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Breslow Intermediates (Amino Enols) and Their Keto Tautomers: First Gas-Phase Characterization by IR Ion Spectroscopy

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Abstract: Breslow intermediates (BIs) are the crucial nucleophilic amino enol intermediates formed from electrophilic aldehydes in the course of N-heterocyclic carbene (NHC)-catalyzed umpolung reactions. Both in organocatalytic and enzymatic umpolung, the question whether the Breslow intermediate exists as the nucleophilic enol or in the form of its electrophilic keto tautomer is of utmost importance for its reactivity and function. Herein, the preparation of charge-tagged Breslow intermediates/keto tautomers derived from three different types of NHCs (imidazolidin-2-ylidenes, 1,2,4-triazolin-5-ylidenes, thiazolin-2-ylidenes) and aldehydes is reported. An ammonium charge tag is introduced through the aldehyde unit or the NHC. ESI-MS IR ion spectroscopy allowed the unambiguous conclusion that in the gas phase, the imidazolidin-2-ylidene-derived BI indeed exists as a diamo enol, while both 1,2,4-triazolin-5-ylidenes and thiazolin-2-ylidenes give the keto tautomer. This result coincides with the tautomeric states observed for the BIs in solution (NMR) and in the crystalline state (XRD), and is in line with our earlier calculations on the energetics of BI keto–enol equilibria.

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 (BIs) [chemically: (diamino enols) E (Scheme 1) in which the 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 the benzoin condensation, the 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) [3, 4]. The first successful generation of diamino enols E (X = NR) from aldehydes and imidazolidin-2-ylidenes, and their characterization by in situ NMR spectroscopy, was reported by us in 2012, followed by isolation and X-ray characterization in 2013. For example, as shown in Scheme 2 a, the reaction of the imidazolidin-2-ylidine C-1 (SIPr) with benzaldehyde (A-1) gives exclusively the diamino enol E-11, and none of the keto tautomer K-11.

Although biologically important as well (see below), the keto tautomer K (Scheme 1) of the Breslow intermediate has received considerably less attention than the amino enol E. In our earlier study on the stoichiometric interaction of the carbene 1,2,4-triazolin-5-ylidene (C-2) with various aldehydes [e.g., benzaldehyde (A-1), Scheme 2a], we observed rapid and exclusive formation of ketone K-21, and no corre-
**Results and Discussion**

**Synthesis of charge-tagged analytes: NHCs and aldehydes**

Due to our quite satisfactory experience with ammonium charge tags in our earlier ESI-MS IR ion spectroscopy studies,

$$[15, 17]$$

we decided to also employ the NMe$_5^+$ substituent in the current investigation. Scheme 3 summarizes the NHCs/azonium salts and aldehydes used in this study. The imidazolin-2-ylidene C-1 (SIPr) is easily accessible by deprotonation of the corresponding azolium salt.\(^{[23]}\) The 1,2,4-triazolin-5-ylidene C-2 (Enders–Teles carbene) is readily available in pure form by mild vacuum pyrolysis of its methanol adduct.\(^{[22]}\) The charge-tagged thiazolium salt C-4+H$^+$ was prepared by a synthetic route (see Supporting Information for detailed information) related to that used by Lee et al. for the preparation of an analogous sulfonate-tagged thiazolium salt.\(^{[29]}\) Among the aldehydes employed, A-1–A-3 are commercially available, and the charge-

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N-Heterocyclic carbenes/azolium precursors:

\[
\text{C-1} \quad \begin{array}{c}
\text{Dipp} \\
\text{N} \\
\text{N}
\end{array} \quad \begin{array}{c}
\text{Dipp} \\
\text{Ph} \\
\text{Ph}
\end{array} \\
\text{C-2} \quad \begin{array}{c}
\text{Dipp} \\
\text{Ph} \\
\text{Ph}
\end{array} \\
\text{C-3} \quad \begin{array}{c}
\text{Dipp} \\
\text{N} \\
\text{N}
\end{array} \quad \begin{array}{c}
\text{Dipp} \\
\text{Me} \text{N} \\
\text{Me} \text{N}
\end{array} \\
\text{C-4} \quad \begin{array}{c}
\text{Dipp} \\
\text{N} \\
\text{N}
\end{array} \quad \begin{array}{c}
\text{Dipp} \\
\text{Me} \text{N} \\
\text{Me} \text{N}
\end{array}
\]

Scheme 3. N-Heterocyclic carbenes/azolium precursors and aldehydes used in this study.

Tagged benzaldehyde A-4 was prepared from commercial 4-(dimethylamino)benzaldehyde as described by us earlier.\(^\text{(13)}\)

**Reaction of the imidazolidin-2-ylidene C-1 (SIPr) with the charge-tagged aldehyde A-4**

Under strictly anaerobic conditions (glovebox), a solution of the NHC C-1 in [D\(_8\)]THF reacted readily with the sparingly soluble aldehyde A-4 at room temperature, as indicated by the development of an orange-colored homogeneous phase. After about 40 min, NMR analysis (see Supporting Information for spectral data) indicated clean and quantitative formation of di-

![Image](image-url)

Figure 1. Top/bottom: black trace: recorded IR ion spectrum of the ion at m/z 554. Top: blue trace: linear IR spectrum calculated for E-14; the minimum-energy ion structure of E-14 is shown on the right. Bottom: purple trace: linear IR spectrum for K-14; the minimum-energy structure of K-14 is shown on the right. Energies quoted are relative electronic energies.

![Image](image-url)

Figure 2. Overlay of the X-ray crystal structure (gray) of the diamino enol E-14 and its calculated energetic-minimum conformation (green) computed at the B3LYP(D3BJ)/cc-pVTZ level of theory.

When the above reaction mixture was subjected to ESI-MS analysis in THF solution, the molecular ion of the 1:1 adduct formed from C-1 and A-4 could clearly be detected at m/z 554 (see Figure S1.1 in the Supporting Information). Figure 1 shows the experimental IR spectrum obtained for this ion, together with the spectra calculated for both the enol ion found in the crystal structure and the keto form of the NHC–aldehyde adduct (see also Table S1.3 in the Supporting Information). The comparison of the experimental spectrum with the two calcu-

![Image](image-url)

Scheme 4. Left: formation of the charge-tagged Breslow intermediate E-14 from SIPr (C-1) and the aldehyde A-4. Right: X-ray crystal structure of the charge-tagged BI E-14, with one molecule of THF hydrogen-bonded to the enol OH group.
tive ion structures, such as a zwitterionic primary adduct of imidazolidin-2-ylidene C-1 with the charge-tagged aldehyde A-4, which was found to be $+24 \text{kJ mol}^{-1}$ less stable than the E-14 ground state. The IR spectrum of the zwitterionic primary adduct is also in reasonable agreement with the recorded IR ion spectrum, with the exception of the imidazolidine methylene C-H wagging mode around 1260 cm$^{-1}$. However, all our experimental efforts conducted so far to identify such primary adduct ion structures in the condensed state, the gas phase, or the solid state have been unsuccessful. Therefore, we conclude that this alternative ion structure is not relevant to the discussion here.

Reaction of the 1,2,4-triazolin-5-ylidene C-2 (Enders–Teles carbene) with charge-tagged aldehyde A-4

When exposed to a solution of NHC C-2 in [D$_6$]THF, the aldehyde iodide A-4 did not dissolve readily, but its reaction could be promoted, at room temperature, by the addition of sodium tetraphenylborate. Examination of the reaction mixture by $^1$H and $^{13}$C NMR revealed that, in this case, NHC–aldehyde interaction had led exclusively to the keto tautomer K-24 (Scheme 5). Indicative NMR resonances are, for example, $^1$H NMR singlets at $\delta = 6.10$ (major conformer) and $\delta = 5.98$ ppm (minor conformer), originating from the proton at C-5 of the heterocyclic ring. Similarly, the presence of the ketene carbonyl group is evidenced by $^{13}$C NMR resonances at $\delta = 195.7$ ppm (major conformer) and $\delta = 194.4$ ppm (minor conformer).

![Scheme 5. Formation of the charge-tagged ketone K-24 from the 1,2,4-triazolin-5-ylidene C-2 and the aldehyde A-4.](image)

ESI-MS analysis of the reaction mixture clearly identified the ion of the NHC (C-2)–aldehyde (A-4) adduct at m/z 461, and its IR ion spectrum is shown in Figure 3, together with the computed IR spectra of the ketone K-24 and its enol tautomer E-24. Comparison of the experimental IR spectrum with the calculated ones clearly indicates that, also in the gas phase, the carbene–aldehyde adduct exists exclusively as the ketone K-24 (see Table S1.2 in the Supporting Information).

The carbonyl band in the experimental spectrum at approximately 1720 cm$^{-1}$ is particularly indicative, and it is well reproduced by theory. Similarly, the calculated C=C stretch for the enol (1532 cm$^{-1}$) is completely absent in the experimental spectrum (see Supporting Information for a complete table of observed and computed IR frequencies). The observed preference of the system C-2 + A-4 to exist as the keto tautomer K-24 reflects the thermodynamic preference for the ketone in THF and methanol solution (the relative energy difference between K-24 and E-24 is 14 kJ mol$^{-1}$ in CH$_3$OH according to calculations with the polarizable continuum model (PCM). This is due to the improved stabilizing interactions of the keto moiety in a polar solvent shell. This suggests that the K-24 isomer is the only one in solution. Moreover, this finding indicates that the keto ion structure K-24 is kinetically trapped after effective electrospray phase transfer and desolvation, and this prevents the formation of the gas-phase ground-state ion structure, that is, the enol tautomer E-24. The calculated barrier height for the transformation from K-24 to E-24 is 283 kJ mol$^{-1}$, in line with the experimental observation. Similar cases of nonthermal behavior have previously been reported.[24–26] A prominent example is ergothionein, a 2-mercaptophistidine trimethyl betaine, which preferably adopts a thione tautomeric ion structure in MeOH solution, which is also carried over to and identified in the gas phase.[27]

Unfortunately, no crystals of the ketone K-24 suitable for X-ray structural analysis could be obtained thus far. However, the reaction of the triazolin-5-ylidene C-2 with the three alkyl-substituted benzaldehydes A-5,6,7 shown in Scheme 6 yielded crystalline adducts that could be analyzed by single-crystal XRD. As could be anticipated from the preceding results in solution and in the gas phase, all three adducts exist as keto tautomers (K-25, K-26, and K-27) in the crystalline state (Scheme 6).

![Figure 3. Top to bottom: black trace: IR ion spectrum. Top: purple trace: calculated spectrum for gas-phase ground state E-24 (B3LYP(D3BJ)/cc-pVTZ); the ion structure of K-24 is shown on the right. Middle: blue trace: calculated linear IR spectrum for keto tautomer K-24 (B3LYP(D3BJ)/cc-pVTZ); the ion structure of K-24 is shown on the right. Scaling factor: 0.97. Bottom: red trace calculated linear IR spectrum for K-24 (M06-L-D3/6–31+G(d,p)); the ion structure of K-24 is shown on the right (relative energy vs. ground state enol structure 13 kJ/ mol; scaling factor: 0.96; see Figure S1.7 and Supporting Information for details on computations). In other words, the energetic ordering in PCM (CH$_3$OH) is reversed relative to the gas phase (see text for discussion).](image)
indicated the formation of the 1:1 adducts. Figure 4 summarizes and compares the experimental and calculated IR spectra of the three adducts obtained.

**Thiazolium salt C-4 + H^+ plus benzaldehyde (A-1) (Figure 4 a)**

The dominant and indicative feature of the recorded IR ion spectrum of the molecular ion at m/z 305 (see Figures S1.2, and S1.3 in the Supporting Information) is the pronounced carbonyl C=O stretching band at 1670 cm^{-1}, which clearly indicates the ketone tautomeric form K-41. Overall, the spectrum calculated for the keto form K-41 matches the recorded one well, which is not the case for the spectrum calculated for the enol form E-41. In particular the bands at 910 cm^{-1} (N-C-S stretch), 1100 cm^{-1} (aromatic C–C stretches) and the most abundant signal at about 1280 cm^{-1} resulting from O–H bending and (HO)C–phenyl stretching modes in the computed IR spectrum of E-41 do not find equivalent bands in the acquired spectrum of the molecular ion at m/z 305.

The observation of the ketone tautomer K-41 is in line with the higher electronic energy calculated for the enol form (41 kJ mol^{-1}). For comparison, our earlier computational analysis (relying on a slightly different method) of the thermodynamics of the keto/enol tautomers derived from N-phenylthiazolin-2-ylidene with benzaldehyde (A-1) had resulted in an energetic difference of 20 kJ mol^{-1}, again in favor of the keto form.\[10\] The gas-phase results presented here are well in line with earlier studies of ours concerning the interaction of benzaldehyde (A-1) with the Dipp-substituted thiazolin-2-ylidene C-3_{Dipp} in solution (see Introduction, Scheme 2b): while the enol E-3_{Dipp} was observed as a transient species, the ketone K-3_{Dipp} was formed as the thermodynamic product, which could be isolated and characterized by X-ray crystallography.\[14\]

**Thiazolium salt C-4 + H^+ plus pentafluorobenzaldehyde (A-2) (Figure 4 b)**

As in the case discussed above for benzaldehyde, the recorded IR ion spectrum of the molecular ion at m/z 395 (see Figures S1.4 and S1.5 in the Supporting Information) identifies the adduct produced from C-4 and the aldehyde A-2 as the keto tautomer K-42. The presence of the carbonyl C=O stretching band at 1705 cm^{-1} is again indicative, supported further by the good match of the experimental spectrum with that calculated for the keto form K-42, and its mismatch with the spectrum calculated for the enol E-42 (Figure 4b).

Also for this pair of reactants, the gas-phase results are paralleled by those obtained with the trimethyl-substituted thiazolin-2-ylidene C-3_{Me} in solution (see Introduction, Scheme 2b): while the enol E-3_{Me} was observed as a transient species, the
Thiazolium salt C-4+H²⁺ plus 2,4-bis(trifluoromethyl)benzaldehyde (A-3) (Figure 4c)

In this case, an IR ion spectrum of the molecular ion at m/z 441 of only limited resolution could be obtained. Nevertheless, the experimental spectrum is again dominated by the carbonyl C=O stretching band at 1702 cm⁻¹, which clearly evidences the formation of the keto tautomer K-43. This assignment is supported by the overall good match with the spectrum calculated for the keto form K-43, which is not the case for the spectrum calculated for the enol form E-43. The energetic difference between ketone and enol forms was calculated as 27 kJ mol⁻¹ in favor of the ketone. This value reflects the electron-deficient character of the aldehyde A-3 and is well in line with the results described above for the combination of the charge-tagged NHC C-4+H²⁺ with the aldehydes A-1 and A-2.

Conclusion

We have for the first time characterized Breslow intermediates—the pivotal species derived from Nature’s umpolung catalyst, vitamin B1—in the gas phase by IRMPD spectroscopy. Our study bridges earlier results obtained in solution and in the solid state to the gas phase, and demonstrates that the general principles found before for enol stabilization (nature of the NHC involved, electronic structure of the aldehyde component) apply just as well to the gas-phase chemistry of Breslow intermediates. In enzymatic catalysis, solvent influence on protein-bound cofactors is largely excluded. Therefore, the results disclosed herein with regard to the keto and enol forms of Breslow intermediates can be assumed to more closely model the chemistry of the enzyme-bound thiamine cofactor. In this context, it is worthy of note that the enol form of the Breslow intermediates derived from the highly active umpolung catalysts thiazoloin-2-yldiene and 1,2,4-triazolin-5-yldiene is in fact not the thermodynamically favored tautomer (in neither phase). Preventing the (irreversible) formation of catalytically incompetent keto tautomers of the Breslow intermediates under catalytic turnover conditions is thus a remarkable feat of Nature’s (and the chemist’s) ingenuity.

Experimental Section

Materials: The aldehydes A-1,2,3,5,6,7 are commercially available and were used without further purification. The aldehyde A-4 was prepared as described by some of us earlier.[20] The imidazolidin-2-yldiene SiPr (C-1) was prepared as reported by Arduengo et al.[21] The 1,2,4-triazolin-5-yldiene C-2 was prepared as described by Enders et al.[22] The details of the synthesis and characterization of the charge-tagged thiazolium salt C-4+H²⁺ are given in the Supporting Information.

Mass spectrometry: Analyte solution of NHC C-1 with charge-tagged aldehyde A-4 was diluted (c ~ 10⁻² M) with dry THF. The solution of NHC C-2 with charge-tagged aldehyde A-4 was measured with addition of CH₃OH. Thiazolium salt C-4+H²⁺ aldehyde adducts were diluted with CH₃CN for (+)esi-MS and IR ion spectroscopy experiments. All (+)esi, tandem-MS and accurate ion mass measurements were conducted with an LTQ-Orbitrap XL instrument (Thermo Fisher, Bremen Germany). Accurate ion mass measurements were executed in the Orbitrap analyzer with a resolution of 30000 fwhm with external calibration (Δm/3 ppm) or with addition of internal standards (Δm/2 ppm) by a lock-mass procedure. Typical (+)esi-MS conditions: flow rate: 5 μL min⁻¹; capillary voltage: 3.20 kV; sheath gas: 4.99 [arab. units]; aux gas: 2.00 [arab. units]; resolution: 30000 fwhm. Additional MS data and spectra are presented in the Supporting Information.

IR ion spectroscopy: A modified 3D quadrupole ion-trap mass spectrometer (Bruker, Amazon Speed) was used for the IR ion spectroscopy study, which has been described in detail elsewhere.[23,24] The 3D quadrupole ion trap was operated at ambient temperature (∼320 K) with He buffer gas at a pressure of approximately 10⁻¹ mbar. Wavelength-tunable laser radiation was generated by the Free Electron Laser for Infrared eXperiments (FELIX) in the 600–1900 cm⁻¹ range for all photodissociation experiments with a repetition frequency of 10 Hz. The FEL pulse energies were approximately 50–100 mJ per 5 μs-long macropulse. The full width at half-maximum (fwhm) bandwidth of the FEL is approximately 0.4% of the central wavelength. Gas-phase precursor ions for IR ion spectroscopy were generated by electrospray ionization in positive-ion mode from 0.5 μm solutions in methanol at a flow rate of 120 μL h⁻¹. Ions were irradiated for 1 s, corresponding to interaction with ten laser pulses. The IR spectra result from a series of mass spectra recorded while the FEL was scanned over the wave-number range from 600–1900 cm⁻¹. For the IR ion spectrum shown in Figure 1, a laser attenuation of 5 dB was applied. The depletion of the precursor ion signal as well as the increase of intensity of the photodissociation product ion peaks are monitored as a function of IR frequency. Unimolecular dissociation results from the absorption of multiple IR photons (IRMPD) with effective intramolecular vibrational redistribution of the excitation energy leading to noncoherent photoactivation until the threshold for dissociation is reached. The IR yield (Σ(phot) / Σ(ion)) was determined after laser irradiation at each frequency and was linearly corrected for frequency-dependent variations in laser power.[15,17,27] All structures and spectra were calculated at the B3LYP/3D8B/cc-pVTZ level of theory and frequencies were scaled by 0.97 unless otherwise stated.

Calculations: DFT calculations were performed with Gaussian 09, version D.01.[20] Gaussian was compiled with Gaussian-supplied versions of BLAS and ATLAS. The B3LYP functional was used throughout with the D3-BJ correction to account for dispersion interactions, whereby it is noted that in this case this correction did not change results significantly compared to the bare B3LYP functional.[32,33] The cc-pVTZ basis set was used throughout with the ultrafine setting for the integrals.[34,35] This computational procedure was found to give good correlation with experiment in previous work.[13] Frequency calculations in the harmonic approximation were carried out to characterize all stationary points obtained to confirm them as either local minima or transition states. All minimum-energy structures were identified through the absence of
imaginary frequencies. Transition states were identified through the presence of a single imaginary frequency. All calculations, except where indicated, performed on these systems were done in vacuo. Where solvent is indicated, all calculations were done with the PCM model with the parameters for MeOH, as implemented in Gaussian.[30,31] Frequencies were scaled by 0.97 in the wavenumber range of 600–1900 cm$^{-1}$ and convoluted with a Gaussian line-shape function with an FWHM of 12 cm$^{-1}$ to facilitate comparison with experiment.[32,33] Energy differences quoted throughout the paper are based on electronic energies. All transition states were checked to connect the correct energy minima through an intrinsic reaction coordinate calculation.[34,35] The Supporting Information on computations was created by using in-house developed software based on the OpenEye toolkit.[36] The overlay (Figure 2) was created by using ROCS.[41]

Additionally, ion structures of C1–Cn denote the carbenes discussed in this study, and A–A$^-$ the aldehydes. Of the ketones and enols formed, K$^-$ indicates the keto formed from carbene Cn and aldehyde A$^-$, and E$^-$ the corresponding enol composed of Cn and A$^-$.

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**Conflict of interest**

The authors declare no conflict of interest.

**Keywords:** Breslow intermediate · density functional calculations · IR spectroscopy · mass spectrometry · umpolung

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Breslow intermediates in the gas phase: In N-heterocyclic carbene (NHC)-catalyzed Umpolung, the reaction of the substrate aldehyde with the NHC gives the Breslow intermediate (BI) as pivotal species. The combination of IR ion spectroscopy with quantum chemical computations can determine whether the BI exists as a nucleophilic amino enol or as its keto tautomer in the gas phase, which is decisive for its reactivity both in enzymatic catalysis and in organocatalysis.