Baylis–Hillman Reaction

Reevaluation of the Mechanism of the Baylis–Hillman Reaction: Implications for Asymmetric Catalysis**

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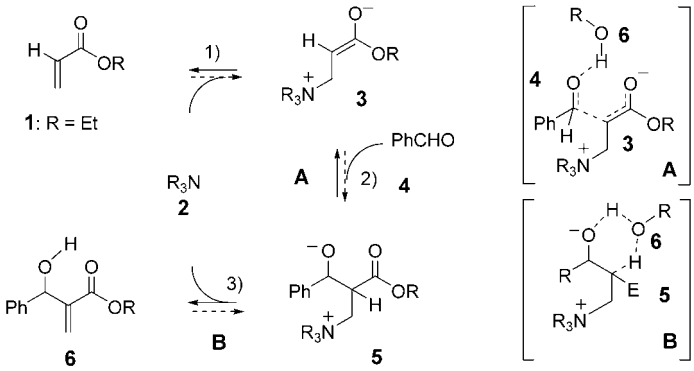
The Baylis–Hillman reaction[1] (BHR, see Scheme 1) involves the amine- (or phosphine-)[2] catalyzed addition of an aldehyde to an activated alkene, such as an acrylate, **1**, to generate an allylic alcohol of type **6**.[3] The commonly accepted mechanism[4] for this process involves reversible conjugate addition of the nucleophilic amine catalyst to the activated alkene to generate an enolate (step 1), nucleophilic attack of the enolate on the aldehyde to generate a second zwitterionic intermediate (step 2), and then elimination (step 3) to generate the product and liberate the amine catalyst (Scheme 1). The reaction shows pseudobimolecular kinetics, and the rate-limiting step (RLS) of the reaction has been determined as step 2 on the basis that no primary kinetic isotope effect (KIE) was observed.[4a] Protic solvents are known to accelerate the BHR, and it has been proposed[5] that this acceleration occurs through activation of the aldehyde by hydrogen bonding to thereby promote step 2 (see intermediate **A**, Scheme 1). However, hydrogen bonding to the aldehyde would have to compete with the enolate, which is a much better hydrogen-bond acceptor. Indeed, this more thermodynamically favorable interaction will stabilize the enolate and render it less reactive and so should slow down



Scheme 1. Proposed mechanism of the Baylis–Hillman reaction with potential for autocatalysis through **A** or **B**.

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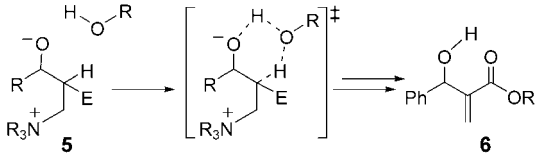
the reaction, albeit with an accumulation of the hydrogen-bonded enolate. Interestingly, in the absence of proton donors the reaction shows autocatalysis, presumably because the product can act as a hydrogen-bond donor and promote the reaction.[6] These issues made us consider an alternative hypotheses for the role of the protic solvent, including the possibility that it could accelerate formal proton transfer from the α-keto methine to the alkoxide in the zwitterion **5** to facilitate liberation of the product and regeneration of the catalyst through elimination (see intermediate **B**, Scheme 1). We now show that step 3 is the RLS in the initial phase of the reaction and that once the concentration of product has built up, step 2 becomes the RLS. The consequences of these findings with respect to asymmetric catalysis are also discussed.

First, we examined the profile of the reaction of ethyl acrylate with benzaldehyde catalyzed by quinuclidine in which the onset of significant autocatalysis was readily apparent between 0 and 20% conversion.[6] Study of the reaction mixture by ^{1}H NMR spectroscopy (600 MHz) showed that there were no species (<1%) other than the substrates, catalyst, and product throughout the entire reaction. Thus all equilibria prior to thermodynamically favorable liberation of **6** must lie predominantly on the side of the starting materials (see Scheme 2).[4b]



Scheme 2. Proton-transfer mechanism.

The rate acceleration was confirmed to arise from autocatalysis owing to the protic nature of the product **6** by the absence of such an induction period in control reactions with catalytic quantities of 1) the product or 2) MeOH.[7] The kinetics of the reaction were readily simulated[8] by the use of two simple models, one (see **A**, Scheme 1) that follows the conventional mechanism in which the product catalyzes the addition of the enolate **3** to the aldehyde **4**, and the second (see **B**, Scheme 1) in which the product catalyzes a rate-limiting breakdown of the zwitterionic intermediate **5**, for example, by proton transfer.

The two mechanistic scenarios (**A** and **B**) can, in principle, be distinguished on the basis that upon employing α-deuterated acrylate (2-[^{2}H$_1$]-**1**; $= d_1$-**1**), a primary KIE should be completely absent in **A** but evident in **B** prior to the autocatalyzed breakdown of zwitterion **5** becoming more efficient than its generation. As the latter condition might only be fulfilled very early in the reaction, the comparison of absolute rates over a number of half-lives, as performed by Isaacs and co-workers with deuterated (>99%) acrylonitrile,[4a] is unlikely to be informative. In fact, a competition experiment between *d*-**1** and **1** would clearly identify the RLS because we would expect a primary KIE to increase the mole fraction of *d*-**1** in the acrylate ($x_{d\text{-}\mathbf{1}}$) if step 3 is rate-limiting and a secondary KIE to decrease $x_{d\text{-}\mathbf{1}}$ if step 2 is rate-limiting.[9] We thus analyzed the effect of C(2)-deuteration by ^{1}H NMR spectroscopic analysis of the BHR of approximately equimolar mixtures of *d*-**1** and **1** ($x_{d\text{-}\mathbf{1}} = 0.505 \pm 0.005$, Figure 1). As evident from Figure 1b, in the early stages of reaction (up to ≈20% conversion), the mole fraction of *d*-**1** increases substantially. As reaction proceeds further into the phase where autocatalysis is by far the dominant process, the ratio then stabilizes ($x_{d\text{-}\mathbf{1}\max} = 0.55$).[9] This shows that in the early phase (<20% conversion), step 3 is rate-limiting (primary KIE evident). By using model **B** as a starting point, we were able to simulate the kinetics of the competition experiments;[8,9] for example, see the comparison of the predicted (lines) and observed (circles) kinetics in Figure 1, graphs a and c. For satisfactory simulation, the model required incorporation of a substantial primary KIE ($k_H/k_D = 5 \pm 2$) for the noncatalyzed step 3. The fact that the simplification of $k_H/k_D = 1$ for autocatalysis of step 3 allows a satisfactory simulation suggests that the autocatalysis causes a change in the RLS from step 3 to step 2 early in the reaction.[9]

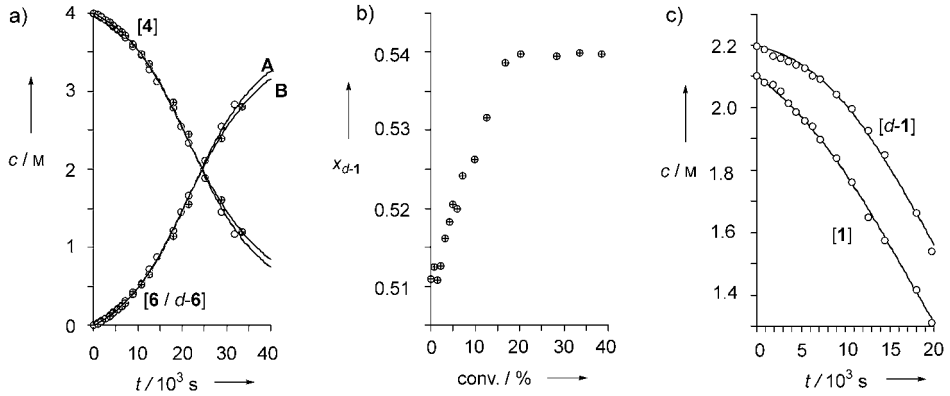
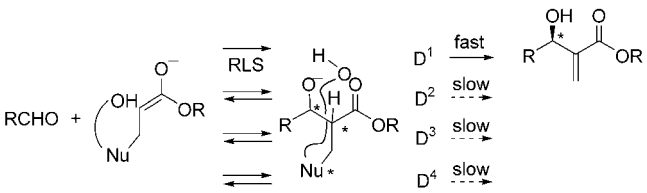


Figure 1. a) Evolution of the Baylis–Hillman reaction of PhCHO (**4**, 4.0 M) with [C(2)-^{2}H$_{0.51}$]-ethyl acrylate (**1**/*d*-**1**, 4.3 M) catalyzed by quinuclidine (**2**, 1.0 M) at room temperature to give a mixture of *O*-*d*-**6** and **6**. Lines through data points are kinetic simulations based on models **A** and **B** with refinement for contraction[7] (see Supporting Information for full details). b) Relationship between conversion (based on PhCHO) and the mole fraction *d*-**1** ($x_{d\text{-}1} = [d\text{-}\mathbf{1}]/[\mathbf{1} + d\text{-}\mathbf{1}]$). c) Simulated variation of the concentrations of **1** and *d*-**1** ([**1**] and [*d*-**1**]) in the first 40% of the reaction by employing model **B** with $k_H/k_D = 4.8$ for step 3 (non-autocatalyzed).

The efficient autocatalysis of step 3 by a simple hydroxyl moiety is easily accommodated by the model outlined in Scheme 2 which involves a six-membered proton transfer from ROH to the alkoxide with concomitant deprotonation of the α-methine to give an enolate, followed by elimination of the amine (E1cB).[10] The intramolecular four-membered direct proton transfer is presumably disfavored owing to strain induced in attaining the appropriate eclipsed conformation of the C(O)–C(H) bond and the transfer angle between O-H-C which is far from optimal. Moreover, the approximately 90° transfer angle between O-H-C in the transition state is expected to limit the primary KIE to roughly 2.3, a much lower value than that observed in the non-autocatalytic phase of the reaction.[11]

In summary, these studies have shown that in the absence of added protic species, the initial stage of the BHR involves rate-limiting proton transfer (step 3). As the product concentration builds, proton transfer becomes increasingly efficient and the RLS step is then step 2, as in the conventional model. This finding has considerable implications for asymmetric catalysis of the BHR. The successful catalysts to date (> 80 % *ee*) have hydrogen-bond donors appended at some point to the nucleophile.[12] It is quite likely that all four diastereomers of the intermediate alkoxide are formed, but only one has the hydrogen-bond donor suitably positioned to allow fast proton transfer.[13] The other diastereomers revert back to starting materials and eventually the reaction filters through the pathway that leads to fast elimination (Scheme 3). The low



Scheme 3. Likely origin of enantioselection in the Baylis–Hillman reaction. D^{1-4} are diastereomers of the alkoxide adduct.

success rate in the design of chiral catalysts for the BHR could be because the focus has been on controlling the stereochemistry of the C–C bond in the RLS (step 2) of the reaction. On the basis of the above study, we now believe that the positioning of suitable hydrogen-bond donors for selective proton transfer of one of the alkoxide diastereoisomers, and not the others, is likely to more successful. The alkoxide diastereomer that undergoes the fast, selective proton-transfer reaction may also be the diastereomer that is preferentially formed, but this is not a prerequisite. As a caveat, the use of an aprotic solvent may be crucial for attaining high enantioselectivity, and enantiomeric excesses could be decreased by competitive nonselective autocatalysis.[14]

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[7] The reactions display a noticeable contraction in volume as they proceed. However, the nonlinear relationship between the conversion and the concentrations of all components is not the origin of the induction period. See Supporting Information for a full discussion.
[8] The kinetics were simulated using MacKinetics (Leipold Associates, USA); see Supporting Information for full discussion.
[9] The magnitude of the secondary KIE on any individual step in the reaction of **1**/*d*-**1** would be small—typically $1.15 \geq k_H/k_D \geq 0.87$—but the net effect across equilibria may be larger and for steps 1 and 2 is expected to favor the reaction of *d*-**1** (i.e. $k_H/k_D < 1$) owing to a change in hybridization at C(2) from sp^2 in **1** to sp^3 in the zwitterion **5**. However, control experiments (see Supporting Information) revealed a slow background exchange of H and D between **1**/*d*-*O*-**6** and *d*-**1**/**6** catalyzed by quinuclidine and presumably through the enolate **3**/*d*-**3**. This observation compromises any meaningful analysis of the decrease in $x_{d\text{-}1}$ observed in the later phase of the reaction when significant **6**/*d*-*O*-**6** has accumulated.
[10] The question remains as to what mediates step 3 in the absence of significant quantities of product. The possibility that a second molecule of quinuclidine acts as a base was eliminated by a study of the effect of doubling the catalyst loading which caused only an approximately 1.75-fold increase in rate in the crucial early stages of reaction—exactly as would be predicted on the basis of first-order dependency on each of the three reaction components when the dilution of aldehyde and alkene caused by increased catalyst loading is taken into account. We therefore suggest that traces of protic species, for example, water, enol, etc., may well be sufficient to initiate reaction. A hemiacetal anion intermediate (derived from **5** and **4**) has been proposed by McQuade and co-workers to effect proton transfer. See Reference [14].
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[13] Such a model to account for asymmetric induction has been suggested by Hatakeyama, see Reference [12a].
[14] Note added in proof: McQuade and co-workers have independently found a substantial kinetic isotope effect during the initial phase of the Baylis–Hillman reaction (< 10 % conversion). See: K. E. Price, S. J. Broadwater, H. M. Jung, D. T. McQuade, *Org. Lett.* **2005**, 147 – 150.

