Kinetic and structure–activity studies of the triazolium ion-catalysed benzoin condensation†

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Steady-state kinetic and structure–activity studies of a series of six triazolium-ion pre-catalysts 2a–2f were investigated for the benzoin condensation. These data provide quantitative insight into the role of triazolium N-aryl substitution under synthetically relevant catalytic conditions in a polar solvent environment. Kinetic behaviour was significantly different to that previously reported for a related thiazolium-ion pre-catalyst 1, with the observed levelling of initial rate constants to \( \nu_{\text{max}} \) at high aldehyde concentrations for all triazolium catalysts. Values for \( \nu_{\text{max}} \) for 2a–2f increase with electron withdrawing N-aryl substituents, in agreement with reported optimal synthetic outcomes under catalytic conditions, and vary by 75-fold across the series. The levelling of rate constants supports a change in rate-limiting step and evidence supports the assignment of the Breslow-intermediate forming step to the plateau region. Correlation of \( \nu_{\text{max}} \) reaction data yielded a positive Hammett \( \rho \)-value (\( \rho = +1.66 \)) supporting the build up of electron density adjacent to the triazolium N-Ar in the rate-limiting step favoured by electron withdrawing N-aryl substituents. At lower concentrations of aldehyde, both Breslow-intermediate and benzoin formation are partially rate-limiting.

Introduction

N-Heterocyclic carbenes (NHCs) have made a major impact on the field of catalysis and are arguably one of the most versatile, efficient classes of organocatalyst. Recent synthetic advances include the development of high yielding, stereoselective NHCs; a strong drive to carry out catalytic reactions in more sustainable, aqueous conditions; and implications in the fields of bio- and enzymatic catalysis.1 A key reaction at the centre of NHC-catalysis is the benzoin condensation (Scheme 1), in which the catalyst facilitates polarity reversal (umpolung) of an aldehyde, enabling nucleophilic reaction at a second aldehyde molecule.1a The benzoin reaction is often the test reaction of choice in evaluating new NHC-catalyst scaffolds. Despite broad interest, there remain many mechanistic ambiguities with respect to NHC-catalysed processes including the benzoin reaction. Since the seminal mechanistic studies of the benzoin reaction by Breslow (Scheme 1), the existence of the enamino, or Breslow intermediate (IV), has been the focus of much research and debate.2 Computational studies, including work by Houk and others, have provided \textit{ab initio} evidence for the Breslow intermediate, whilst also predicting experimentally observed product outcomes.3 Mechanistic studies have mainly focussed on isolation of IV; this initially included the isolation in 2012 of aza-Breslow intermediates (IV′) and O-methylated derivatives (IV″) by Rovis

Scheme 1. The NHC-catalysed benzoin condensation, with key intermediates highlighted.
In a series of seminal publications since 2012, Berkessel and co-workers reported the NMR and/or X-ray structural characterisation of unmodified IV, for imidazolyl, imidazolinyl and thiazolyl-derived NHCs (e.g. IV′′′, Fig. 1).\(^5\) Isolation and characterisation of unmasked, synthetically relevant Breslow intermediates of triazolium ions are yet to be reported and remain a key target in the field of NHC catalysis.

In terms of triazolium catalysis, our groups have reported the isolation and structural characterisation of a series of triazolium-derived adducts (III; \(X = Y = N\)) and demonstrated that (III) form reversibly from free aldehyde and triazolium precatalyst. Kinetic analysis of the H/D-exchange reactions at the \(\alpha\)-position enabled structural effects on Breslow intermediate formation from (III) to be directly assessed (Fig. 1). Stoichiometric studies provided access to rate constants for initial adduct (III) formation and decay from triazolium precatalyst.\(^6\) An earlier study by Huskey and Jordan reported a related kinetic analysis of triazolium-aldehyde adducts and the determination of a \(C(\alpha)-H\) \(pK_a\) of 15.7 for one example.\(^7\) To date, there has been no report of experimental adduct (III) \(C(\alpha)-H\) \(pK_a\) values for the triazolyl series.

Regarding detailed kinetic analysis of the overall NHC-catalysed benzoin condensation and the catalysts studied in this work.

The determination of a C(\(\alpha\))–H \(pK_a\) value for the triazolyl series.

### Results and discussion

Initial work focused on repetition of Leeper’s work on commercially available thiazolium catalyst 1, whose structure...
resembles the enzymatic co-factor thiamine, and extension to a broader range of catalyst concentrations.\textsuperscript{1,8,9} Freshly distilled benzaldehyde (0.32–1.6 M) was added to triethylamine-buffered MeOH solutions of I (12, 24, 30 mM) at 50 °C. At regular intervals, aliquots of the reaction mixture were quenched with MeCN and both benzaldehyde and benzoin concentrations were quantified via HPLC. A first-order dependence on benzaldehyde concentration was observed at all concentrations of I (ESI, section S2, Fig. S13†). The pseudo-first-order rate constant, \( k_{\text{cat}} \), is determined as the gradient of a plot of initial benzaldehyde concentration ([PhCHO]\(_0\)) against initial rate (\( \nu \), eqn [1]). Our value of \( k_{\text{cat}} = 5.53 \times 10^{-6} \) s\(^{-1} \) for 30 mM pre-catalyst is in excellent agreement with Leeper’s reported value.\textsuperscript{9}

\[
\nu = k_{\text{cat}}[\text{PhCHO}]^n
\]  
(1)

Using identical reaction conditions as employed for thiazolium salt I (triethylamine-buffered MeOH at 50 °C), triazolium pre-catalysts 2a-f showed distinctly different kinetic behaviour. Triazolium pre-catalysts 2a-f clearly demonstrate saturation kinetic profiles at higher benzaldehyde concentrations (e.g. Fig. 2 for 2c; ESI, section 2, Fig. S14–18† for 2a–b, 2d–f). By contrast, saturation was not observed for plots of \( \nu \) versus [PhCHO]\(_0\) for I at 12, 24 and 30 mM thiazolium catalyst (ESI, Fig. S13†).

Initial rate data for 2a–f were fit to a steady-state rate equation (eqn [2]), derived for the Breslow intermediate IV in Scheme 2, with the assumption that the concentration of adduct ([III]) was equal to that of catalyst ([I]). This assumption is validated by our previous kinetic NMR studies with stoichiometric aryl aldehyde and triazolium salt concentrations in the same triethylamine-buffered methanol medium, which showed that adduct [III] forms rapidly and reversibly from these reactants at 25 °C.\textsuperscript{6b} These previous studies for a range of aryl aldehydes and triazolium catalysts included the stoichiometric kinetic analysis of 2a–d and benzaldehyde, permitting access to rate and equilibrium constants for formation of [III].\textsuperscript{1,6b} Half-lives (\( t_{1/2} \)) for adduct III formation at 25 °C could be calculated as \( \sim 670 \) s and \( \sim 16 \) s for the lowest and highest [PhCHO]\(_0\), which would be predicted to be a minimum of \( \sim 10 \)-fold lower again at 50 °C, and significantly smaller than the kinetic experiment measurement times employed in the initial rate analysis (ESI, section S4†). Using the experimental equilibrium constants for adduct formation determined under stoichiometric conditions, values for the percentage of free pre-catalyst (%I) at equilibrium can also be estimated (Table S14†).

Under the catalytic conditions of the initial rate study with a 10–100 fold excess of benzaldehyde relative to pre-catalyst, the equilibrium significantly favours adduct. Additionally, the use of the IRM approach permits the assumption that the reverse reaction of benzoin is not significant under the reaction conditions.†

\[
\nu = \frac{k_{\text{p}}[\text{PhCHO}]}{k_{-\text{BI}} + k_{\text{p}}[\text{PhCHO}]}
\]  
(2)

The experimental data under catalytic conditions fit well to eqn [2] and, at high [PhCHO]\(_0\), the values for the initial rates plateau and approach \( \nu_{\text{max}} \). There is some deviation of data points at the lowest [PhCHO]\(_0\) perhaps owing to a more significant % of pre-catalyst I still present initially at the lowest excess of aldehyde. Uncertainties in \( \nu_{\text{max}} \) were obtained from the kinetic fits and, with the exception of 2e, are relatively small. The uncertainty for the \( \nu_{\text{max}} \) value for 2e is larger due to this system not reaching a final plateau at the highest benzaldehyde concentration employed. Table 1 summarises the kinetic constants obtained from the fit to eqn [2] for catalysts 2a–f (ESI, section S2† for kinetic fits for 2a,b,d–f). The absolute values of these kinetic parameters are unique to the triethylamine buffer system employed in methanol as solvent, however, their comparison allows the effects of structural changes of catalyst on individual reaction steps to be determined. Values for \( \nu_{\text{max}} \) vary greatly depending on the catalyst, with a large 75-fold difference between the slowest 2a and fastest 2f triazolium catalysts, and the largest value observed for a N-pentafluorophenyl substituent. This highlights the importance of targeted tuning of the electronic nature of the N-aryl substituent for efficient catalysis.

The plateauing of initial rate plots with respect to [PhCHO]\(_0\) confirms a change in order of reaction and therefore change in rate-limiting step. Using eqn [2], at high [PhCHO]\(_0\) when \( k_{\text{p}}[\text{PhCHO}] \gg k_{-\text{BI}} \), values for \( \nu_{\text{max}} \) approach \( k_{\text{p}}[I] \), i.e. deproto-

†The IRM was chosen, with the reaction followed to <10% product formation, to minimize any contribution of the reverse benzoin condensation. In our previous stoichiometric studies involving I:1 triazolium:aldehyde, which were followed to high % product, we investigated the contribution of the reverse reaction for the 2,4,6-trichlorophenyltriazolium tetrafluoroborate salt.\textsuperscript{6c} Using two representative substituted benzoins as starting material, <12% retro benzoin reaction was detectable under these conditions over long timescales.
Scheme 2  Key mechanistic steps considered within this kinetic study under catalytic conditions. The initial addition step for formation of III has been experimentally shown to occur rapidly and reversibly, with the equilibrium lying significantly towards adduct (III) when [PhCHO]₀ is in large excess.

Table 1  Summary of the kinetic parameters obtained from fitting experimental data to eqn (2) a

| Catalyst | [I] mM | νmax × 10⁻² M⁻¹ s⁻¹ | kₐII/s⁻¹ | kₐII (rel) | kᵣ/kₐII |
|----------|--------|------------------|---------|----------|---------|
| 2a       | 12     | 4.08 ± 0.53      | 3.40 × 10⁻⁵ | 0.37     | 5.7     |
|          | 6      | 2.27 ± 0.30      | 3.78 × 10⁻⁵ | 0.41     | 5.0     |
| 2b       | 12     | 6.52 ± 0.49      | 5.44 × 10⁻⁵ | 0.59     | 4.8     |
| 2c       | 24     | 19.2 ± 3.9       | 8.02 × 10⁻⁵ | 1.6      |         |
|          | 12     | 11.1 ± 2.5       | 9.24 × 10⁻⁵ | 1.0      | 2.0     |
|          | 6      | 5.52 ± 1.18      | 9.21 × 10⁻⁵ | 1.0      | 2.4     |
| 2d       | 12     | 16.2 ± 2.1       | 1.35 × 10⁻⁴ | 1.5      | 4.2     |
| 2e       | 12     | 143 ± 43         | 1.19 × 10⁻⁳ | 13       | 0.94    |
| 2f       | 6      | 171 ± 3.8        | 2.65 × 10⁻³ | 31       | 4.0     |

a Values determined using an initial rate method (IRM) to a maximum of 10% conversion to benzoin product with initial benzaldehyde concentrations ranging from 0.16–1.6 M, in 2:1 0.16 M Et₃N/Et₃NH⁺Cl buffered MeOH solutions at 50 ± 0.01 °C. Reaction in the presence of catalyst 2f was particularly fast, thus requiring lower loadings to enable study by the IRM. Uncertainties in kₐII can be approximated as similar to those in νmax, as kₐII = νmax[I], with uncertainties in [I] unlikely to have significant impact. kᵣ(rel) determined as kᵣ(2a-2f)/kᵣ(2c) at the same catalyst concentration.

O-Methylation prevents both reverse equilibration to free aldehyde and catalyst, in addition to onward reaction to benzoin product, thus permitting focus just on the Breslow-intermediate forming step. Although this H/D-exchange study was performed in a predominantly aqueous D₂O medium at a lower temperature of 25 °C, the relative values of kex and kₐII for a given triazolium pre-catalyst are closely similar. Again, this supports our conclusion that the plateau region of the initial rate plots corresponds to the Breslow intermediate (IV) forming step and highlights the similarity of triazolium substituent effects in methanol and water media.

Synthetic observations for the benzoin reaction with catalysts 2a–2f report increased yields of products with more electron withdrawing N-aryl substituents. Values for νmax and kₐII increase with more electron withdrawing N-aryl substituents, thus substituent effects on νmax under catalytic conditions correlate with synthetic outcome. An excellent linear Hammett correlation is observed for para-substituted catalysts 2a and 2c-e with ρ = +1.66 ± 0.05 (Fig. 3). The same Hammett ρ-value is obtained from either log(νmax) or log(kₐII) correlations given the common catalyst concentration. Our experimental Hammett ρ-value is intermediary between reference values of ρ = +1.44 and ρ = +3.32 for the acid dissociations of benzoic acids and protonated anilines in methanol, respectively (Fig. 4). This significant sensitivity to substituent change supports the formation of an enamino-like transition state for the conversion of III to IV with significant charge neutralisation on the N-aryl nitrogen of catalyst in the rate-limiting
support enaminol-like structures, thus the present Hammett analysis permits unification with behaviour in solution.

Data for \textit{ortho}-substituted triazolium salts \textbf{2b} and \textbf{2f} were not included in the correlation. Three literature Hammett \(\sigma\)-values have been reported for the pentafluoro-substituent of \textbf{2f}, however, there is no reported value for the \(N\)-mesityl group of \textbf{2b}. As is frequently observed owing to the presence of additional steric and electronic factors in \textit{ortho}-substituted cases, the datapoint for \textbf{2f} significantly deviates from the correlation line for the \textit{para}-substituted triazolium salts (section S5, ESI†). Irrespective of the Hammett \(\sigma\)-value employed, the log \(\nu_{\text{max}}\) value for \textbf{2f} falls significantly below the correlation line.

Values of \(\log(k_{\text{rat}}/[I])\) may also be correlated with \(pK_a\) of the triazolium ion pre-catalysts \textbf{2a–2f} in both water and DMSO (Fig. S24, ESI†). Although strictly not Brønsted plots, which would require correlation with \(\alpha\)-H \(pK_a\) values of \textbf{III}, these plots serve to demonstrate the increase in \(k_{\text{rat}}\) with more acidic triazolium pre-catalysts. Harper \textit{et al.} have reported Hammett analyses of \(pK_a\) (C3–H) values for three different series of triazolium salts in both water and DMSO.\textsuperscript{10d} A Hammett \(\rho\)-value of \(-0.93 \pm 0.05\) was obtained for the aqueous \(pK_a\)s of the same family of triazolium catalysts as utilised in the present study with a decrease in \(pK_a\) observed for more electron-withdrawing \(N\)-aryl substituents. Thus, electron-withdrawing \(N\)-aryl substituents favour acid dissociation of triazolium pre-catalyst in addition to the deprotonation step from adduct \textbf{III} to Breslow intermediate \textbf{IV}\textsuperscript{§}

The effect of \(N\)-aryl substituent on product partitioning of the Breslow intermediate \textbf{IV} may also be evaluated by comparison of values for \(k_{p}/k_{\text{rat}}\) obtained from the fit to eqn (2) (Table 1). With the exception of catalyst \textbf{2e}, all ratios are greater than 1, suggesting greater contribution from the product benzoin forming step. Values for \(k_{p}/k_{\text{rat}}\) vary in the range 0.94–5.7, with the reliance on two separate kinetic constants being the likely reason for the absence of a clear trend with the electronic nature of the substituent. Interestingly, the highest product ratio is obtained for the most electron-donating \(N\)-aryl substituent in \textbf{2a}, suggesting that the nucleophilicity of \textbf{IV} possibly dominates in the benzoin forming step.

**Conclusions**

In conclusion, a detailed initial rates study of the benzoin condensation using triazolium-ion pre-catalysts under catalytic conditions has been undertaken.\textsuperscript{6b} Kinetic behaviour for triazolium salts \textbf{2a–2f} under these conditions differ significantly from that of a widely studied thiazolium ion pre-catalyst \textbf{1},

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\(\textsuperscript{§}\text{Rate constants for proton transfer from } 2\textbf{a–f} \text{ to HO}^- \text{ are in the range } 10^{5}–10^{7} \text{ M}^{-1} \text{ s}^{-1} \text{ and reprotonation of the triazolyl carbene by water has been demonstrated to be close to the diffusion limit for dielectric relaxation of water (10}^{11} \text{ s}^{-1}).\textsuperscript{10}\text{ As protonation of diphenyl carbene by methanol has also been shown to be limited by dielectric relaxation of solvent,}\textsuperscript{11} \text{ the proton transfer step between triazolium ions } 2\textbf{a–f} \text{ and the corresponding triazolyl carbenes is very unlikely to be rate-limiting in methanol solvent.}
with plateauing of the former within the initial rates regime to constant $\nu_{\text{max}}$ values. Thus, for triazolium pre-catalysts $\text{2a-2f}$ at low [PhCHO]$_0$, when $k_p[\text{PhCHO}] < k_{\text{BI}}$, the reaction appears first-order; conversely, at higher [PhCHO]$_0$, $k_p[\text{PhCHO}] > k_{\text{BI}}$ and reaction appears zero-order (eqn (2)). Assignment of the plateau, zero-order region to the Breslow intermediate forming step is supported by: (i) the increase in $\nu_{\text{max}}$ with electron-withdrawing substituents; (ii) the Hammett plot (Fig. 4), which suggests increase in electron density near the triazolium N-Ar group in the rate-limiting transition state; (iii) similar $k_{\text{BI}}$(rel) values and relative $k_{\text{ex}}$ values from our previous study of the H/D-exchange reactions of O-methylated hydroxaryl adducts 3.$^{11}$ Conversely, at low [PhCHO], eqn (2) simplifies to rate $\propto$ [PhCHO], confirming first-order dependence, with contribution to the rate-limiting step from $k_p$ in addition to $k_{\text{BI}}$.

Values for $\nu_{\text{max}}$ vary greatly depending on the catalyst, with a large 75-fold difference between the slowest $2\text{a}$ and fastest $2\text{f}$ triazolium catalysts. These data provide quantitative insight into the role of catalyst N-aryl substitution on the rate-limiting step under synthetically-relevant catalytic conditions in a polar solvent environment. In particular, Hammett structure–activity analysis provides evidence for the formation of an enaminol-like transition state $\text{IV-b}$ for the Breslow intermediate-forming step, permitting the alignment of previous solid state structural characterisation of $\text{IV}$ with solution state behaviour. With a drive to further the organocatalysis field to more aqueous conditions, providing mechanistic insight into synthetic observations.

**Experimental**

**Kinetic measurements**

Initial benzaldehyde concentrations of 0.32–1.6 M and catalyst loadings of 12 mM, 24 mM and 30 mM were used, in 12.5 mL vials at 50 ± 0.01 °C. Reactions, on a 2.5 mL scale, were initiated by addition of pre-catalyst(I) to pre-warmed solutions containing benzaldehyde and the Et$_3$N/ Et$_3$NHCl buffer (0.16 M) and sampled at regular intervals, quenching with acetonitrile and analysing by HPLC.

**Conflicts of interest**

There are no conflicts to declare.

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