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Mechanism of α-Ketol-Type Rearrangement of Benzoin Derivatives under Basic Conditions

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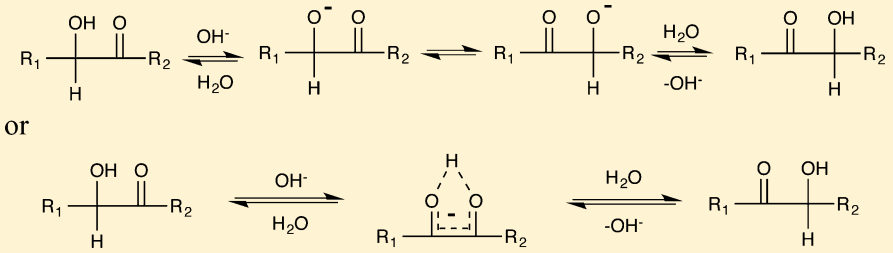
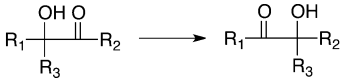
Supporting Information



ABSTRACT: The mechanism of base-catalyzed rearrangement of ring-substituted benzoins in aqueous methanol was examined by kinetic and product analyses. Substituent effects on the rate and equilibrium constants revealed that the kinetic process has a different electron demand compared to the equilibrium process. Reactions in deuterated solvents showed that the rate of H/D exchange of the α-hydrogen is similar to the overall rate toward the equilibrium state. A proton-inventory experiment using partially deuterated solvents showed a linear dependence of the rate on the deuterium fraction of the solvent, indicating that only one deuterium isotope effect contributes to the overall rate process. All these results point to a mechanism in which the rearrangement is initiated by the rate-determining α-hydrogen abstraction rather than a mechanism with initial hydroxyl hydrogen abstraction as in the general α-ketol rearrangement.

INTRODUCTION

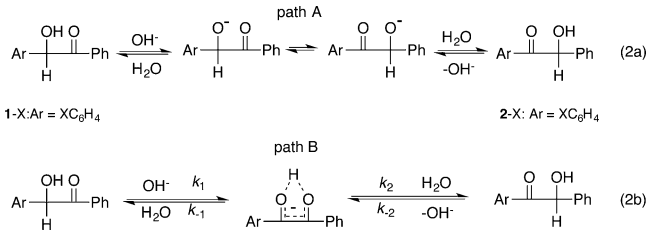
α-Hydroxyketones are versatile species in synthetic chemistry and have been used to prepare a variety of compounds via α-ketol rearrangement (eq 1).[1,2] A possible involvement of the α-ketol rearrangement in biological reactions has also been a matter of controversy for many years.[3]



(1)

The mechanism of the base-catalyzed α-ketol rearrangement appears simple, in which the reaction is initiated by deprotonation of the hydroxyl group, followed by 1,2-R_3 migration and protonation. However, when R_3 is hydrogen, namely, for the reaction of acyloin or benzoin, an alternative pathway with an initial α-hydrogen abstraction becomes possible. The mechanism of the α-ketol rearrangement of this type of compound is complex and has not yet been fully elucidated.

In the present study, we have carried out the reactions of ring-substituted benzoins ($XC_6H_4CHOHCOPh$, **1**-X) with KOH in 70% (v/v) aqueous MeOH and determined the substituent effects on the rate and equilibrium constants. These substituent effects, together with solvent isotope effects and the result of a H/D exchange experiment, showed that the reaction proceeds via an initial α-H abstraction (path B in eq 2) rather than via an initial hydroxyl hydrogen abstraction (path A).



(2a)

(2b)

RESULTS AND DISCUSSION

Rate and Equilibrium Constants. A series of benzoins (**1**-X; X = *p*-MeO, *p*-Me, *m*-Me, *p*-F, *p*-Cl, *m*-F, *m*-Cl, *p*-CF_3, *m*-CN, *p*-CN) were prepared according to the literature.[4,5] The reactions of **1**-X with KOH in 70% (v/v) aqueous MeOH were carried out under N_2. The reactions under O_2-contaminated conditions were deteriorated by oxidation to give benzils as side products.

The rates of the reactions were measured photometrically, and the equilibrium constants were determined by ^{1}H NMR at 25.0 °C and are listed in Table 1. The determined rate constants are for the rates toward the equilibrium mixtures and are given as $k_{eq} = k_f + k_r$. Here, k_f is the forward rate constant from **1**-X to **2**-X, and k_r is the reverse rate constant from **2**-X to

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Table 1. Rate and Equilibrium Constants for the Reactions of 1-X with KOH in 70% (v/v) MeOH at 25.0 °C

X	$10^2 k_{eq}/s^{-1}\ M^{-1}$	K	$10^2 k_f/s^{-1}\ M^{-1}$	$10^2 k_r/s^{-1}\ M^{-1}$
p-MeO	3.21 ± 0.07	7.84 ± 0.02	2.85 ± 0.06	0.36 ± 0.01
p-Me	4.34 ± 0.04	2.58 ± 0.01	3.13 ± 0.03	1.21 ± 0.02
m-Me	6.65 ± 0.30	1.10 ± 0.02	3.48 ± 0.16	3.17 ± 0.14
p-F	*a*	1.24 ± 0.02	*a*	*a*
p-Cl	13.4 ± 0.3	0.675 ± 0.005	5.4 ± 0.1	8.0 ± 0.2
m-F	*a*	0.370 ± 0.011	*a*	*a*
m-Cl	30.5 ± 7.1	0.337 ± 0.014	7.7 ± 1.8	22.8 ± 5.3
p-CF_3	49.6 ± 1.1	0.157 ± 0.001	6.7 ± 0.1	42.9 ± 1.0
m-CN	*a*	0.130 ± 0.005	*a*	*a*
p-CN	*a*	0.081 ± 0.004	*a*	*a*

[a]Not determined.

1-X. The reaction rates for the F-substituted derivatives could not be measured due to extremely small absorbance changes during the reactions, and those for the CN-substituted derivatives could not be determined with acceptable accuracy due to side reactions. The rate constants of the forward and reverse reactions were calculated from the second-order rate constants ($k_{eq} = k_f + k_r$) and the equilibrium constants ($K = k_f/k_r$).

Substituent Effect. Substituent effects on the equilibrium constant (K) and the forward (k_f) and reverse (k_r) rate constants were analyzed by means of an extended Hammett equation (the Yukawa−Tsuno equation, eq 3), in which r is a parameter to measure the relative importance of the resonance effect over the inductive effect and $r = 1.0$ for $\sigma_{app} = \sigma^+$ by definition and $r = 0.27$ for $\sigma_{app} = \sigma$.[6] The Hammett plots for the equilibrium, the forward and reverse reactions, are illustrated in Figures 1 and 2.

$$\log(k/k_0) = \rho\{\sigma^\circ + r(\sigma^+ - \sigma^\circ)\} = \rho(\sigma^\circ + r\Delta\bar{\sigma}_R{}^+) = \rho\sigma_{app} \quad (3)$$

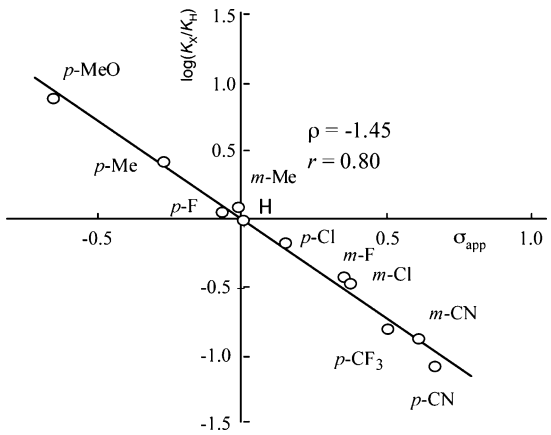

Figure 1. Hammett plots for the equilibrium constant for the reaction of **1**-X and KOH in 70% (v/v) aqueous MeOH at 25.0 °C.

Since the number of substituents is small for the analyses with the dual-parameter equation, the calculated parameters, especially the r values, should not be taken quantitatively. Nevertheless, important information could be extracted from the plots. (1) The plot for the equilibrium gave a negative slope with a significant size of the r value. This indicates that the product **2**-X is stabilized by substituent X both inductively and resonatively in its intramolecularly hydrogen-bonded structure (Chart 1). (2) The Hammett plot for the forward reaction gave a small positive ρ value, in spite of the fact that the corresponding equilibrium gave a negative ρ value. This indicates that the charge type on the benzylic carbon of **1**-X is different at the rate-determining transition state (TS) and the product state. The result is thus consistent with an enolate-forming TS in mechanism B. At the TS, the benzylic carbon bears a partial negative charge, and hence, the ρ value for the forward rate is small positive. The zero r value is reasonable for the mechanism, since the electron-donating resonance effect is absent at the TS. (3) The substituent effect on the reverse reaction, on the other hand, gave a relatively large positive slope with a significant size of the r value. These values are in line with an initial state (**2**-X), stabilized by an electron-donating substituent both inductively and resonatively, and the enolate-forming TS, stabilized by an electron-withdrawing substituent. It should be noted, however, that these substituent effects are also in line with mechanism A, in which the hydride migration step is rate determining.

Isotope Exchange Experiment. To gain information on the role of the α-H abstraction in the reaction mechanism, the reaction of **1**-*m*-Me with KOH was carried out in 70% (v/v) D_2O−CD_3OD. The reaction was followed with ^1H NMR by measuring the changes of the intensities of the Me signals (δ 2.31 and 2.35) of **1**-*m*-Me and **2**-*m*-Me and the α-H signals (δ 5.91 and 5.94) of **1**-*m*-Me and **2**-*m*-Me with respect to the internal standard ($PhOCH_3$). The signal intensities (I) were normalized by the number of hydrogens on the groups. The initial intensities of **1**-*m*-Me at $t = 0$ could not be determined due to the delay of sampling time in the NMR measurement. The OH signals of **1**-*m*-Me disappeared right after the reaction was started ($t = 0$). At $t = 5000$ s, the two Me signals gave the intensities expected for the equilibrium mixture, and the α-H signal disappeared due to H/D exchange. The α-H signal of **2**-*m*-Me could not be detected. The time dependence of the signal intensities in Figure 3 indicates that the Me and α-H signals of **1**-*m*-Me decreased and the Me signal of **2**-*m*-Me increased at similar rates. In particular, it is important to point out that the pseudo-first-order rate constants for the decay of the Me and α-H signals of **1**-*m*-Me were calculated to be 9.76×10^{-4} and 9.73×10^{-4} s^{-1}, respectively, under the reaction conditions, showing that the α-H abstraction and the benzoin rearrangement occur at nearly the same rates.

The result, at first glance, appears to be consistent with mechanism A with the rate-determining 1,2-H shift. However, since the intensity of the α-H signal of **2**-*m*-Me was absent, this

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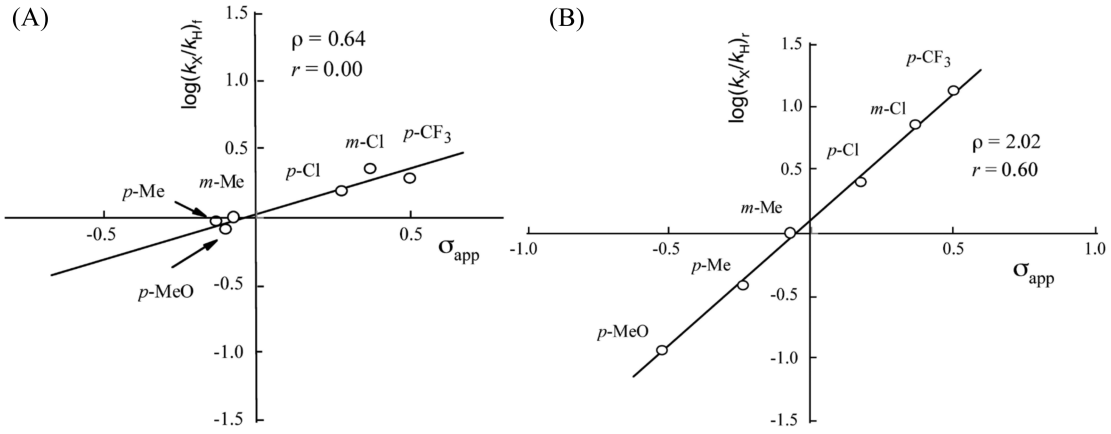
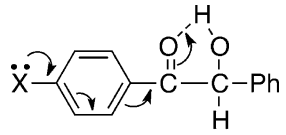


Figure 2. Hammett plots for the (A) forward and (B) reverse rate constants for the reaction of **1**-X and KOH in 70% (v/v) aqueous MeOH at 25.0 °C.

Chart 1



2-X

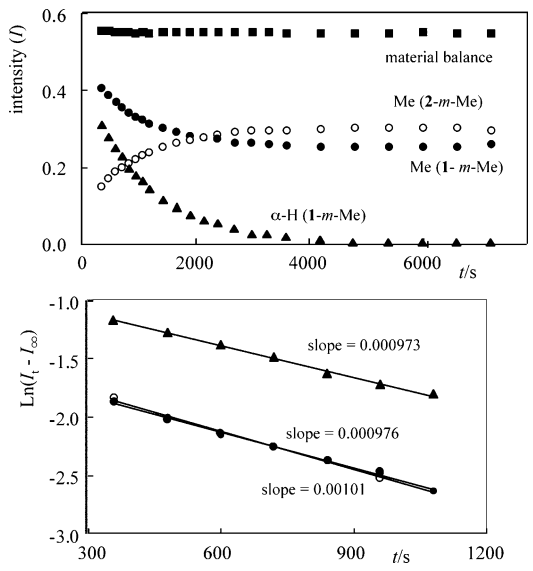


Figure 3. Time dependence of ^{1}H NMR intensities of Me and α-H signals of **1**-*m*-Me and **2**-*m*-Me and pseudo-first-order kinetic plots. [**1**-*m*-Me] = 10 mM, [KOH] = ca. 21 mM, and CD_3OD:D_2O = 7:3 (v/v).

mechanism requires much faster α-H/D exchange in **2**-*m*-Me than in **1**-*m*-Me, which is very unlikely. Alternatively, the reaction may proceed through the rate-limiting α-H abstraction in mechanism B to give a quasi-symmetrical enolate intermediate. The intermediate gives **2**-*m*-Me by the fractionation factor $k_2/(k_2 + k_{-1})$, and thus, k_f is given as $k_1k_2/(k_2 + k_{-1})$. Similarly, k_r is given as $k_{-1}k_{-2}/(k_2 + k_{-1})$. The fact that the H/D exchange rate in **1**-*m*-Me and the rate of the equilibrium mixture formation are essentially the same is consistent with mechanism B, since the latter rate constant is given by $k_f + k_r$, and hence, if the equilibrium constant K is near unity, then $k_f + k_r$ becomes similar to k_1 in eq 2b. When the reaction is downhill and K is larger than unity as in the case of the reaction from **1**-*p*-MeO to **2**-*p*-MeO, the mechanism requires that the rate toward the equilibrium mixture is only slightly smaller than the rate of α-H abstraction (see the Supporting Information).

The same kinetic experiments were carried out for the reverse process with **2**-*m*-Me as the starting material, and the results are illustrated in Figure 4. Two important points are

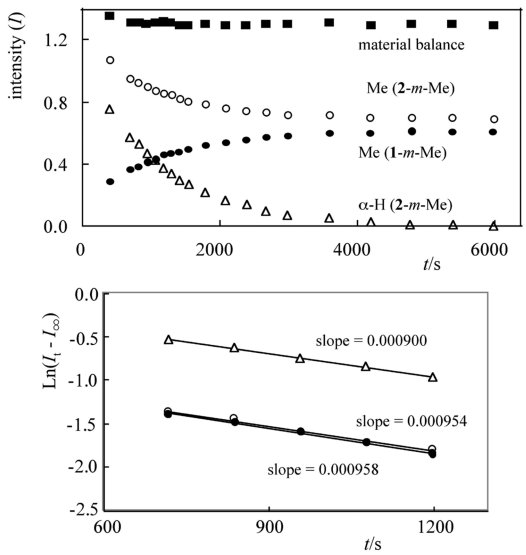


Figure 4. Time dependence of ^{1}H NMR intensities of Me and α-H signals of **2**-*m*-Me and **1**-*m*-Me and pseudo-first-order kinetic plots. [**2**-*m*-Me] = 11 mM, [KOH] = ca.19 mM, and CD_3OD:D_2O = 7:3 (v/v).

apparent in the plots. First, the rate of disappearance of the α-H signal of **2**-*m*-Me is similar to the rate of the rearrangement measured by intensity changes of the Me signals of **1**-*m*-Me and **2**-*m*-Me. Second, the α-H signal of **1**-*m*-Me did not show up in the NMR spectrum. Similar experiments were performed for **1**-*p*-MeO, **2**-*p*-MeO, **1**-*p*-Me, and **2**-*p*-Me in duplicate. The time dependence plots are shown in the Supporting Information, and the calculated rate constants are summarized in Table 2. In these measurements, the reaction temperature and the base concentration were not strictly controlled, and hence, comparison of the obtained rate constants is allowed only within each run. Nevertheless, the data in Table 2 clearly show that the pseudo-first-order rates of disappearance of **1**-X and the rates of appearance of **2**-X are the same, which are the rates of reaction toward the equilibrium states (k_{obsd}). Furthermore,

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Table 2. Pseudo-First-Order Rate Constants Determined by NMR for the Reactions of 1-X and 2-X in Deuterated Aqueous 70% (v/v) MeOH

X	$10^4k_1/s^{-1}$	10^4k_{obsd}(**1**-X)/s^{-1}	10^4k_{obsd}(**2**-X)/s^{-1}
1-*p*-MeO	10.9	9.82	9.88
	11.0	9.70	9.70
2-*p*-MeO	3.86	4.66	4.75
	5.14	7.77	7.54
1-*p*-Me	9.77	9.34	9.02
	7.12	6.27	6.37
2-*p*-Me	6.64	7.29	7.54
	7.22	6.89	7.96
1-*m*-Me	9.73	9.76	10.1
	7.98	9.25	9.67
2-*m*-Me	9.47	9.73	9.53
	9.00	9.54	9.58

the rates of α-H abstraction (k_1) are similar to k_{obsd}. These results clearly indicate that the rearrangement proceeds via mechanism B.

Solvent Deuterium Kinetic Isotope Effect. To obtain information on the role of the solvent, in particular a possible involvement of a proton-transfer relay mechanism, in the reaction, a proton-inventory experiment was carried out for **1**-*p*-MeO in aqueous methanol with different molar fractions of deuterated solvent.[7,8] The chemical meaning of k_{eq} in deuterated solvent is a little complex, since $k_{eq} = k_f + k_r$, and here k_f at the initial stage of the reaction is the rate constant of the reaction of nondeuterated **1**-*p*-MeO, whereas k_f at a later stage corresponds to the forward rate constant of α-deuterated **1**-*p*-MeO. Furthermore, k_r is the rate constant of the reaction of α-deuterated **2**-*p*-MeO in deuterated solvent. However, since k_f is large enough compared to k_r for **1**-*p*-MeO (Table 1), the size of the solvent deuterium kinetic isotope effects (KIEs) should primarily reflect the size of the isotope effect on the k_f step if the kinetic analyses were made only with the first half-life kinetic data. The equilibrium constant determined independently in the fully deuterated solvent was 7.84, which is identical with the constant in the nondeuterated solvent. By assuming that the equilibrium constant in a partly deuterated solvent is the same, the forward rate constant (k_f) could be calculated. The rate constants thus obtained are listed in Table 3.

The observed solvent KIE (k_H/k_D) was determined to be 0.43 (=2.85/6.58) for fully deuterated solvent. The magnitude of the solvent deuterium isotope effects is conveniently interpreted with isotopic fractionation factors, ϕ, which are given as the equilibrium constant in eq 4.[7] As shown in eq 4, ϕ is the preference for deuterium over protium in SL (L = H or D) relative to that in hydroxylic solvent, ROL. A number of fractionation factors have been experimentally determined and used to estimate the size of the solvent isotope effects.[7]

$$SH + ROD \rightleftharpoons SD + ROH \quad (4)$$

$$K = \frac{[SD]/[ROH]}{[SD]/[ROH]} = \frac{[SD]/[SH]}{[ROH]/[ROD]} = \phi \quad (5)$$

In the present reaction, the equilibrium isotope effect (K_H/K_D) for the proton-abstraction step from **1**-*p*-MeO and OH^-/OD^- is given by eqs 6 and 7. Since the isotopic fractionation factor for a C_{sp^3}–H bond is around unity, the deuterium equilibrium isotope effect (K_H/K_D) is calculated to be 0.5. Although the KIE should be somewhere between 0.5 and 1.0 depending on the position of the TS along the reaction coordinate, the observed KIE of 0.46 is qualitatively consistent with the mechanism assuming the rate-determining α-proton abstraction by OH^-/OD^- as discussed above.

$$SH + OL^- \rightleftharpoons S^- + HOL \quad (6)$$

$$\frac{K_H}{K_D} = \frac{\phi_{OL}\phi_{CL(sp3)}}{\phi_{HOL}} = \frac{0.5 \times 1.0}{1.0} = 0.5 \quad (7)$$

In Figure 5 is shown the plot of the rate constant (k_{eq}) vs the fraction of deuterium in the solvent system. The linear proton-inventory plot suggests that only one type of isotope effect contributes to the overall KIE, eliminating multiple active participation of solvent molecules.[8]

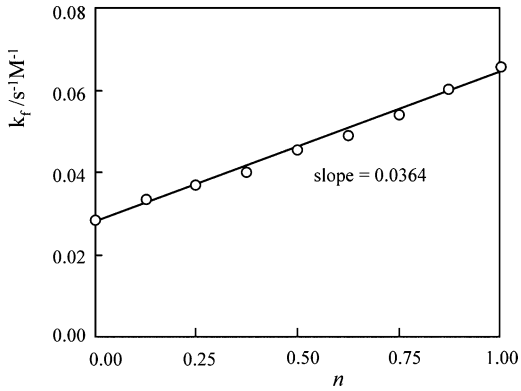

Figure 5. Proton-inventory plot for the reaction of **1**-*p*-MeO with KOH in 70% (v/v) aqueous MeOH at 25.0 °C.

In conclusion, all these results point to the mechanism in which the rearrangement is initiated with the rate-determining α-hydrogen abstraction rather than the mechanism with initial hydroxyl hydrogen abstraction as in the general α-ketol rearrangement.

Table 3. Rate Constants for Equilibration of 1-*p*-MeO with KOH in 70% (v/v) Aqueous MeOH at 25.0 °C with Variable D Content

n^a	$10^2k_{eq}/s^{-1}$ M^{-1}	$10^2k_f/s^{-1}$ M^{-1}	n^a	$10^2k_{eq}/s^{-1}$ M^{-1}	$10^2k_f/s^{-1}$ M^{-1}
0	3.21 ± 0.07	2.85 ± 0.06	0.657	5.55 ± 0.15	4.93 ± 0.13
0.125	3.79 ± 0.10	3.37 ± 0.09	0.750	6.09 ± 0.12	5.41 ± 0.11
0.250	4.15 ± 0.12	3.68 ± 0.11	0.875	6.77 ± 0.10	6.01 ± 0.09
0.375	4.50 ± 0.11	3.99 ± 0.09	1.00	7.42 ± 0.10	6.58 ± 0.09
0.500	5.11 ± 0.06	4.54 ± 0.05			

[a]Fraction of deuterated solvent.

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EXPERIMENTAL SECTION

Materials. Asymmetrically substituted benzoins **1**-X and **2**-X were synthesized either by the reaction of XC_6H_4CHO (X = H for preparation of **2**-X) with $SiMe_3CN$[4a] followed by the Grignard reaction with XC_6H_4MgBr (X = H for **1**-X)[4b] or by the reaction of PhCHO with $(EtO)_3P$ and Me_3SiCl followed by the reactions with LDA and then with XC_6H_4CHO.[4b]

Reactions. Methanol and water were fractionally distilled and degassed by bubbling N_2 gas for 1 h before use. The concentration of KOH solution was determined titrimetrically before use. All reactions were carried out strictly under N_2 conditions; otherwise, the reaction was deteriorated by oxidative side reactions.

Equilibrium Constants. As a typical example, a 70% (v/v) aqueous MeOH solution of **1**-*p*-Me (10 mM) and KOH of known concentration was allowed to react at 25.0 ± 0.1 °C for 10−20 half-lives. The reaction solution was poured into ice−water and extracted with ether. The ^{1}H NMR analysis of the intensities of the Me signals of **1**-*p*-Me and **2**-*p*-Me allowed one to calculate the relative abundance of **1**-*p*-Me and **2**-*p*-Me. The same measurement was carried out four times, two starting from **1**-*p*-Me and two from **2**-*p*-Me and with different KOH concentrations (8.79 and 19.1 mM). For *p*-MeO- and *m*-Me substituted-compounds, the Me signals were used, and for F-, Cl-, and CF_3-substituted compounds, the α-CH signals were used to calculate the relative abundance of **1**-X and **2**-X. Standard deviations for multiple measurements of the equilibrium constants are listed in Table 1.

Rate Measurements. The rates of the reactions were measured photometrically at 25.0 ± 0.1 °C in aqueous 70% (v/v) MeOH. As an example, a reaction solution of **1**-*p*-MeO (7.3 mM) and KOH (19.3 mM) was placed in a tightly sealed constant-temperature UV cell. Both the substrate and base solutions were fully bubbled with N_2 before mixing. The rate was measured by following the absorbance at 283 nm, at which the change of absorbance is largest during the reaction. A good linear first-order rate plot was obtained up to 2 half-lives with a correlation coefficient of better than 0.999. The experimental absorbance after enough reaction time (infinity absorbance) agreed well with that calculated from the extinction coefficients of **1**-*p*-MeO and **2**-*p*-MeO and the equilibrium constant measured separately. However, in some cases, these experimental and calculated infinity absorbances disagreed due to the occurrence of a side reaction (oxidation to benzil). In those cases, the calculated infinity absorbance was used to obtain pseudo-first-order rate constants. The effect of the base concentration on the rate was examined with **1**-*p*-Me, for which the rate constants showed a linear dependence on [KOH] with a near zero intercept.

Isotope Exchange Experiment. Reactions were carried out in deuterated 70% (v/v) D_2O−CD_3OD in an NMR tube at room temperature. For the reactions of **1**-*p*-MeO and **2**-*p*-MeO, the changes of the ^{1}H intensity of the MeO signals and α-H signals were followed with time with respect to the internal standard (PhMe). For the reactions of **1**-*p*-Me, **1**-*m*-Me, **2**-*p*-Me, and **2**-*m*-Me, PhOMe was used as the internal standard. The intensities of the signals of the starting materials relative to the internal standard at t = 0 could not be measured due to the elapsed time for measurement setting, and thus, data acquisition could be started only several minutes after mixing. Due to the H/D exchange of the α-H during the reaction, the kinetic analyses were made with data for the first half-life.

Solvent Isotope Effect. Reactions in deuterated solvent were carried out in either fully deuterated CD_3OD:D_2O = 7:3 (v/v) or in a preset mixture of CD_3OD:D_2O = 7:3 (v/v) and CH_3OH:H_2O = 7:3 (v/v) and were followed photometrically as described above. Reactions were followed for the first half-life.

ASSOCIATED CONTENT

Supporting Information

Results of isotope exchange experiments (Figures S1−S4) and kinetic equations. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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