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The Complete Mechanism of an Aldol Condensation

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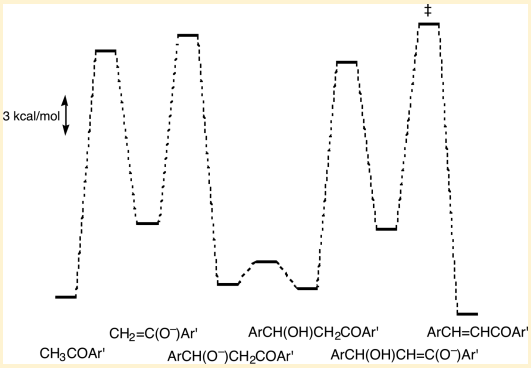
Supporting Information

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. We now conclude 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 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 D_2O than in H_2O, regardless of substitution.

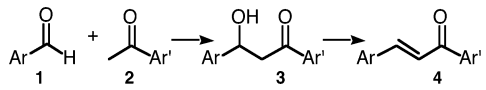


INTRODUCTION

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 an electrophile and the other as a 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 chalcone (benzylideneacetophenone) **4**, as shown in Scheme 1.

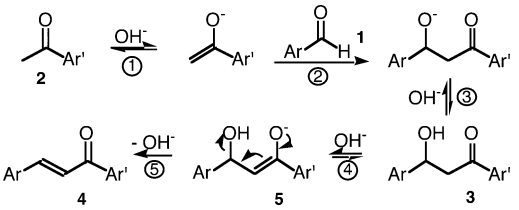
Scheme 1. Formation of Chalcone (4) from a Benzaldehyde (1) and an Acetophenone (2) via Ketol 3



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.

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 the sake of brevity.

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



According to an early kinetic study,[20] the rate, for Ar = Ph = 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 ArCHO concentration. 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 in which the enolization of step 1 is rate-limiting).[21−23]

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

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** (Ar = Ph = Ar′) is converted in base to a mixture of 80% **1** and **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 1−3 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, $Ar'COCH_3$ in D_2O becomes $Ar'COCD_3$ and **3** becomes $ArCHODCD_2COAr'$. The deuterated **3** may be expected to form enolate **5** more slowly than undeuterated **3** does, as is generally seen in base-catalyzed enolizations, because of 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 being 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 the solubility of substrates and of the chalcone product, it was found to be necessary to add acetonitrile as a 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 D_2O than in H_2O, 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. Upon being treated 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 (=[**1**]/[**4**] = [**2**]/[**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 value of 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 Ratios (R) of Ketol 3 to Precursors 1 and 2, Relative to Product 4

Ar	Ar′	R
Ph	Ph	6.4
pClPh	Ph	5.4
pO_2NPh	Ph	5.8
pMePh	Ph	6.9
Ph	pClPh	6.9
Ph	pO_2NPh	6.9

Solvent Kinetic Isotope Effect on Rates of Chalcone Formation. Third-order rate constants for base-catalyzed conversion of benzaldehyde **1** and acetophenone **2** to chalcone **4** in both H_2O and D_2O at an ambient temperature of 25.2 °C are listed in Table 2, along with the k_{D_2O}/k_{H_2O} ratios. Values of k are averages over all kinetic runs, and the error reported for each k and for each k_{D_2O}/k_{H_2O} 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_{D_2O}/k_{H_2O} 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.

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

Because reaction is faster in D_2O, H (or D) removal (step 4 of Scheme 2) cannot be rate-limiting, because it would show $k_{D_2O} \ll k_{H_2O}$. For example, enolizations of simple ketones show a kinetic isotope effect k_D/k_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 from 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 D_2O because OD^- is a stronger base than OH^-, as judged from the comparison between K_w values of 1.01×10^{-14} in H_2O but 1.12×10^{-15} in D_2O.[38] Consequently, there is a higher steady-state concentration of **5** in D_2O. This is consistent with the observations that base-catalyzed formation of epoxide from 2-haloethanols is faster in D_2O than in H_2O.[39,40] Thus, the rate

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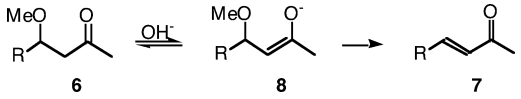
Table 2. Rate Constants (M^{-2} s^{-1}) for Base-Catalyzed Conversion of Benzaldehyde 1 and Acetophenone 2 to Chalcone 4 in H_2O or D_2O and k_{D_2O}/k_{H_2O} Ratios

% CH_3CN	Ar	Ar′	k_{H_2O}	k_{D_2O}	k_{D_2O}/k_{H_2O}
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_2NPh	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_2NPh	0.158 ± 0.004	0.227 ± 0.014	1.43 ± 0.10

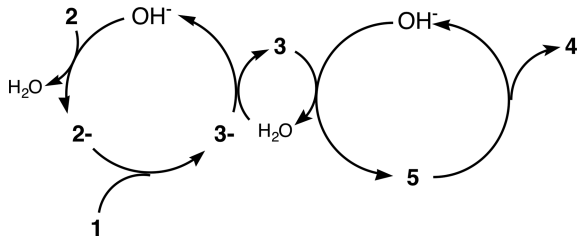
Scheme 3. E1cb Elimination of Methoxide



law for chalcone formation is $v = k_5[\mathbf{5}] = k_5K_4K_3K_2K_1[\mathrm{Ar'COCH_3}][\mathrm{ArCHO}][\mathrm{OH^-}]$, where K_1–K_4 are equilibrium constants for steps 1–4 in Scheme 2, respectively, and k_5 is the rate constant for step 5. It should be noted that this solvent kinetic isotope effect is not from rate constant k_5 but from the steady-state concentration of **5**. This is higher in D_2O than in H_2O, because of the larger K_4 in D_2O.

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 shown in Scheme 4. Such a drawing

Scheme 4. Catalytic Cycles for Base-Catalyzed Chalcone Formation from Aldehyde 1 and Acetophenone 2, Where 3 = a Ketol Intermediate, 3^- = the Alkoxide of 3, 5 = the Enolate of 3, and 4 = Chalcone



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, in which 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 $PhCOCH_3$ (**2**) is 18.24,[42] so that the $[\mathbf{2}^-]/[\mathrm{OH^-}]$ ratio at the typical $[PhCOCH_3]$ 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 described 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 the simplification of 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]

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

Table 3. Rate Constants (M^{-1} s^{-1}) for the Disappearance of Ketols 3, for Conversion to Chalcones 4, and for Reversion to Benzaldehydes 1 and Acetophenones 2

Ar	Ar′	% CH_3CN	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_2NPh	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_2NPh	60	0.60	0.077	0.53

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

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

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or S),[45] where acetate is admittedly a much better leaving group. Certainly though, the results here are convincing experimental evidence of 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** and **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 bond.

Intermediate ketol **3** partitions predominantly (7:1) to precursors **1** and **2** regardless of substitution. Therefore, the first three steps in Scheme 2 are rapid and reversible. Because the rates of chalcone formation are faster in D_2O than in H_2O, 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 Figure 1, constructed from these results (and others,

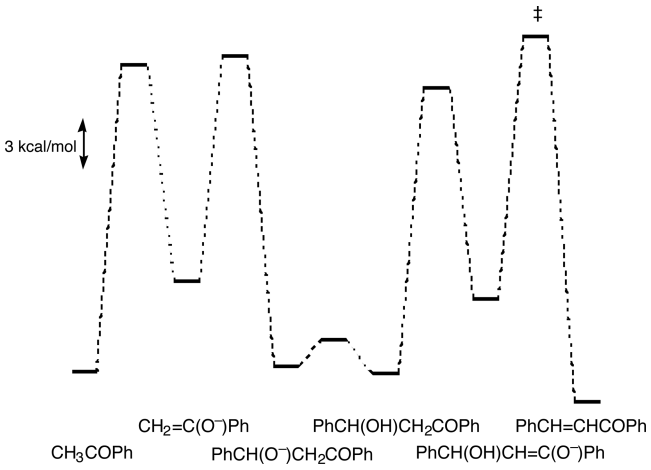

Figure 1. (Free) energy diagram for aldol condensation of Scheme 2 (Ar = Ph = Ar′).

as explained in the 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 forms. Thus, we now know the complete free energy profile for this simple aldol condensation.

EXPERIMENTAL SECTION

Materials. Acetonitrile was of a grade formulated for UHPLC-UV and purchased from Fisher Scientific. Commercial benzaldehyde and acetophenone and their substituted derivatives were purified by vacuum distillation or recrystallization and stored under N_2. 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 MgI_2 and iPr_2NEt,[46] but on a 5-fold larger scale. The crude product was purified by flash chromatography with hexane and ethyl acetate. Collected fractions were spotted on a TLC plate, developed with a 6:1 hexane/ethyl acetate solvent, and visualized under UV light. Fractions containing ketol were combined, evaporated, and recrystallized from CH_2Cl_2 and hexane. Authenticity and purity were checked through melting points and ^{1}H NMR spectra.

3-Hydroxy-1,3-diphenylpropan-1-one. mp 47.2–48.1 °C (lit.[46] 44–46 °C); ^{1}H 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, 2H), 3.68 (d, J = 3.0, OH), 5.32 (m, 1H), 7.31 (m, 1H), 7.39 (m, 2H), 7.46 (m, 4H), 7.59 (m, 1H), 7.95 (m, 2H)].

3-Hydroxy-3-(4-chlorophenyl)-1-phenylpropan-1-one. mp 93.6–95.2 °C (lit.[47] 96–96.5 °C); ^{1}H 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, 1H, J = 5.7 Hz), 3.299 (d, 1H, J = 6.4 Hz), 3.81 (br s, 1H), 5.28 (br t, 1H), 7.10–7.65 (m, 7H), 7.72–7.96 (m, 2H)].

3-Hydroxy-3-(4-nitrophenyl)-1-phenylpropan-1-one. mp 111.3–112.7 °C (lit.[48] 112.9 °C); ^{1}H 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. mp 49.1–51.6 °C (lit.[47] 47–48 °C); ^{1}H 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, 3H), 3.31 (d, 1H, J = 5.3 Hz), 3.32 (d, 1H, J = 6.8 Hz), 3.64 (br d, 1H, J = 2.6 Hz), 5.08–5.36 (m, 1H), 6.92–7.61 (m, 7H), 7.68–7.96 (m, 2H)].

3-Hydroxy-1-(4-chlorophenyl)-3-phenylpropan-1-one. mp 52.5–56.7 °C; ^{1}H 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. mp 86.5–87.4 °C (lit.[50] 90 °C); ^{1}H 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 Hz, 1H), 8.08 (d, J = 8.9 Hz, 1H), 7.47–7.26 (m, 5H), 5.35 (dd, J = 9.0, 3.1 Hz, 1H), 3.48 (dd, J = 17.6, 9.0 Hz, 1H), 3.32 (dd, J = 17.6, 3.1 Hz, 1H), 3.05 (br s, 1H)].

Rate Measurements. Rates of base-catalyzed condensation of benzaldehyde **1** and 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 $[ArCHO] = [ArCHO]_0 \exp(-k_{obs}t)$, the spectrophotometer measures absorbance A of product **4**, as in eq 3, which was fit by nonlinear least squares.

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

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

Extraction of Forward Rate Constant *k*. Because this 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 4–17 experiments at various initial concentrations of **1**, **2**, and OH^- or OD^-. Further details of procedure are described in the Supporting Information.

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

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b00959.

Details of the procedure and construction of the energy diagram, representative time curves, reaction conditions, fitting parameters, and rate constants for formation of chalcones (PDF)

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Notes

The authors declare no competing financial interest.

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REFERENCES

(1) Smith, M. B. *March's Organic Chemistry: Reactions, Mechanisms, and Structure*, 7th ed.; John Wiley: New York, 2013.
(2) Wender, P. A.; Schrier, A. J. *J. Am. Chem. Soc.* **2011**, *133*, 9228−9231.
(3) DeLorbe, J. E.; Jabri, S. Y.; Mennen, S. M.; Overman, L. E.; Zhang, F.-L. *J. Am. Chem. Soc.* **2011**, *133*, 6549−6552.
(4) Laws, S. W.; Scheerer, J. R. *J. Org. Chem.* **2013**, *78*, 2422−2429.
(5) Egger, J.; Bretscher, P.; Freigang, S.; Kopf, M.; Carreira, E. M. *J. Am. Chem. Soc.* **2014**, *136*, 17382−17385.
(6) Shvartsbart, A.; Smith, A. B., III *J. Am. Chem. Soc.* **2015**, *137*, 3510−3519.
(7) Nicolaou, K. C.; Ding, H.; Richard, J.-A.; Chen, D. Y.-K. *J. Am. Chem. Soc.* **2010**, *132*, 3815−3818.
(8) Snyder, S. A.; Wespe, D. A.; von Hof, J. M. *J. Am. Chem. Soc.* **2011**, *133*, 8850−8853.
(9) Daub, M. E.; Prudhomme, J.; Le Roch, K.; Vanderwal, C. D. *J. Am. Chem. Soc.* **2015**, *137*, 4912−4915.
(10) Lam, Y.-h.; Houk, K. N. *J. Am. Chem. Soc.* **2015**, *137*, 2116−2127.
(11) List, B.; Lerner, R. A.; Barbas, C. F., III *J. Am. Chem. Soc.* **2000**, *122*, 2395−2396.
(12) Evans, D. A.; Nelson, J. V.; Taber, T. R. *Topics in Stereochem* **1982**, *13*, 1−115.
(13) Silverman, R. B. *The Organic Chemistry of Enzyme-Catalyzed Reactions*; Academic Press: San Diego, 2000; pp 453−478.
(14) Butch, C.; Cope, E. D.; Pollet, P.; Gelbaum, L.; Krishnamurthy, R.; Liotta, C. L. *J. Am. Chem. Soc.* **2013**, *135*, 13440−13445.
(15) Sagi, V. N.; Punna, V.; Hu, F.; Meher, G.; Krishnamurthy, R. *J. Am. Chem. Soc.* **2012**, *134*, 3577−3589.
(16) Singh, P.; Anand, A.; Kumar, V. *Eur. J. Med. Chem.* **2014**, *85*, 758−777.
(17) Dialer, C.; Imbri, D.; Hansen, S. P.; Opatz, T. *J. Org. Chem.* **2015**, *80*, 11605−11610.
(18) Hong, K. K. C.; Ball, G. E.; Black, D. StC.; Kumar, N. *J. Org. Chem.* **2015**, *80*, 10668−10674.
(19) Geng, X.; Mague, J. T.; Pascal, R. A., Jr. *J. Org. Chem.* **2015**, *80*, 4824−4827.
(20) Coombs, E.; Evans, D. P. *J. Chem. Soc.* **1940**, 1295−1300.
(21) Bell, R. P. *J. Chem. Soc.* **1937**, 1637−1640.
(22) Richard, J. P.; Nagorski, R. W. *J. Am. Chem. Soc.* **1999**, *121*, 4763−4770.
(23) Nozière, B.; Chabert, P. *Int. J. Chem. Kinet.* **2010**, *42*, 676−686.
(24) Noyce, D. S.; Pryor, W. A.; Bottini, A. T. *J. Am. Chem. Soc.* **1955**, *77*, 1402−1405.
(25) Carey, F. A.; Sundberg, R. J. *Advanced Organic Chemistry*, 5th ed.; Springer: Berlin, 2007; Part A, p 285.
(26) Hine, J. *Physical Organic Chemistry*, 2nd ed.; McGraw-Hill: New York, 1962; p 261.
(27) Rocek, J.; Westheimer, F. H.; Eschenmoser, A.; Moldoványi, L.; Schreiber, J. *Helv. Chim. Acta* **1962**, *45*, 2554−2567.
(28) Pluth, M. D.; Bergman, R. G.; Raymond, K. N. *J. Org. Chem.* **2009**, *74*, 58−63.
(29) Um, I.-H.; Kim, M.-Y.; Bae, A.-R.; Dust, J. M.; Buncel, E. *J. Org. Chem.* **2015**, *80*, 217−222.
(30) Richard, J. P.; Williams, G.; Gao, J. *J. Am. Chem. Soc.* **1999**, *121*, 715−726.
(31) Guthrie, J. P.; Cossar, J.; Cullimore, P. A.; Kamkar, N. M.; Taylor, K. F. *Can. J. Chem.* **1983**, *61*, 2621−2626.
(32) Fedor, L. R. *J. Am. Chem. Soc.* **1969**, *91*, 908−913.
(33) Emmons, W. D.; Hawthorne, M. F. *J. Am. Chem. Soc.* **1956**, *78*, 5593−5596.
(34) Riley, T.; Long, F. A. *J. Am. Chem. Soc.* **1962**, *84*, 522−526.
(35) Green, A. J.; Kemp, T. J.; Littler, J. S.; Waters, W. A. *J. Chem. Soc.* **1964**, 2722−2726.
(36) O'Ferrall, R. A. M.; Slae, S. *J. Chem. Soc. B* **1970**, *0*, 260−268.
(37) Saunders, W. H., Jr.; Edison, D. *J. Am. Chem. Soc.* **1960**, *82*, 138−142.
(38) *CRC Handbook of Chemistry and Physics*, 96th ed.; Lide, D. R., Ed.; CRC Press: Boca Raton, FL, 2016; Internet Version 2016 (http://hbcpnetbase.com).
(39) Ballinger, P.; Long, F. A. *J. Am. Chem. Soc.* **1959**, *81*, 2347−2352.
(40) Swain, C. G.; Ketley, A. D.; Bader, R. F. W. *J. Am. Chem. Soc.* **1959**, *81*, 2353−2359.
(41) Haindl, M. M.; Hioe, J.; Gschwind, R. M. *J. Am. Chem. Soc.* **2015**, *137*, 12835−12842.
(42) Chiang, Y.; Kresge, A. J.; Wirz, J. *J. Am. Chem. Soc.* **1984**, *106*, 6392−6395.
(43) Kozuch, S.; Martin, J. M. L. *ChemPhysChem* **2011**, *12*, 1413−1418.
(44) Guthrie, J. P. *J. Am. Chem. Soc.* **1991**, *113*, 7249−7255.
(45) Kim, Y.; Mohrig, J. R.; Truhlar, D. G. *J. Am. Chem. Soc.* **2010**, *132*, 11071−11082.
(46) Wei, H.; Li, K.; Zhang, Q.; Jasoni, R. L.; Hu, J.; Pare, P. W. *Helv. Chim. Acta* **2004**, *87*, 2354−2358.
(47) Hasegawa, E.; Ishiyama, K.; Horaguchi, T.; Shimizu, T. *J. Org. Chem.* **1991**, *56*, 1631−1635.
(48) Nakagawa, T.; Fujisawa, H.; Nagata, Y.; Mukaiyama, T. *Bull. Chem. Soc. Jpn.* **2004**, *77*, 1555−1567.
(49) Xie, K.; Cui, Y.; Liu, Y.-C.; Fu, Y. *Chin. J. Chem.* **2007**, *25*, 839−842.
(50) Olmos, A.; Alix, A.; Sommer, J.; Pale, P. *Chem. - Eur. J.* **2009**, *15*, 11229−11234.

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