Rate and Equilibrium Constants for the Addition of N-Heterocyclic Carbenes into Benzaldehydes: A Remarkable 2-Substituent Effect**

Christopher J. Collett, Richard S. Massey, James E. Taylor, Oliver R. Maguire, AnnMarie O’Donoghue,* and Andrew D. Smith*

Abstract: Rate and equilibrium constants for the reaction between N-aryl triazolium N-heterocyclic carbene (NHC) precatalysts and substituted benzaldehyde derivatives to form 3-(hydroxybenzyl)azolium adducts under both catalytic and stoichiometric conditions have been measured. Kinetic analysis and reaction profile fitting of both the forward and reverse reactions, plus onwards reaction to the Breslow intermediate, demonstrate the remarkable effect of the benzaldehyde 2-substituent in these reactions and provide insight into the chemoselectivity of cross-benzoin reactions.

Acylation equivalents generated from the reaction of N-heterocyclic carbenes (NHCs) with aldehydes are important catalytic intermediates that can undergo a range of carbon–carbon bond forming processes.[1] In this regard, NHC-catalyzed benzoin and Stetter reactions have been widely studied, with a number of efficient catalytic asymmetric methods available for both intra- and intermolecular reactions.[1,2] However, the development of cross-benzoin reactions has proven difficult in terms of the chemoselective formation of a single reaction product.[3] While efficient chemoselective NHC-catalyzed protocols for both intra- and intermolecular cross-benzoin reactions between aldehydes and ketones have been reported,[4] the reaction between two distinct aldehydes remains a significant synthetic challenge. As 2-substituted benzaldehydes are generally poor substrates for homo-benzoin reactions they have been widely utilized in cross-benzoin processes.[5] For example, Miller and Mennen reported the intramolecular cross-benzoin reaction between an arylaldehyde and a tethered aliphatic aldehyde to effect macrocyclization.[6,7] Connon and co-workers found that N-C$_3$F$_7$ triazolium NHC catalyst 3 catalyzes intermolecular cross-benzoin reactions between 2-substituted benzaldehydes and aliphatic aldehydes with high levels of chemoselectivity (Scheme 1a).[5c] A selective cross-benzoin reaction between two benzaldehydes catalyzed by thiamine diphosphate dependent benzaldehyde lyase (BAL) was reported by Müller et al., with one 2-substituted benzaldehyde a prerequisite for good chemoselectivity.[8,9] Glorius and co-workers subsequently utilized this phenomenon in aryldiene cross-benzoin reactions using thiazolium NHC precatalyst 7 (Scheme 1b).[5e,7] Gravel et al. have reported a triazolium NHC-catalyzed cross-benzoin process between benzaldehydes and alkyl aldehydes, with preliminary kinetic studies showing the reaction is at least first-order with respect to both aldehydes and that the chemoselectivity was determined at or after the C–C bond forming step.[5h]

Current explanations of the observed chemoselectivity in cross-benzoin reactions of aryldienes are usually simplified based upon steric arguments. Previous to this investigation, it was commonly assumed that the presence of a 2-substituent decreases the rate of NHC addition into an aryldiene (Scheme 2).[6,8] The NHC I therefore preferably adds into aldehyde II to form least-hindered 3-(hydroxybenzyl)azolium adduct IV, which undergoes deprotonation to form Breslow intermediate V.[8] However, to account for the observed selectivity, intermediate V must now add into the more “hindered” 2-substituted benzaldehyde VI.[5c,d,8] This
steric argument is therefore inherently contradictory. There are currently no detailed mechanistic studies that offer insight into the rate of NHC additions into 2-substituted benzaldehydes, the effect of the N-aryl NHC substituent upon the rates of these processes, or the role of the 2-substituent in chemoselective cross-benzoin reactions of arylaldehydes. Building upon our previous mechanistic studies of NHC-catalyzed processes,[13] herein the remarkable effect of 2-arylaldehyde substitution upon equilibrium constants for 3-(hydroxybenzyl)azolium adduct formation is demonstrated. For the first time, individual rate constants for adduct formation have been determined under stoichiometric conditions and the effects of both aldehyde and N-aryl NHC substitution have been probed, with the results offering potential insight into the chemoselectivity of cross-benzoin processes.

First, the catalytic reactions between a range of substituted benzaldehydes (0.01 m) and NHC precatalyst 9–11 (0.002 m, 20 mol %) using Et3N (0.002 m, 20 mol %) in CDCl3 were monitored through in situ 1H NMR spectroscopy. Analysis of the resulting reaction profiles allowed equilibrium constants for adduct formation (Kexp) to be determined (Table 1).[13] The results demonstrate the remarkable effect of having a heteroatom substituent in the 2-position of the benzaldehyde on Kexp. For example, the reaction between NHC precatalyst 9 and 2-methoxybenzaldehyde 2 gave Kexp = 56 m−1 compared with Kexp = 3 m−1 for reaction with benzaldehyde 5 (Table 1, entries 1 and 2). As observed previously,[13] the 2,6-substituted NHC precatalysts 10 and 11 gave significantly higher Kexp values, although 2-methoxy aldehyde substitution again led to further prominent increases (Table 1, entries 3–6). The importance of the 2-heteroatom for this effect is demonstrated by reaction of NHC precatalyst 10 with 2-tolualdehyde 12, which gives Kexp = 16 m−1 (Table 1, entry 7). The effect is not limited to 2-alkoxy substituents, as the reaction with 2-bromobenzaldehyde 14 gave Kexp = 332 m−1 whereas reaction with 4-bromobenzaldehyde 15 gave Kexp = 15 m−1 (Table 1, entries 9 and 10). The introduction of an additional heteroatom substituent in the 6-position further shifted the equilibrium in favor of adduct formation. For example, reaction of 10 with 2,6-difluorobenzaldehyde 17 gave Kexp = 785 m−1 whereas 2-fluorobenzaldehyde 16 Kexp = 150 m−1 (Table 1, entries 11 and 12). The use of 2-pyrindinecarboxaldehyde 18 also gave an equilibrium strongly in favor of the corresponding adduct, while reaction with 6-bromo-2-pyridinecarboxaldehyde 19 exclusively gave 3-(hydroxybenzyl)azolium adduct 33 such that Kexp could not be measured (Table 1, entries 13 and 14). In most cases, the 3-(hydroxybenzyl)azolium salts could also be isolated from a stoichiometric reaction between the NHC precatalyst and the corresponding aldehyde in the presence of excess Et3N.

To gain further insight into the dramatic effect of 2-heteroatom substitution, rate constants for 3-(hydroxybenzyl)azolium adduct formation were measured. First, the effect of the N-aryl NHC substituent was assessed, as no kinetic measurements have previously been made for triazolium-catalyzed benzoin or Stetter processes.[13,14] Reactions of aldehyde 13, which is often employed as a model substrate for intramolecular Stetter reactions, were performed under pre-steady-state conditions using stoichiometric concentrations of NHC precatalysts in CD2OD with a Et3N:Et3N·HCl (2:1) buffer at 15°C,[13] analogous to the conditions used by Leeper and White in their study of the thiazolium-catalyzed benzoin reaction.[15] Kinetic analysis of the reaction profiles obtained before significant product formation (<5 %) allowed pseudo
second-order rate constants for 3-(hydroxybenzyl)azolium adduct formation ($k_1$, M$^{-1}$s$^{-1}$) and equilibrium constants ($K^{\text{eq}}$, M$^{-1}$) to be measured (Table 2). Formation of the 3-(hydroxybenzyl)azolium adduct involves two distinct steps: the initial deprotonation of precatalyst by base and the subsequent reaction of the NHC with aldehyde. After the formation of adduct oxygen, the base can be regenerated upon protonation at oxygen resulting in an overall pseudo second-order process under these experimental conditions.

This is confirmed by the excellent fitting of reaction data to a kinetic expression describing a second-order reaction proceeding to a position of equilibrium. The pseudo first-order rate constants for adduct dissociation ($k_{\text{diss}}$, s$^{-1}$) could also be calculated as $K^{\text{eq}} = k_1/k_{\text{diss}}$. Additional estimates for $k_1$ and $k_{\text{diss}}$ were obtained from reaction profile fitting, with the values used to calculate the corresponding equilibrium constants ($K^{\text{eq}}$). Pleasingly, the fitted values obtained are in good agreement with those obtained from kinetic analysis, with the largest discrepancy occurring for the reaction using NHC precatalyst 36 where adduct dissociation is negligible (Table 2, entry 4).[17]

Next, the reverse decay towards equilibrium was studied. Analysis of the $^1$H NMR reaction profiles for dissociation of the adducts of aldehyde 13 allowed rate and equilibrium constants of dissociation to be measured ($k_{\text{diss}}$, s$^{-1}$) and $K^{\text{eq}}$, M$^{-1}$) and rate constants for association ($k_a$, M$^{-1}$s$^{-1}$) to be calculated (Table 3).[18] Although $K_a = k_1$ and $k_{\text{diss}} = k_2$, a distinction has been made to differentiate between the two methods of measurement. The dissociation analysis was not possible for the N-2,6-(MeO)$_2$C$_6$H$_4$ adduct as the equilibrium lies so far towards the adduct that insufficient data could be obtained. Notably, as its $pK_a$ is similar to N-Ph precatalyst 9 ($pK_a$ 17.7 and 17.8, respectively) but it reacts 2.5 times faster. This is postulated to be due to the orthogonal orientation of the mesityl substituent to the triazolium ring providing a more favorable approach of the aldehyde. In all cases 3-(hydroxybenzyl)azolium adduct formation shows a degree of reversibility, however the kinetic data shows the rate of dissociation for the adduct derived from 13 and 10 is particularly slow, meaning that adduct formation is effectively irreversible in this case.[21]

Having established reliable methods for measuring equilibrium and rate constants for adduct formation this analysis was extended to look at substituted benzaldehydes (Table 4).[22] The reactions were performed using NHC precatalyst 9, with comparable data obtained from both kinetic analysis and reaction profile fitting in all cases. The presence of a heteroatom in the aldehyde 2-position again has a marked effect, leading to significantly higher equilibrium constants for adduct formation.[23] The kinetic data gives an insight into the origin of this trend. For example, the rate of NHC addition into 2-methoxybenzaldehyde 2 is over 2.5 times greater than that of the 2,6-(MeO)$_2$C$_6$H$_4$ adduct (Table 3).

Table 2: Measurement of rate and equilibrium constants for 3-(hydroxybenzyl)azolium adduct formation.[16]

| Entry | Ar             | $k_1$ [M$^{-1}$s$^{-1}$] | $k_{\text{diss}}$ [s$^{-1}$] | $K^{\text{eq}}$ [M$^{-1}$] | $K^{\text{eq}}$ [M$^{-1}$] |
|-------|----------------|-------------------------|-------------------------------|---------------------------|---------------------------|
| 1     | Ph             | 1.52 × 10$^{-2}$       | 4.76 × 10$^{-3}$             | 319                       | 394                       |
| 2     | 4-FC$_2$H$_4$  | 4.89 × 10$^{-3}$       | 9.45 × 10$^{-3}$             | 383                       | 433                       |
| 3     | 4-MeOC$_2$H$_4$| 1.28 × 10$^{-2}$       | 3.09 × 10$^{-2}$             | 414                       | 555                       |
| 4     | 2.6-(MeO)$_2$C$_6$H$_4$ | 1.07 × 10$^{-2}$ | < 1.01 × 10$^{-4}$ | > 1.01 × 10$^{-4}$ | 7034 |
| 5     | Mes            | 3.85 × 10$^{-3}$       | 1.25 × 10$^{-2}$             | 3082                      | 3414                      |

[a] Starting concentrations: aldehyde 13 (0.04 M), NHC precatalyst (0.04 M) in CD$_2$OD and 0.18 M Et$_3$N; Et$_3$N-HCl (2:1) buffer at 15 °C. [b] Calculated through fitting of reaction profiles.

Table 3: Measurement of rate and equilibrium constants for 3-(hydroxybenzyl)azolium adduct dissociation.[14]

| Entry | Ar             | $k_2$ [s$^{-1}$] | $k_{\text{diss}}$ [s$^{-1}$] | $K^{\text{eq}}$ [M$^{-1}$] | $1/K^{\text{eq}}$ [M$^{-1}$] |
|-------|----------------|----------------|-------------------------------|---------------------------|---------------------------|
| 1     | Ph             | 3.33 × 10$^{-4}$ | 5.14 × 10$^{-2}$             | 6.47 × 10$^{-3}$         | 155                       |
| 2     | 4-FC$_2$H$_4$  | 3.94 × 10$^{-4}$ | 8.76 × 10$^{-2}$             | 4.50 × 10$^{-3}$         | 222                       |
| 3     | 4-MeOC$_2$H$_4$| 1.22 × 10$^{-4}$ | 2.76 × 10$^{-2}$             | 4.42 × 10$^{-3}$         | 226                       |
| 4     | 2.6-(MeO)$_2$C$_6$H$_4$ | ND             | ND                           | ND                        | ND                        |
| 5     | Mes            | 5.34 × 10$^{-2}$ | 9.90 × 10$^{-2}$             | 5.40 × 10$^{-2}$         | 1852                      |

[a] Starting concentrations: 3-(hydroxybenzyl)azolium adduct (0.04 M) in CD$_2$OD and 0.18 M Et$_3$N; Et$_3$N-HCl (2:1) buffer at 25 °C.
times faster than addition into benzaldehyde 5, and over ten times as fast as addition into 4-methoxybenzaldehyde (Table 4, entries 1–3). A similar trend is seen comparing intramolecular Stetter substrate 13 with its 4-substituted analogue, demonstrating that the 2-substituent effect is not purely electronic in nature (Table 4, entries 4 and 5). In both cases the rate of the reverse process is also up to five times slower for 2-substituted benzaldehydes, reflecting the increased stability of these adducts. The importance of the heteroatom substituent is highlighted by the use of an analogue of 13 without the oxygen atom linker and 2- and 4-toluualdehyde, which all give equilibrium and rate constants comparable with benzaldehyde 5 (Table 4, entries 6–8). However, even in this case the rate of NH addition into 2-toluualdehyde is nearly twice as fast as addition into 4-toluualdehyde (although the effect is smaller compared with heteroatom substituents).

Further kinetic analysis of the reaction profiles following the decreasing concentrations of the 3-(hydroxybenzyl)azolium adducts over time allows estimation of the pseudo first-order rate constants for deprotonation ($k_2$, s$^{-1}$) into the transiently formed Breslow intermediates (Table 4). The rate constants for deprotonation are of the same order of magnitude for all the aldehydes, including those containing a 2-substituent. Unlike the observed substituent effect on the first step ($k_1$ and $k_2$), the observed order of reactivity on $k_2$ reflects normal through-bond electronic effects on carbon acidity where electron-donating groups on the aldehydes, including those containing a 2-substituent, increase the rate of deprotonation. This is in agreement with our previous observations of normal electronic effects of the NHC N-aryl substituent on this deprotonation step.$^{[11]}$

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The kinetic and equilibrium data of NH addition into the benzaldehydes potentially offers insight into the observed chemoselectivity of cross-benzoin reactions. A representative cross-benzoin reaction between benzaldehyde 5 and 2-methoxybenzaldehyde 2 was performed using NHC precatalyst 3 (20 mol%) in CH$_2$Cl$_2$ at 45°C (Scheme 3a). The observed chemoselectivity is consistent with that previously reported$^{[10]}$ with cross-product 37 favored and smaller amounts of homo-benzoin 38 and benzoin 39 also formed (Scheme 3a). Similar product ratios were observed using NHC precatalyst 11, although the conversion was lower (ca. 15%). Monitoring the cross-reaction at 25°C using NHC precatalyst 11 revealed a 10:1 mixture of 3-(hydroxybenzyl)azolium adducts 25:24 at equilibrium, again demonstrating a prominent 2-substituent effect in this system (Scheme 3b). However, despite formation of adduct 25 being favored, cross-product 37 is derived from reaction of minor adduct 24, indicating the chemoselectivity must be determined later in the reaction pathway.$^{[20]}$ This leads to three main possibilities for the origin of the observed chemoselectivity: 1) formation of the Breslow intermediate; 2) onwards reaction of the Breslow intermediate; 3) dissociation of the resulting tetrahedral adducts (Scheme 3c).

The measured rate constants for Breslow intermediate formation show that 2-MeO substitution decreases $k_2$ by a factor of about two relative to benzaldehyde 5 (Table 4, entries 1 and 2), however this does not outweigh the tenfold increase in equilibrium constant for adduct formation with a 2-MeO substituent and cannot account for the observed chemoselectivity. A difference in rate of the onwards reaction of the two Breslow intermediates 40 and 41 would account for the cross-benzoin selectivity. In both cases reaction with 2-methoxybenzaldehyde 2 will be comparatively fast over
reaction with benzaldehyde 5 owing to the previously described 2-substituent effect. However, the increased steric hindrance around the nucleophilic carbon of 41 compared with 40 may decrease its relative rate of addition sufficiently to explain the formation of cross-benzoin 37.[25]

Alternatively, NHC dissociation from tetrahedral intermediate 43 may be slow compared with 42, again resulting in preferential formation of cross-product 37. This would be consistent with the measured rate constants for dissociation (k−1) of the related 3-(hydroxybenzyl)azolium adducts in which a 4-fold difference was observed (Table 4, entries 1 and 2). However, accumulation of intermediates such as 42 and 43 have not been observed in any of our NMR experiments to date, or in earlier NMR studies by Leeper and White of the thiazolium-catalyzed benzoin reaction,[13a] suggesting a faster rate of breakdown relative to the rate of formation from the relevant Breslow intermediate and aldehyde. Furthermore, monitoring reactions of NHC precatalyst 11 with either 37 or 38 gave about 10% retro-benzoin products but no observable products consistent with formation of the corresponding tetrahedral adducts.[26] Additionally, a control experiment reacting NHC precatalyst 11 with acetophenone gave no observable products, suggesting that any NHC-ketone adducts formed rapidly dissociate. Therefore, it seems more likely that the chemoselectivity in cross-benzoin reactions is determined by the onwards reaction of the Breslow intermediate.

Although the increased rate of nucleophilic addition into benzaldehydes bearing a 2-heteroatom substituent is clearly evident, the origin of this phenomenon is unclear.[27] One possibility is that the presence of a lone pair on an atom in the 2-position changes the conformation of the aldehyde carbonyl such that it twists out of conjugation with the aryl ring. This ground state destabilization of aldehyde could result in increased reactivity towards nucleophiles. Alternatively increased product stability due to hydrogen bond formation between the 2-heteroatom substituent and the OH group of the 3-(hydroxybenzyl)azolium adducts could also contribute to the observed increase in both rate and equilibrium constants. These ground and product state effects could be realized in any nucleophilic addition to 2-substituted aldehydes of this type, including in the onward reaction of Breslow intermediates in cross-benzoin reactions.

In conclusion, measurements of equilibrium and rate constants for the reaction of trizolium NHC precatalysts with substituted benzaldehydes to give 3-(hydroxybenzyl)azolium adducts under both catalytic and stoichiometric conditions have been made. The results obtained from kinetic analysis and fitting data for both the forward and backwards processes show that nucleophilic addition into benzaldehydes bearing a 2-heteroatom substituent is particularly fast. By contrast, smaller substituent effects are observed on the rate of deprotonation of 3-(hydroxybenzyl)azolium adducts, which fall within the same order of magnitude regardless of aldehyde substitution. The results offer insight into the apparent inconsistency over the second aldehyde addition in cross-benzoin reactions, overturning the assumption that 2-substituted benzaldehydes are less reactive based upon steric arguments.

Keywords: 2-substituent effect · kinetics · mechanistic studies · N-heterocyclic carbenes · organocatalysis

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[16] A correction factor to account for hemiacetal formation was required to accurately determine aldehyde concentrations. The formation of 3-deutero 3-(hydroxybenzyl)azolium adducts were also observed, presumably through deuteration of the transiently formed Breslow intermediate. See the Supporting Information for details.

[17] The same trends were observed at 25 °C, indicating that kinetic analysis up to adduct equilibrium remains valid in cases where Stetter product formation is more significant. See the Supporting Information.

[18] Rate and equilibrium constants for dissociation were also obtained from fitting analysis. See the Supporting Information.

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[22] The reactions of benzaldehyde 5 with a range of NHC precatalysts show the same trends as previously, suggesting that the effect of the N-aryl NHC substituent is independent of aldehyde substitution. See the Supporting Information.

[23] Whilst the trends in $K^{\text{eq}}$ are same between the reactions performed in CD$_3$OD and CD$_2$Cl$_2$, quantitative comparisons cannot be made owing to the different concentrations and temperatures.

[24] An alternative mechanism in which Breslow intermediate 41 reacts with benzaldehyde 5 to form an adduct (analogous to 42/43) that undergoes a 1,2-hydride shift to eliminate the NHC would also lead to major product 37. This mechanism has been ruled out based upon a deuteration experiment. See the Supporting Information for details.

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