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The *Complete* Mechanism of an Aldol Condensation

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Abstract

Although aldol condensation is one of the most important organic reactions, capable of forming new C-C bonds, its mechanism has never been fully established. It is now concluded that the rate-limiting step in the base-catalyzed aldol condensation of benzaldehydes with acetophenones, to produce chalcones, is the final loss of hydroxide and formation of the C-C double bond. This conclusion is based on a study of the partitioning ratios of the intermediate ketols and on the solvent kinetic isotope effects, whereby the condensations are faster in D₂O than in H₂O, regardless of substitution.

Introduction

The aldol reaction and the aldol condensation are among the most versatile of organic reactions,¹ with > 25000 entries in SciFinder. Each of these uses two carbonyl compounds, one as electrophile and the other as nucleophile. Each succeeds in forming a new carbon-carbon single bond, or else a carbon-carbon double bond, which distinguishes the aldol *condensation*. There are many variants, including the Claisen, Dieckmann, Henry, and Darzens Condensations and the Knoevenagel and Perkin Reactions. Because of their ability to construct larger molecules from smaller ones,²⁻⁶ or to effect cyclization,⁷⁻⁹ often with control of stereochemistry,¹⁰⁻¹² these reactions are a mainstay of organic synthesis. They are also common in metabolism, where aldolase, citrate synthase, and other enzymes catalyze aldol reactions and aldol condensations, or their reverse,¹³ leading to the suggestion that they reflect primordial metabolism.¹⁴⁻¹⁵

We are interested in the particular aldol reaction of a benzaldehyde **1** and an acetophenone **2** to form ketol (β -hydroxyketone) **3**, which is then dehydrated to the chalcone (benzylideneacetophenone) **4**, as in Scheme 1. Chalcones have many medicinal and pharmacological properties, with antimicrobial, anticancer, anti-inflammatory, antimalarial, antibacterial, and antiproliferative activities.¹⁶ They are intermediates in the synthesis of various natural products,¹⁷⁻¹⁸ as well as unusual polycyclic aromatics.¹⁹ The aromatic rings stabilize **4** and increase the equilibrium constant for its formation, so that the reaction becomes more feasible for study.

Scheme 1. Formation of Chalcone (**4**) from a Benzaldehyde (**1**) and an Acetophenone (**2**) via Ketol **3**.

The question we address is the mechanism of base-catalyzed chalcone formation, as a representative of the aldol condensation. It may be thought that this mechanism is well

understood, but, surprisingly, it has never been fully established. There are five steps, as shown in Scheme 2, although the last two are sometimes merged into a single dehydration step, perhaps merely for brevity.

Scheme 2. Steps in Chalcone Formation: (1) First Enolization, (2) C-C Bond Formation, (3) Proton Equilibration, (4) Second Enolization, (5) Hydroxide Elimination and C=C Bond Formation.

According to an early kinetic study,²⁰ the rate, for $\text{Ar} = \text{Ph} = \text{Ar}'$, is given by eq 1, where k is a third-order rate constant. Therefore Step 1 cannot be rate-limiting, because if it were, the rate would be independent of $[\text{ArCHO}]$. For the aldol *reaction*, arrested at **3**, Step 2 must be rate-limiting, because the proton equilibration of Step 3 is fast (although there are examples where the enolization of Step 1 is rate-limiting).²¹⁻²³

$$v = d[\text{chalcone}]/dt = k[\text{ArCHO}][\text{Ar}'\text{COCH}_3][\text{OH}^-] \quad (1)$$

Which step is the rate-limiting step of the aldol *condensation*, as distinguished from the aldol *reaction*? Noyce, Pryor, and Bottini studied the fate of the ketol intermediate, independently synthesized.²⁴ They found that **3** ($\text{Ar} = \text{Ph} = \text{Ar}'$) is converted in base to a mixture of 80% **1** + **2** and 20% **4**. There has been disagreement about the mechanistic inference to be drawn from this 4:1 ratio. Noyce, Pryor, and Bottini inferred that "in dilute solutions the C-C bond forming step is rate-determining, with dehydration being rapid". This inference is echoed in a recent advanced textbook: "Studies ... have shown that about 80% (*sic*) of [ketol] goes on to product. These reactions are faster than the overall reaction, so the second step must be rate

controlling."²⁵ An earlier monograph concluded, "observation that alkali transforms the intermediate β -hydroxy ketone to benzaldehyde and acetophenone more rapidly than it dehydrates it shows that the second step is not rate-controlling".²⁶ It should be noted that these two books draw exactly opposite conclusions about Step 2, and that the recent one misquoted the experimental observation. We now resolve these contradictions.

According to one definition,²⁷ the rate-limiting step of a multistep mechanism is the last one whose rate constant remains in the kinetic equation. Because ketol **3** reverts to precursors faster than it continues to chalcone, Steps 1, 2, and 3 of Scheme 2 are rapid and reversible and cannot be rate-limiting. This holds even in dilute solution, where Step 2 is slower in the forward direction but not retarded in the reverse direction.

Therefore dehydration must be rate-limiting. Although this can be represented as a single step, it is possible to distinguish enolization (Step 4) from elimination of OH^- (Step 5). Which one is rate-limiting, Step 4, Step 5, or their composite?

Kinetic isotope effects are often useful in elucidating reaction mechanisms and distinguishing the rate-limiting step.²⁸⁻²⁹ Indeed, this question can be answered by measuring the solvent deuterium kinetic isotope effect. Because Step 1 is rapid and reversible, $\text{Ar}'\text{COCH}_3$ in D_2O becomes $\text{Ar}'\text{COCD}_3$ and **3** becomes $\text{Ar}'\text{CHODCD}_2\text{COAr}'$. The deuterated **3** may be expected to form enolate **5** more slowly than undeuterated **3** does, as is generally seen in base-catalyzed enolizations, owing to the lower zero-point energy of a C-D bond. A faster reaction in D_2O would then be strong evidence against Step 4 as rate-limiting. We also choose to ascertain whether the answer depends on substituents in the aryl rings and even the extent to which the partition ratio of intermediate **3** might depend on substituents. We therefore have extended the earlier studies to some substituted benzaldehydes **1** and acetophenones **2**.

Although earlier studies were often performed in ethanol, a solvent isotope effect is more readily interpreted in an aqueous medium. Then, to maintain solubility of substrates and of chalcone product, it was found necessary to add acetonitrile as cosolvent to the H_2O or D_2O . Fortunately, CH_3CN is sufficiently inert to base-catalyzed H/D exchange.³⁰ We now report that

the reaction is faster in D₂O than in H₂O, and we conclude that elimination of OH⁻ is the rate-limiting step, regardless of substituents in the aromatic rings.

Results and Discussion

Partitioning of Ketol Intermediates. On treatment with dilute base, ketols **3** partition between reversion to precursors **1** and **2** and progression to chalcone product **4**. The partitioning ratio was evaluated from the absorbances of the product mixture at both the λ_{max} of chalcone **4**, near 312 nm, and the isosbestic wavelength of benzaldehyde **1** and acetophenone **2**, near 250 nm. Table 1 presents the ratio R , $= [\mathbf{1}]/[\mathbf{4}] = [\mathbf{2}]/[\mathbf{4}]$. Thus the dominant reaction is reversion to precursors, as found for unsubstituted **3** by Noyce, Pryor, and Bottini.²⁴ Moreover, this is general for all ketols **3**, regardless of aryl substitution. However, all ratios are slightly greater than the 4:1 originally reported. We attribute this to our more modern scanning spectrophotometer, rather than to the difference in solvents, because a ratio of 7.4 was also found in ethanol.³¹

Table 1. Partitioning ratio R of ketol **3** to precursors **1** + **2**, relative to product **4**.

Ar	Ar'	R
Ph	Ph	6.4
pClPh	Ph	5.4
pO ₂ NPh	Ph	5.8
pMePh	Ph	6.9
Ph	pClPh	6.9
Ph	pO ₂ NPh	6.9

Solvent Kinetic Isotope Effect on Rates of Chalcone Formation. Third-order rate constants for base-catalyzed conversion of benzaldehyde **1** plus acetophenone **2** to chalcone **4** in both H₂O and D₂O at ambient temperature of 25.2 °C are listed in Table 2, along with the ratios $k_{\text{D}_2\text{O}}/k_{\text{H}_2\text{O}}$. Values of k are averages over all kinetic runs, and the error reported for each k and

for each $k_{\text{D}_2\text{O}}/k_{\text{H}_2\text{O}}$ is the standard error of the mean. In all cases the reaction is faster in D_2O . Although the errors are large enough that $k_{\text{D}_2\text{O}}/k_{\text{H}_2\text{O}}$ does not always differ from unity at a high level of statistical significance, the fact that none is less than 1 excludes mechanistic alternatives where this ratio would be much less than 1, as justified below.

Table 2. Rate constants ($\text{M}^{-2}\text{s}^{-1}$) for base-catalyzed conversion of benzaldehyde **1** and acetophenone **2** to chalcone **4** in H_2O or D_2O and ratio $k_{\text{D}_2\text{O}}/k_{\text{H}_2\text{O}}$.

%CH ₃ CN	Ar	Ar'	$k_{\text{H}_2\text{O}}$	$k_{\text{D}_2\text{O}}$	$k_{\text{D}_2\text{O}}/k_{\text{H}_2\text{O}}$
26	Ph	Ph	0.0111±0.0004	0.0127±0.0005	1.14±0.06
40	pClPh	Ph	0.0412±0.0008	0.0506±0.0007	1.23±0.03
40	pO ₂ NPh	Ph	0.440±0.019	0.512±0.013	1.16±0.06
40	Ph	pClPh	0.0298±0.0009	0.0334±0.0007	1.12±0.04
40	Ph	pO ₂ NPh	0.158±0.004	0.227±0.014	1.43±0.10

These results might have been anticipated. The elimination of methanol from **6** ($\text{R} = \text{H}$, CH_3) is faster in D_2O than in H_2O , by a factor of 1.15 ($\text{R} = \text{H}$) or 1.30 ($\text{R} = \text{CH}_3$).³² Therefore it was concluded that this mechanism is E1cb , as in Scheme 3, with the rate-limiting step being the loss of methoxide from the enolate intermediate **8**.

Scheme 3. E1cb Elimination of Methoxide.

Because reaction is faster in D_2O , H (or D) removal (Step 4 of Scheme 2) cannot be rate-limiting, because it would show $k_{\text{D}_2\text{O}} \ll k_{\text{H}_2\text{O}}$. For example, enolizations of simple ketones show a kinetic isotope effect $k_{\text{D}}/k_{\text{H}}$ of 1/4 to 1/7.³³⁻³⁵ A mechanism more closely analogous to

Steps 4 and 5 of Scheme 2 is often operative for elimination of H and a good leaving group, such as halide. Such a mechanism is, designated as E1cb(irrev), but it is less likely here for the poorer leaving group hydroxide. Indeed, this mechanism would have shown a k_D/k_H of 1/7.³⁶ Nor can a concerted E2 elimination of H and OH be operative, for it would have shown a k_D/k_H of 1/3 to 1/7.³⁷

Instead the rate-limiting step must be Step 5, the final loss of hydroxide from enolate intermediate **5**. The reaction is faster in D₂O because OD⁻ is a stronger base than OH⁻, as judged from the comparison between $K_w = 1.01 \times 10^{-14}$ in H₂O but 1.12×10^{-15} in D₂O.³⁸ Consequently, there is a higher steady-state concentration of **5** in D₂O. This is consistent with the observations that base-catalyzed epoxide formation from 2-haloethanols is faster in D₂O than in H₂O.³⁹⁻⁴⁰ Thus the rate law for chalcone formation is $v = k_5[\mathbf{5}] = k_5K_4K_3K_2K_1[\text{Ar}'\text{COCH}_3][\text{ArCHO}][\text{OH}^-]$, where K_{1-4} are equilibrium constants for Steps 1-4 in Scheme 2 and k_5 is the rate constant for Step 5. It should be noted that this solvent kinetic isotope effect is not from the rate constant k_5 but from the steady-state **[5]**. This is higher in D₂O than in H₂O, owing to a larger K_4 in D₂O.

It is necessary to justify the simplification to pseudo-first-order kinetics. In principle, the stoichiometric OH⁻ concentration might partition itself among the anionic species of Scheme 2, leading to a catalytic cycle with a more complicated rate expression. Thus Scheme 2 can alternatively be drawn as a set of catalytic cycles, as in Scheme 4. Such a drawing places onto the cycle not only the catalyst but also any species to which the catalyst is converted, while reactants and products are shown as entering or leaving the cycle. A catalytic cycle is advantageous for cases like Michaelis-Menten kinetics, where a high concentration of substrate S can convert catalyst E to E-S. Such a complication does arise in proline-catalyzed aldol reactions, where the enamine intermediate is present at levels that can be detected by NMR.⁴¹ In contrast, the anionic species of Scheme 2, as well as ketol **3**, are all high-energy intermediates whose steady-state concentrations are too low to deplete hydroxide. For example, the pK_a of PhCOCH₃ (**2**) is 18.24,⁴² so that the ratio $[\mathbf{2}^-]/[\text{OH}^-]$ at the typical [PhCOCH₃] of 0.02 M is 10^{-6} ,

which indeed represents negligible depletion. Nor does the concentration of ketol **3** accumulate, because it too is unstable, as verified experimentally by evidence below. We therefore consider Scheme 2 preferable to Scheme 4, because it focuses on the reactants, intermediates, and products, rather than on the catalyst, whose constancy permits simplifying eq 1 to eq 2. However, it should be noted that the transition state for conversion of **5** to **4** is still a rate-determining state even when this terminology is applied to the catalytic cycles of Scheme 4.⁴³

Scheme 4. Catalytic cycles for base-catalyzed chalcone formation from aldehyde **1** and acetophenone **2**, where **3** = ketol intermediate, **3**⁻ = alkoxide of **3**, **5** = enolate of **3**, and **4** = chalcone.

Reaction Rates of Ketol Intermediates. For completeness, Table 3 lists rate constants k_3 for base-catalyzed disappearance of ketols **3**. By using the partition ratios in Table 1, each of them can be separated into rate constants for conversion to **4** and reversion to **1** + **2**, as also listed in Table 3. The value of $0.084 \text{ M}^{-1}\text{s}^{-1}$ for $\text{Ar} = \text{Ph} = \text{Ar}'$ in 80% aqueous CH_3CN is in semiquantitative agreement with the values of 0.22 and $0.30 \text{ M}^{-1}\text{s}^{-1}$ in the different solvents water and 95% aqueous ethanol.³¹

Table 3. Rate constants ($\text{M}^{-1}\text{s}^{-1}$) for disappearance of ketols **3**, for conversion to chalcones **4**, and

for reversion to benzaldehydes 1 + acetophenones 2 .					
Ar	Ar'	%CH ₃ CN	k_3	$k_{\rightarrow 4}$	$k_{\rightarrow 1+2}$
Ph	Ph	80	0.084	0.011	0.073
pClPh	Ph	26	0.41	0.065	0.35

pO ₂ NPh	Ph	60	0.40	0.059	0.34
pMePh	Ph	70	0.20	0.025	0.17
Ph	pClPh	70	0.32	0.041	0.28
Ph	pO ₂ NPh	60	0.60	0.077	0.53

In terms of Scheme 2 it is readily seen that $k_3 = (k_5K_4 + k_{-2}/K_3)[OH^-]$, where k_{-2} is the rate constant for the reverse reaction of Step 2, which is rate-limiting for the reversion of **3** to **1** + **2**. The individual terms of this rate constant correspond to the separate rate constants $k_{\rightarrow 4}$ and $k_{\rightarrow 1+2}$.

Above it was claimed that the intermediate product **3** does not build up to any appreciable extent under our reaction conditions, because it is not sufficiently stable. As evidence for this claim, the second-order rate constants k_3 for ketol disappearance in Table 3 are considerably larger than the rate constants k_{H_2O} for chalcone formation in Table 2, converted to pseudo-second-order rate constants $k_{H_2O}[Ar'COCH_3]$ at the typical $[Ar'COCH_3]$ of 0.02 M.

Summary and Conclusions

Our conclusion that Step 5 of Scheme 2 is rate-limiting was also reached, although implicitly, by calculating rate and equilibrium constants by Marcus theory.⁴⁴ In hindsight, we should not be surprised at this conclusion. If Step 1 (enolization of CH_3COAr') is not rate-limiting, then we might expect the similar Step 4 (enolization of $ArCH(OH)CH_2COAr'$) not to be rate-limiting. This conclusion is not inescapable though, because enolization of CH_3COAr' is followed by a bimolecular reaction whereas enolization of $ArCH(OH)CH_2COAr'$ is followed by a unimolecular step, and because enolization is calculated to be rate-limiting in the similar elimination of H^+ and $CH_3CO_2^-$ from $CH_3YCOCH_2CH(OCOCH_3)CH_3$ ($Y = O$ or S),⁴⁵ where acetate is admittedly a much better leaving group. Certainly though, the results here are convincing experimental evidence for rate-limiting loss of OH^- .

Moreover, these results also provide evidence concerning the mechanism of the reverse reaction, the hydration of chalcone **4** followed by the retro-aldol condensation reverting to **1** + **2**. According to the Principle of Microscopic Reversibility, the rate-limiting step for the reverse reaction must be the initial Michael addition of OH⁻ to the C-C double bond.

Intermediate ketol **3** partitions predominantly (7:1) to precursors **1** + **2** regardless of substitution. Therefore the first three steps in Scheme 2 are rapid and reversible. Because the rates of chalcone formation are higher in D₂O than in H₂O, regardless of substitution, all of the first four steps in Scheme 2 are rapid and reversible, and the rate-limiting step must be the loss of OH⁻ (Step 5). This conclusion resolves the contradictions among Refs. 24-26.

All these results can be summarized in the energy diagram shown in Fig. 1, constructed from these results (and others, as explained in Supporting Information). The highest-energy transition state is for the final loss of OH⁻, but it is not higher than the others by much. Another transition state might have been the highest, and it is these experiments that support this conclusion, not only for the parent chalcone but also for the substituted ones. Thus we now know the *complete* free-energy profile for this simple aldol condensation.

Figure 1. (Free) energy diagram for aldol condensation of Scheme 2 (Ar = Ph = Ar').

Experimental Section

Materials. Acetonitrile was of a grade formulated for UHPLC-UV. Commercial benzaldehyde and acetophenone and their substituted derivatives were purified by vacuum distillation or recrystallization and stored under N₂. Each was dissolved in acetonitrile and diluted in oven-dried volumetric flasks to the concentrations needed.

Ketol intermediates were synthesized by aldol reaction of a benzaldehyde and an acetophenone promoted by MgI₂ + iPr₂NEt,⁴⁶ but on a five-fold larger scale. The crude product was purified by flash chromatography with hexane/ethyl acetate. Collected fractions were spotted on TLC plate, developed with 6:1 hexane/ethyl acetate, and visualized under UV light. Fractions containing ketol were combined, evaporated, and recrystallized from CH₂Cl₂-hexane. Authenticity and purity were checked through melting points and ¹H NMR spectra.

3-Hydroxy-1,3-diphenylpropane-1-one: m.p. 47.2-48.1 °C, lit.⁴⁶ 44-46 °C, ¹H NMR δ 3.38 (d, 2H), 3.58 (br s, 1H), 5.35 (m, 1H), 7.32 (m, 1H), 7.39 (m, 2H), 7.46 (m, 4H), 7.59 (m, 1H), 7.96 (m, 2H); lit.⁴⁶ 3.33 (m, 2 H); 3.68 (d, *J* = 3.0, OH); 5.32 (m, 1H); 7.31 (m, 1H); 7.39 (m, 2 H); 7.46 (m, 4 H); 7.59 (m, 1H); 7.95 (m, 2 H).

3-Hydroxy-3-(4-chlorophenyl)-1-phenylpropan-1-one: m.p. 93.6-95.2 °C, lit.⁴⁷ 96-96.5 °C, ¹H NMR δ 3.34 (m, 2H), 3.64 (br s, 1H), 5.32 (m, 1H), 7.37 (m, 4H), 7.48 (m, 3H), 7.60 (m, 1H), 7.95 (m, 2H); lit.⁴⁷ 3.295 (d, 1 H, *J* = 5.7 Hz), 3.299 (d, 1 H, *J* = 6.4 Hz), 3.81 (br s, 1 H), 5.28 (br t, 1 H), 7.10-7.65 (m, 7 H), 7.72-7.96 (m, 2 H)

3-Hydroxy-3-(4-nitrophenyl)-1-phenylpropan-1-one: m.p. 111.3-112.7 °C, lit.⁴⁸ 112.9 °C, ¹H NMR δ 3.37 (m, 2H), 3.82 (br s, 1H), 5.46 (m, 1H), 7.49 (m, 2H), 7.61 (m, 3H), 7.94 (m, 2H), 8.24 (m, 2H); lit.⁴⁸ 3.29-3.46 (m, 2H), 3.93 (br s, 1H), 5.46 (dd, *J* = 4:1, 8.1 Hz, 1H), 7.45-7.50 (m, 2H), 7.59-7.64 (m, 3H), 7.93-7.96 (m, 2H), 8.20-8.23 (m, 2H).

3-Hydroxy-3-(4-methylphenyl)-1-phenylpropan-1-one: m.p. 49.1-51.6 °C, lit.⁴⁷ 47-48

°C, ^1H NMR δ 2.35 (s, 3H), 3.37 (m, 2H), 3.51 (br s, 1H), 5.32 (t, 1H), 7.19 (d, 2H), 7.33 (d, 2H), 7.47 (m, 2H), 7.59 (m, 1H), 7.95 (m, 2H); lit.⁴⁷ 2.32 (s, 3 H), 3.31 (d, 1 H, $J = 5.3$ Hz), 3.32 (d, 1 H, $J = 6.8$ Hz), 3.64 (br d, 1 H, $J = 2.6$ Hz), 5.08-5.36 (m, 1 H), 6.92-7.61 (m, 7 H), 7.68-7.96 (m, 2 H);

3-Hydroxy-1-(4-chlorophenyl)-3-phenylpropan-1-one: m.p. 52.5-56.7 °C, ^1H NMR δ 3.37 (m, 3H), 5.34 (m, 1H), 7.25-7.45 (m, 7H), 7.90 (m, 2H); lit.⁴⁹ 7.89-7.86 (m, 2H), 7.44-7.25 (m, 7H), 5.31 (dd, $J = 3.5, 8.4$ Hz, 1H), 3.51 (br s, 1H), 3.41-3.25 (m, 2H).

3-Hydroxy-1-(4-nitrophenyl)-3-phenylpropan-1-one: m.p. 86.5-87.4 °C, lit.⁵⁰ 90 °C, ^1H NMR δ 3.14 (br s, 1H), 3.41 (m, 2H), 5.38 (m, 1H), 7.23-7.63 (m, 5H), 8.11 (m, 2H), 8.29 (m, 2H); lit.⁵⁰ 8.28 (d, $J = 8.9$, 1H), 8.08 (d, $J = 8.9$, 1H), 7.47-7.26 (m, 5H), 5.35 (dd, $J = 9.0, 3.1$, 1H), 3.48 (dd, $J = 17.6, 9.0$, 1H), 3.32 (dd, $J = 17.6, 3.1$, 1H), 3.05 (br s, 1H).

Rate measurements. Rates of base-catalyzed condensation of benzaldehyde **1** plus acetophenone **2** to chalcone **4** were followed on a recording UV spectrophotometer by monitoring the absorbance of **4** at its λ_{max} near 312 nm.

Because NaOH is a catalyst and because **2** is in excess, neither of their concentrations varies with time. Therefore pseudo-first-order conditions apply, and the third-order kinetics of eq 1 simplifies to eq 2. Although the solution to eq 2 is $[\text{ArCHO}] = [\text{ArCHO}]_0 \exp(-k_{\text{obs}}t)$, the spectrophotometer measures the absorbance A of product **4**, as in eq 3, which was fit by nonlinear least squares.

$$v = d[\text{chalcone}]/dt = -d[\text{ArCHO}]/dt = k_{\text{obs}}[\text{ArCHO}] \quad (2)$$

$$A = A_{\infty} - (A_{\infty} - A_0)\exp(-k_{\text{obs}}t) \quad (3)$$

Extraction of Forward Rate Constant k . Because reaction does not go to completion, it is necessary to extract the forward rate constant k of eq 1 from k_{obs} of eq 2. These are related by eq 4, in which an average equilibrium constant K_{e} can be evaluated from the final concentrations of benzaldehyde **1**, acetophenone **2**, and chalcone **4**. Rate constants were averaged over 4 to 17 experiments at various initial concentrations of **1**, **2**, and OH^- or OD^- . Further details of

procedure are described in the Supporting Information.

$$k = \frac{k_{\text{obs}}}{[\text{OH}^-]} \frac{K_e}{1 + K_e[\mathbf{2}]} \quad (4)$$

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Supporting Information. details of procedure and construction of energy diagram. representative time curves. reaction conditions, fitting parameters, and rate constants for formation of chalcones.

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