mol}^{-1}$ 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.

II.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.

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 *ortho*-CF₃ 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*-mono-substituted benzaldehydes (entries 1–6 in Table 2), the substituents still have a substantial effect on the thermodynamic stabilities of the Breslow intermediates ($-12.5 < \Delta G < -3.2$

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 [$\Delta\Delta G_{\text{KE}}$].^a

Entry	Aldehyde	ΔG_{Enol}	ΔG_{Ketone}	$\Delta\Delta G_{\text{KE}}$
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

^aall in kcal mol⁻¹, Mo6-2XD3/def2-TZVPP/IEFPCM(THF)//Mo6-L-D3/6-31+G(d,p)

kcal mol⁻¹). In contrast, the corresponding ketones are significantly less affected by a change in substituents (-7.8 < ΔG < -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 -CF₃ stabilize the diamino enol significantly, while electron-donating groups such as -OMe or -NMe₂ 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

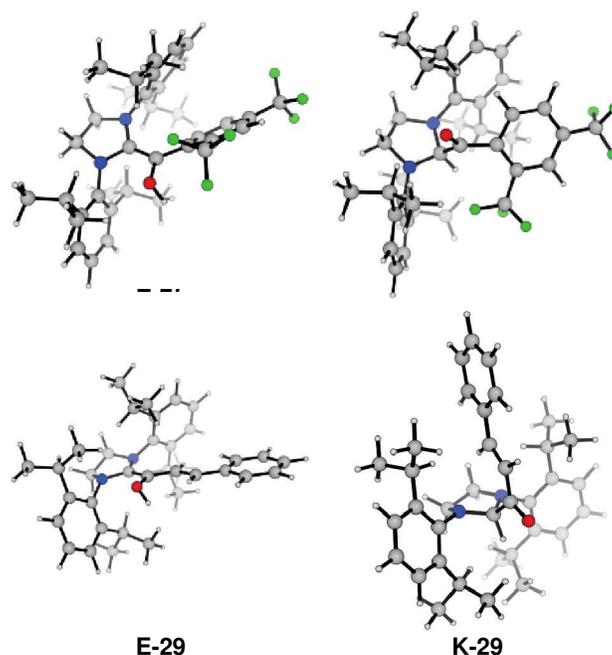


Figure 4: Lowest energy structures for the enol-ketone pairs E-27/K-27 and E-29/K-29.

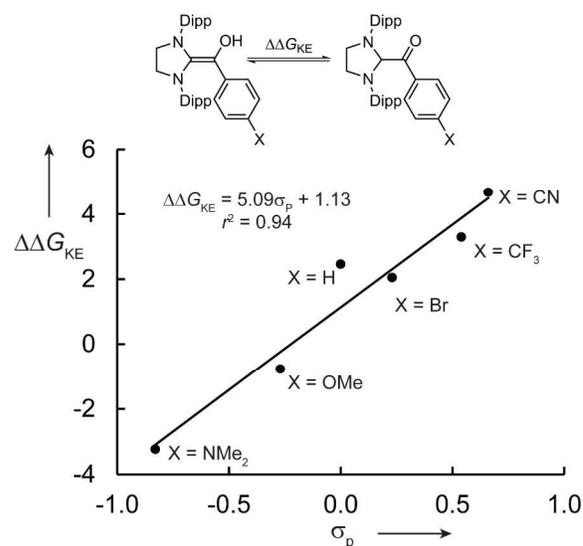


Figure 5: Correlation of the $\Delta\Delta G_{\text{KE}}$ and the corresponding substituent constant σ_p ¹⁴ [in kcal mol⁻¹, Mo6-2X-D3/def2-TZVPP/IEFPCM(THF)//Mo6-L-D3/6-31+G(d,p)].

Breslow intermediates. As a consequence of the relative insensitivity of the ketone stabilities towards substituent effects, the free energies for the keto-enol tautomerism ($\Delta\Delta G_{\text{KE}}$) 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 SI for the additional correlations of ΔG_{Ketone} vs. σ_p , ΔG_{Enol} vs. σ_p , and $d_{\text{C=C}}$ 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 ($-15.4 \text{ kcal mol}^{-1}$). 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).

III. DISCUSSION

III.1 Keto-Enol 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 are significantly exergonic, but again for both carbenes, the enol is the energetically more favorable product tautomer. For the ketone-enol pair **E-41** - **K-41**, the $\Delta\Delta G_{KE}$ amounts to 5 kcal mol^{-1} , meaning basically exclusive enol tautomer in equilibrium at room temperature. For the ketone-enol pair **E-21** - **K-21**, the $\Delta\Delta G_{KE}$ amounts to $2.5 \text{ kcal mol}^{-1}$, 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 non-heteroatom substituted enols, the stabilizing effect of *e.g.* Dipp- and Mes-substitution has been recognized and experimentally quantified earlier.^{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 earlier for *e.g.* Dipp-substituents.^{4,15}

The fact that the (thermodynamically 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 neither the addition of acids nor bases effects any conversion of **K-41**/**K-21** to **E-41**/**E-21**. Even for the ketone-enol pair **K-27**/**E-27** with the highest $\Delta\Delta G_{KE}$ ($-14.5 \text{ kcal mol}^{-1}$; Table 2, entry 7), no ketone-to-enol tautomerization could be effected. For keto-enol tautomerization to occur, a proton needs to be added to/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*, did not result in H/D-exchange at the ketone's α -carbon atom over three 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 clearcut 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 $-3.2 \text{ kcal mol}^{-1}$ (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 reported by Wanzlick and Schikora already 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 ($-13.5 \text{ kcal mol}^{-1}$; Table 1, entry 3), as compared to its ΔG_{Enol} ($-4.9 \text{ kcal mol}^{-1}$). 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 non-existence of monomeric Wanzlick/Schikora 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-31** could not be detected (see Supporting Information). The benzoin condensation is indicative for the formation of the Breslow intermediate **E-21**, but once again, the tautomerization of **E-21** to the thermodynamically favored ketone **K-21** did not occur.

III.2 Keto-Enol 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 $-7.0 \text{ kcal mol}^{-1}$ (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 $+3.5 \text{ kcal mol}^{-1}$ 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, C-6: For the bis-Dipp imidazolylidene **C-5**, ketone formation with benzaldehyde (**A-1**) is endergonic by $+3.6 \text{ kcal mol}^{-1}$, and the driving force for

1 enol formation is almost zero, resulting in an overall preference for enol formation ($\Delta\Delta G_{KE} = +3.4$ kcal mol⁻¹; Table
2 1, entry 5). As may be expected from the thermodynamic
3 data of the C-5 - A-1 system, NMR-monitoring of the carbene's interaction with benzaldehyde (A-1) did not point
4 to the accumulation of either E-51 or K-51. Instead, the
5 conversion of the benzaldehyde to benzoin was observed.
6 The enol-stabilizing and ketone-destabilizing effect of the
7 Dipp-substituents in C-5 (IPr) becomes apparent again
8 when the thermodynamic data of the C-5 plus benzaldehyde (A-1) system are compared with those of the *N,N'*-
9 diphenyl imidazolyliene C-6. For the latter, the formation of ketone K-61 is exergonic by -3.1 kcal mol⁻¹, while
10 the formation of the enol E-61 becomes significantly endergonic (+2.4 kcal mol⁻¹), resulting in an overall preference
11 for ketone formation ($\Delta\Delta G_{KE} = -5.6$ kcal mol⁻¹; Table
12 1, entry 6). Unfortunately, the experimental assessment of
13 this prediction is thus far frustrated by the non-
14 availability of the monomeric carbene C-6.

15 *Thiazolyliene C-7*: Within the series of phenyl-substituted carbenes studied, both enol and ketone formation
16 are most exergonic when the *N*-phenyl thiazolyliene C-7
17 acts as carbene component. For benzaldehyde (A-1) as the
18 aldehyde component, ketone formation is preferred by ca.
19 5 kcal mol⁻¹, well in line with the other *N*-phenyl substituted carbenes C-1 (triazolyliene), C-3 (imidazolidinyliene),
20 and C-6 (imidazolyliene).

21 IV. CONCLUSIONS

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

25 (i) *Ketone formation from triphenyltriazolyliene (C-1) and aldehydes*: The failure to observe Breslow intermediate E-11
26 when reacting triphenyltriazolyliene (C-1) with benzaldehyde (A-1) can be explained by the 7.0 kcal mol⁻¹
27 thermodynamic preference for ketone formation, and the
28 absence of kinetic inhibition of enol/ketone tautomerization
29 by the carbene's *N*-phenyl substituents. Once at the
30 ketone stage, the concentration of enol E-11 will be much
31 too low to be detected.

32 (ii) *Formation of Breslow intermediates from the imidazolidinylienes C-2 (SIPr) and C-4 (SIMes) and aldehydes*:
33 The introduction of *N*-Mes and *N*-Dipp substituents at
34 the carbene significantly stabilizes the enol-form, and
35 destabilizes the ketone. The synergism of these effects
36 makes the enol the thermodynamically favored tautomer
37 for both the saturated [imidazolidinylienes C-2 (SIPr)
38 and C-4 (SIMes)] and the unsaturated [imidazolyliene C-
39 5 (IPr)] carbenes studied. The enol-stabilizing effect of the
40 Dipp-substituents could be attributed to intramolecular
41 dispersive interactions between the 2-propyl groups and
42 the enol moiety. In other words, for all carbene applications
43 where fostering of enol formation is desired, resorting
44 to *N*-Dipp and/or *N*-Mes substitution is advisable
45 Note that the beneficial effect of mesityl substitution, for
46 triazolyliene catalytic reactions where the formation of

Breslow intermediates is crucial, has been reported earlier
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

30 V. EXPERIMENTAL

31 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, see also ref. 5 for the isolation and characterization of ketone K-11.

32 VI. COMPUTATIONAL METHODS

33 First, the conformational space of all structures was explored using the OPLS-2005 force field¹⁸ 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 Mo6-L²⁰ with Grimme's dispersion-correction D3²¹ 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 quasi-harmonic 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 Mo6-L geometries employing the meta-hybrid Mo6-2X functional,²³ Grimme's dispersion-correction D3 (zero damping),²¹ 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

VII. ASSOCIATED CONTENT

Supporting Information: Experimental details of the preparation and characterization of the ketones **K-11**, **K-21-26**, **K-31** and **K-41**; X-ray data of *p*-bromophenyl glyoxal hydrate and of the ketone **K-31**,²⁹ Cartesian coordinates and energies of all calculated structures, graphical visualization of lowest-energy conformers, and details of computational methods.

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X. ABBREVIATIONS

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

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