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Baylis–Hillman Mechanism: A New Interpretation in Aprotic Solvents

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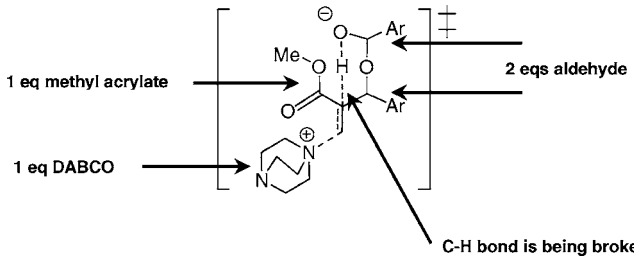
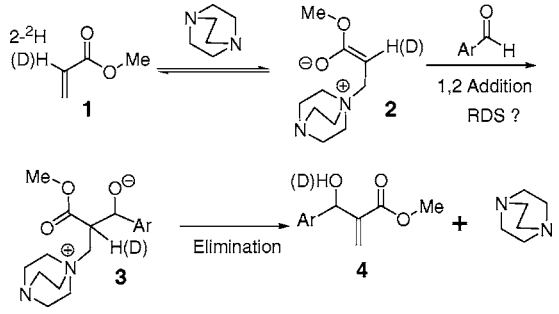
ABSTRACT



Using reaction rate data collected in aprotic solvents, we have determined that the Baylis–Hillman rate-determining step is second order in aldehyde and first order in DABCO and acrylate. On the basis of these data, we have proposed a new mechanism involving a hemiacetal intermediate. The proposed mechanism was then supported using two different kinetic isotope experiments.

The Baylis−Hillman (BH) reaction, also known as the Morita−Baylis−Hillman reaction, efficiently converts simple starting materials into highly functionalized products.[1−3] This reaction became popular in the early 1980s with the first application to synthesis,[4] the first "arrow pushing" mechanism,[5] and the first physical organic studies. On the basis of pressure-dependence data, Hill and Isaacs proposed the well-accepted mechanism depicted in Scheme 1.[6,7] Bode and Kaye

Scheme 1. Accepted Baylis−Hillman Mechanism



supported this mechanism with rate data and a rate law.[8] Fort et al. showed that the BH reaction is faster with electron-poor aldehydes and is reversible in some cases.[9] Many groups have reported the influence of solvents,[10−13] Lewis acids,[14,15] Lewis bases,[2] temperatures,[16] and substrates on the BH reaction.[17]

We recently reported the synthesis of a novel polymerizable amphiphile using the BH reaction.[18] To optimize the

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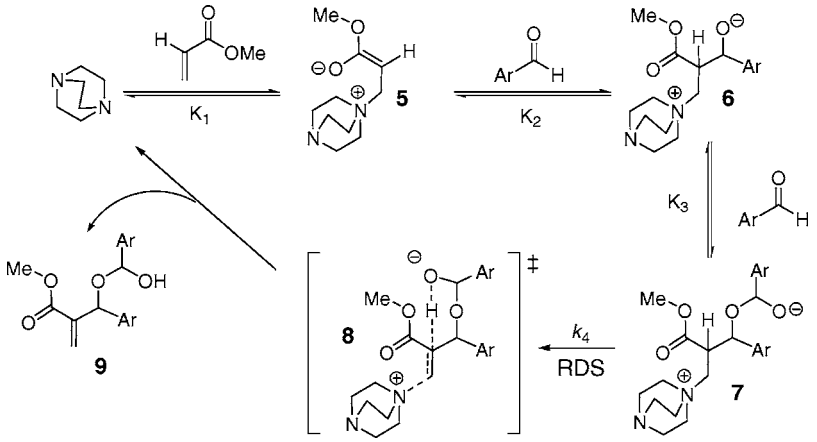
Scheme 2. Proposed Mechanism



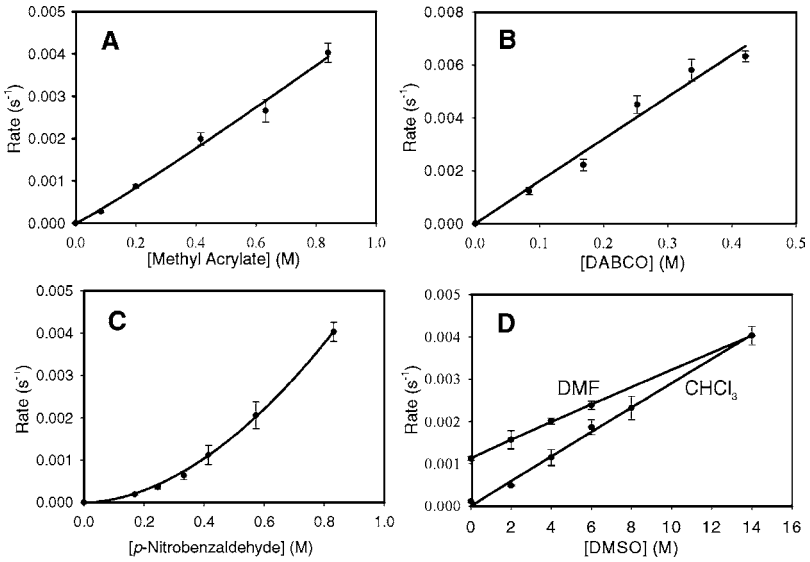


Figure 1. Changes in rate as a function of reagent or solvent concentration. (A) Methyl acrylate. (B) DABCO. (C) 4-Nitrobenzaldehyde. (D) DMSO using DMF or $CHCl_3$ as the cosolvent. A, B, and C were run in THF/DMSO mixtures where the DMSO concentration was held constant. An F-test comparing a nonlinear and a linear fit for the data in C indicates with >99% confidence that the nonlinear fit is valid.

reaction, we performed rate studies using a variety of solvents and *p*-nitrobenzaldehyde, an ideal aldehyde that reacts quickly and cleanly.[19] We also examined the mechanism by measuring isotope effects with isotopically labeled aldehyde and methyl acrylate. We now report that the rate-determining step (RDS) is not the 1,2-addition as previously reported but the proton abstraction (elimination) from intermediate **7** (Scheme 2). In addition, we report that the rate law is second order in aldehyde.

As shown in Figure 1A and B, the BH reaction is first order in DABCO and methyl acrylate;[8] however, in contrast to previous reports, the BH reaction is second order in aldehyde (Figure 1C). On the basis of the order plots depicted in Figure 1, we propose the rate law shown in eq 1. This rate law indicates that 2 equiv of aldehyde must be present in the RDS of the BH reaction. Therefore, the 1,2-addition cannot be the RDS and the product-forming elimination must be more complicated than previously proposed (Scheme 1). We therefore propose the mechanism outlined in Scheme 2. The reaction begins with combination of acrylate and Lewis base (**5**) and 1,2-addition of **5** onto the aldehyde (**6**) as initially proposed; however, the mechanism continues by reacting with a second equivalent of aldehyde to yield a hemiacetal (**7**). The hemiacetal then undergoes a rate-limiting deprotonation to yield **9**, which breaks down to the BH product in a series of post-rate-limiting steps.

$$\text{rate} = k_{obs}[\text{aldehyde}]^2[\text{DABCO}][\text{acrylate}] \qquad (1)$$

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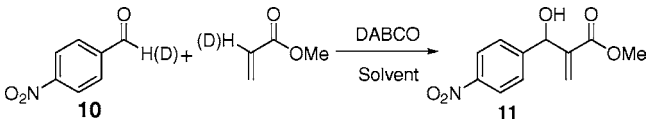
The dual role of the aldehyde is necessary because the alkoxide resulting from the 1,2-addition (**6**) is unable to act as an intramolecular base due to geometric constraints. Hemiacetal **7** can deprotonate the α-position in the RDS via a six-membered transition state (**8**), cleaving the C−H bond and eliminating DABCO. The deuterium label removed from the α-position resides on the alcohol of the BH product, providing modest evidence that multiple post-rate-limiting steps must occur. The hemiacetal intermediate was inspired by the aldol−Tishchenko reaction, another reaction involving 2 equiv of aldehyde.[20] The aldol−Tishchenko reaction shows large inverse equilibrium isotope effects (a product of two inverse equilibrium isotope effects) when the aldehyde proton is labeled, a result similar to that in our system (vide infra).

To support the proposed mechanism, we used two different kinetic isotope experiments. The first isotope experiment we performed used methyl α-^{2}H acrylate. The labeled acrylate was prepared using known methods, and the results of the isotope experiments are shown in Table 1.[21] If the proposed

Table 1. Rate Data for the Baylis−Hillman Reaction



aldehyde[a]	solvent	k_H/k_D[b]	k_H/k_D[c]	k_{rel}	$\epsilon/E_T(30)$
10	DMSO	5.2 ± 0.6	0.75 ± 0.05	36	47/45
10	DMF	2.9 ± 0.2	N/A	10	38/43
10	MeCN	4.2 ± 0.1	N/A	7	37/46
10	THF	2.4 ± 0.1	0.80 ± 0.07	2	8/37
10	$CHCl_3$	2.2 ± 0.2	0.72 ± 0.03	1	5/39

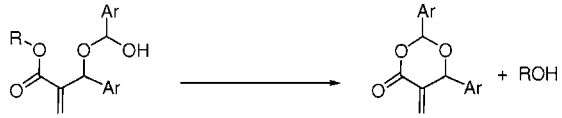
[a] Reactions were performed using 0.84 M methyl acrylate, 0.83 M aldehyde, and 0.27 M DABCO. [b] Observed kinetic isotope effect (KIE) using α-deuterio methyl acrylate. [c] Observed KIE using deuterio-labeled aldehyde.

mechanism is correct, a primary kinetic isotope effect (KIE) will be observed because the α-^{2}H acrylate bond is cleaved in the proposed RDS. The magnitude of the KIE is expected to be muted because the observed KIE will be a product of the KIE for C−H bond cleavage and an inverse equilibrium isotope effect resulting from geometry changes during the 1,2-addition preequilibrium. We observed a primary KIE in all solvents tested. The magnitude of the KIE was observed to be highest in polar solvents. These data are clear evidence for a rate-limiting C−H cleavage, which is consistent with our proposed mechanism. Others have reported similar solvent-dependent changes in KIEs for proton abstractions.[22] In these cases, maximum KIEs were observed when the proton was equally shared among heavy atoms in the transition state (i.e., ΔpK_a is zero).[23] For the BH reaction, ΔpK_a equals zero when the pK_a of the α-^{2}H acrylate and resulting hemiacetal (**7**) are equivalent. We propose that as the solvent polarity decreases, the ΔpK_a between the abstracting base and the α-proton increases, producing a muted KIE.

The second isotope experiment we performed used α-deuterio-*p*-nitrobenzaldehyde (Scheme 2).[24] The 2 equiv of aldehyde used in the reaction both undergo sp^2 to sp^3 geometry changes. These changes are expected to yield large inverse equilibrium isotope effects manifested as KIEs (because the k_{obs} will be a product of K_1, K_2, K_3, and k_4).[21,25] The observed values of aldehyde-isotope effects were 0.72−0.80, which are large inverse isotope effects, providing further support for the proposed mechanism.

In addition to the results of KIE experiments, support for the mechanism is found in a number of reports of dioxanone (**12**) byproducts.[26−29] These byproducts result when hemiacetal intermediates **7** or **9** undergo intramolecular transesterification with the ester, forming a six-membered ring (Scheme 3). As expected, the dioxanone byproducts form only when the acrylate is an activated ester.

Scheme 3. Proposed Dioxanone Formation



The BH reaction rate shows a nonlinear but systematic dependence on solvent polarity (Table 1). In particular, reactions using DMSO exhibit rates much faster than those of reactions using other comparable polar solvents such as DMF and acetonitrile. As shown in Figure 1D, the BH reaction rate increases linearly with DMSO concentration for both low- and high-polarity cosolvents (chloroform and DMF, respectively). These results suggest that the BH reaction has a first-order dependence on DMSO; however, after careful consideration, we cannot assign a molecular role for DMSO. As such, we suggest that DMSO may uniquely solvate the transition state and thus provide accelerated rates.

Using multiple isotope-labeling experiments and order data, we propose that the RDS is the elimination of the

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α-proton by a hemiacetal intermediate. Preliminary evidence suggests that this mechanism is general for aryl aldehydes. We will present results from experiments using a greater variety of aldehydes and reactions run with alcohol additives shortly.

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Supporting Information Available: General experimental procedure, rate plots, and selected NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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