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Aldol Condensation of Trifluoroacetophenone and Acetone: Testing a Prediction

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Abstract: Rate and equilibrium constants have been determined for both stages of the aldol condensation of acetone with trifluoroacetophenone. The extensive hydration of trifluoroacetophenone and the acid dissociation of the hydrate complicated the kinetic analysis. Dehydration of the intermediate ketol leads to two enones which equilibrate in base more rapidly than they undergo hydration to the ketol. This is consistent with interconversion via the enolate of the ketol, which loses OH^- faster than it undergoes C-protonation. The rate constant determined for the aldol addition step is in satisfactory agreement with the value predicted from a Marcus correlation {*J. Am. Chem. Soc.* **1991**, *113,* 7249−7255}.

Introduction

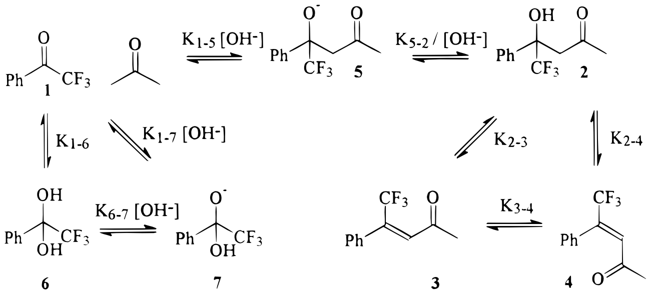
The aldol condensation is a very important synthetic reaction. Despite this importance there have been relatively few kinetic studies.[1] We have reported that both stages of the aldol condensation can be described in terms of the Marcus relation with the approximation of a constant intrinsic barrier for each stage.[1a] This allowed prediction of the rate constants for unknown aldol additions, and in particular the rate constant for the reaction of acetone with trifluoroacetophenone was predicted to be 10^4 times faster than the reaction of acetone with acetophenone. We now report a study of the kinetics of this reaction, showing that the prediction is correct.

There have been relatively few studies of substituent effects on the aldol addition reaction,[2−9] and most of those have addressed the effects of ring-substituted aromatic compounds. The present study of the detailed kinetics and equilibria for the acetone−trifluoroacetophenone system supplies a measure of the importance of the effects of polar substituents on the alkyl group of the ketone.

Results

The reactions studied are summarized in Scheme 1. Samples of the ketol and enone products were prepared. (*Z*)-2-Phenyl-1,1,1-trifluoro-2-penten-4-one (**3**) was prepared by the literature method.[10] 1,1,1-Trifluoro-2-hydroxy-2-phenyl-4-pentanone (**2**) was synthesized by a directed aldol reaction employing a preformed lithium enolate. (*E*)-2-Phenyl-1,1,1-trifluoro-2-penten-4-one (**4**) was prepared by photoisomerization of **3** followed by separation of the mixture of isomers by low-pressure column chromatography.

Scheme 1. Aldol Condensation of Acetone with Trifluoroacetophenone; Ketone Hydration/Dissociation and Ketol Dissociation Shown



General Strategy. The reaction system that was subjected to kinetics analysis is shown in Scheme 1. This system is complicated by hydration and ionization equilibria. Because of the complexity of this system we will first outline the strategy used to study the kinetics.

Because the aldol equilibria lie well to the side of starting materials, the kinetics of the reactions are most easily studied in the retroaldol sense, which results in much cleaner kinetics. The kinetics were followed by either UV spectrophotometry or HPLC analysis of quenched samples and fitted to single or double exponential equations as appropriate. When HPLC analysis was used, and the data supported it, simultaneous fitting of peak integrations of multiple species from multiple experiments was used to obtain the best fit to all of the available data.

In aqueous base, isomerization of enones was observable as a kinetic phase faster than hydration. The isomerization equilibrium constant could be determined by analysis of HPLC data. It is a striking feature of the kinetics that isomerization is fast relative to hydration. This requires that the ketol not be an intermediate on the reaction path from *E*-enone to *Z*-enone. This observation was also made in a study of the corresponding condensation of acetone with acetophenone.[11] The suggested mechanism is shown in Scheme 2 where attack of hydroxide on enone gives the enolate corresponding to the ketol. Most

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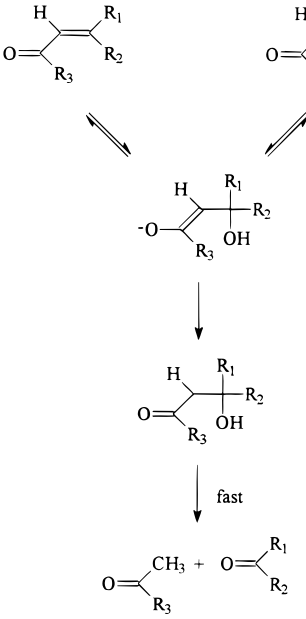
Scheme 2. Base-Catalyzed Enone Hydration and Retroaldol Mechanism



often this is followed by reversal: expulsion of hydroxide ion to give one or the other enone. Protonation at carbon to give ketol proceeds at a slower rate. A second, kinetically equivalent isomerization mechanism with γ-proton removal followed by isomerization was also considered.[11] There is no γ-proton for the aldol product of acetone with trifluoroacetophenone, which rules out the second mechanism and suggests that the first mechanism is likely to be the correct one in this and the earlier studies.

Hydroxide-catalyzed retroaldol cleavage of the ketol was studied by UV spectrophotometry or by HPLC analysis of quenched samples. In no experiment was there an accumulation of dehydration product. The reactions were always pseudo-first order. For **2** the pK_a was within the pH range of interest so the pK_a was determined from the pH rate profile for the retroaldol reaction. This had the added benefit that the first-order rate constant for the retroaldol cleavage of the ketolate was determined.

HPLC analysis of equilibrated solutions of ketones in aqueous buffer or hydroxide was used to determine the aldol formation equilibrium constants. Except for some acetone self-aldol, the condensation of acetone with trifluoroacetophenone cannot be complicated by competing aldol reactions because trifluoroacetophenone lacks α-hydrogens. It was complicated by extensive hydration of the trifluoroacetophenone and pK_a's of the trifluoroacetophenone hydrate and product ketol within the pH region of interest. The self-aldol condensation of acetone has been studied previously[12] and was not examined in this work. It is known to proceed only to a minor extent under our conditions.[12]

Kinetics of Isomerization. Now we will turn to a detailed examination of the kinetics, starting with the isomerization of the enones. The kinetics of isomerization of the enones **3** and **4** were studied by injecting *E*-enone into dilute alkaline solution and following the appearance of the *Z*-enone chromophore by UV spectrophotometry. Experiments starting with *Z*-enone were unsuccessful because the equilibrium strongly favors the *Z*-enone and as a consequence the resulting absorbance change was too small for accurate kinetics. The observed rate constants are then the sum of the forward and reverse rate constants for isomerization and are summarized in Table 1. The isomerization was considerably faster than hydration which was observable as a second kinetic phase at longer times.

Table 1. Rate Constants for the Hydroxide-Catalyzed Isomerization of (*E*)-2-Phenyl-1,1,1-trifluoro-2-penten-4-one (**4**)[a]

10^3[OH$^-$] (M)	α	β	$10^3\lambda$ (s^{-1})	λ/[OH$^-$] (M^{-1} s^{-1})
99.6	0.502	1.075	253.2 ± 3.3	2.542 ± 0.033
99.6	0.041	0.165	180.4 ± 4.7	1.811 ± 0.047
9.91	0.580	0.792	18.23 ± 0.01	1.839 ± 0.001
9.91	0.579	0.637	18.01 ± 0.01	1.818 ± 0.001
9.91	0.566	0.777	17.98 ± 0.01	1.815 ± 0.001
9.96	0.408	1.042	18.3 ± 0.1	1.842 ± 0.015
9.96	0.529	0.693	18.23 ± 0.04	1.830 ± 0.004
9.96	0.512	0.671	18.54 ± 0.01	1.861 ± 0.001
9.96	0.495	0.643	17.65 ± 0.03	1.772 ± 0.003
1.17[b]	0.522	0.721	2.503 ± 0.001	2.135 ± 0.001
1.17[b]	0.512	0.712	2.421 ± 0.001	2.066 ± 0.001
1.17[b]	0.520	0.714	2.426 ± 0.001	2.069 ± 0.001
0.1352[b]	0.526	0.744	0.2878 ± 0.0003	2.129 ± 0.002
0.1352[b]	0.510	0.725	0.2893 ± 0.0003	2.140 ± 0.002
				av 1.94 ± 0.04

[a] In aqueous solution at 25.0 °C, ionic strength 0.1 (KCl), followed by UV spectrometry at 245 nm. [*E*-enone]$_i$ = 91 μM. Data were fitted to the following: $A = \alpha + \beta \exp(-\lambda t)$. Standard deviations for the parameters are calculated by the least-squares procedure. Average value is the weighted mean. [b] [OH$^-$] determined by measurement of buffer pH; [OH$^-$] = $10^{(\mathrm{pH}-14)}$.

The kinetics were also followed in pH 10 borate buffers by HPLC analysis of quenched samples, starting with both *Z*- and *E*-isomers. The separation achieved by HPLC allowed isomerization to be followed in both directions. HPLC peak integration−time data were fit simultaneously to the system

$$A \rightleftharpoons B$$

for reaction in both directions, allowing determination of both the forward and reverse rate constants and hence the equilibrium constant. The rate and equilibrium constants obtained from these experiments are the following: $k_{3-4}[\mathrm{OH}^-] = (8.22 \pm 0.16) \times 10^{-6}$ s^{-1}, $k_{4-3}[\mathrm{OH}^-] = (3.22 \pm 0.05) \times 10^{-4}$ s^{-1}, and $K_{3-4} = (2.55 \pm 0.07) \times 10^{-2}$. The HPLC data obtained are plotted in Figure 1 with the lines of best fit determined by the method of least squares. The scale for the experiment starting with *Z*-enone is expanded to improve readability.

An additional experiment used HPLC analysis of equilibrated solutions of enones to determine the equilibrium constant. The enones were rapidly equilibrated in 0.1 M aqueous sodium hydroxide, quenched, and then analyzed. The results were the same whether starting with the *E*-enone or *Z*-enone. The equilibrium constant determined was $K_{3-4} = (3.08 \pm 0.08) \times 10^{-2}$ with negligible hydration to ketol at short times. This equilibrium constant is significantly different than that obtained at pH 10. Because the enone peaks are not completely resolved by HPLC, it was necessary to use PEAKFIT,[13] a mathematical curve-fitting program, to fit the peaks and thus to estimate the peak areas. Since the *Z*-enone peak was much larger than the *E*-enone peak, it is probable that studying only the equilibrated solutions resulted in a systematic error in quantitation. The

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(11) (a) Guthrie, J. P.; Wang, X. P. *Can. J. Chem.* **1992**, *70*, 1055−1068. (b) This result seems counterintuitive but follows from the existence of an intermediate common to the interconversion of **3** and **4** and the (slower) conversion of either to **2**. Therefore $K_{3-4} = k_{3-2}/k_{4-2}$. There is of course only one k_{obs} for hydration of the equilibrating system, but it may be expressed in terms of either k_{3-2} or k_{4-2}.

(12) Koelichen, K. *Z. Phys. Chem.* **1900**, *33*, 129−177.

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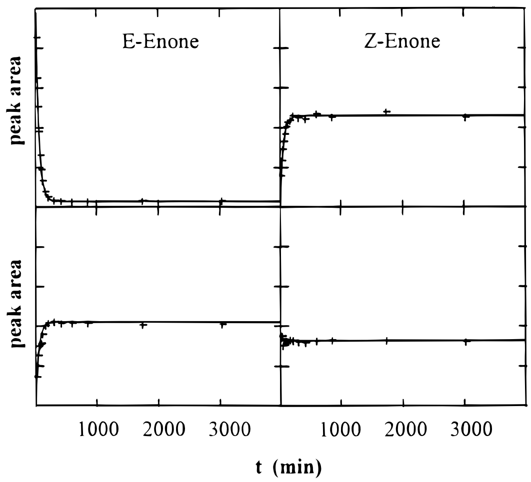


Figure 1. *E*−*Z* isomerization of 2-phenyl-1,1,1-trifluoro-2-penten-4-one in pH 10 borate buffer. Vertical axes are scaled for viewing convenience. For reaction starting with *E*-enone, full scales are as follows: *E*-enone 19.9 mM, *Z*-enone 50.3 mM. For reaction starting with *Z*-enone, full scales are as follows: *E*-enone 1.0 mM, *Z*-enone 50.3 mM.

Table 2. Rate Constants for the Hydroxide-Catalyzed Hydration of (*Z*)-2-Phenyl-1,1,1-trifluoro-2-penten-4-one (**3**)[a]

$[OH^-]^b$ (M)	α	β	$10^5\lambda$ (s^{-1})	$10^4\lambda/[OH^-]$ ($M^{-1}\ s^{-1}$)
0.100	0.152	0.796	1.661 ± 0.001	1.668 ± 0.001
0.100	2.026	0.483	1.739 ± 0.005	1.746 ± 0.005
0.100	2.023	0.477	1.639 ± 0.002	1.646 ± 0.002
0.100^c	0.000	0.467	1.614 ± 0.002	1.621 ± 0.002
0.050	0.091	0.798	0.816 ± 0.003	1.638 ± 0.007
0.050	0.104	0.798	0.846 ± 0.004	1.698 ± 0.007
				av 1.658 ± 0.012

[a] In aqueous solution at 25.0 °C, ionic strength 0.1 (KCl), followed by UV spectrophotometry at 245 nm. Data were fitted to the following: $A = \alpha + \beta \exp(-\lambda t)$. Standard deviations for the parameters are calculated by the least-squares procedure. Average value is the weighted mean. [b] Determined by titration against standardized aqueous hydrochloric acid. [c] Hydration phase of *E*−*Z* isomerization/hydration starting with *E*-enone.

kinetics study at pH 10 where peaks of varying size are being fit should be less susceptible to this systematic error. For this reason the equilibrium constant determined from the HPLC data at pH 10 is considered the most accurate.

It follows from Table 1 and K_{3-4} that the second-order rate constants for the hydroxide-catalyzed isomerization of the enones are as follows: $k_{3-4} = (4.83 \pm 0.15) \times 10^{-2}\ M^{-1}\ s^{-1}$ and $k_{4-3} = 1.89 \pm 0.03\ M^{-1}s^{-1}$.

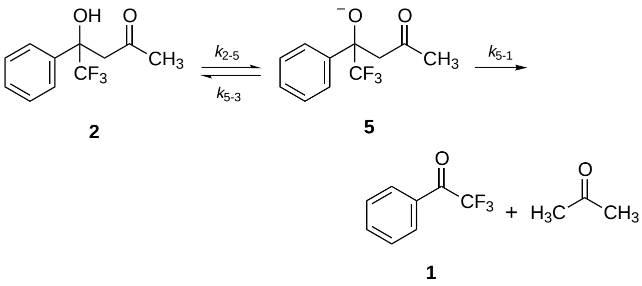
Kinetics of Enone Hydration. The kinetics of *Z*-enone hydration were followed by UV spectrophotometry and were found to be first order in hydroxide concentration. The data are summarized in Table 2. *E*-enone isomerization experiments, when followed for extended times, showed a second kinetic phase with a rate consistent with enone hydration. Because the hydration is the hydration of a mixture of *E*- and *Z*-enones, and because the hydration of both proceeds through a common intermediate, the hydration rates of each can be calculated. This is because it has been shown[11] that $k_{obs} = 2k_{3-2}/(1 + K_{3-4})$ and similarly $k_{obs} = 2k_{4-2}/(1 + K_{4-3})$. The second-order rate constants for hydroxide-catalyzed hydration are then $k_{3-2} = (8.09 \pm 0.06) \times 10^{-5}\ M^{-1}\ s^{-1}$ and $k_{4-2} = (2.1 \pm 0.9) \times 10^{-6}\ M^{-1}\ s^{-1}$.

Retroaldol Cleavage. The retroaldol cleavage of ketol **2** was studied under pseudo-first-order (excess base or buffered) conditions by HPLC analysis of quenched samples. The disappearance of the ketol peak in the HPLC showed first-order kinetics and was followed for at least 3 half-lives for pH >11. At pH 10 and 11, initial rate kinetics were used observing the first 10% of reaction. The rate constants obtained (see Table 3) allow the construction of a pH rate profile (Figure 2). Dehydration was not detected when starting with ketol, and retroaldol cleavage was essentially complete and pseudo-first order. Therefore, extracting the relevant portions from Scheme 1, the reaction can be considered as:

Table 3. Rate Constants for the Hydroxide-Catalyzed Retroaldol Cleavage of 1,1,1-Trifluoro-2-hydroxy-2-phenyl-4-pentanone (**2**)[a]

$[OH^-]^b$ (M)	$[KETOL]_i^c$ (mM)	α	β	$10^6\lambda$ (s^{-1})
0.0983	1.94	−0.00	1.02	12.8 ± 0.2
0.0934	0.986	0.02	1.04	13.0 ± 0.4
0.0483	2.19	0.07	2.42	13.1 ± 0.6
0.0460	0.918	−0.03	1.04	10.8 ± 3.0
0.0244	0.977	0.03	1.05	9.80 ± 0.18
0.0091	2.17	0.00	2.22	5.24 ± 0.41
0.0047	1.28	0.00	1.35	3.37 ± 0.03
0.0024	0.467	0.14	0.41	2.60 ± 0.08
0.0012^d	1.00	1.44	−1.7E−06	1.16 ± 0.03
0.00020^d	1.06	1.06	−2.7E−07	0.25 ± 0.01
0.00014^d	1.00	1.47	−2.7E−07	0.183 ± 0.003

[a] In aqueous solution at 25 °C, ionic strength 0.1 (KCl), followed by HPLC analysis on quenched samples; disappearance of the peak due to ketol, **3**, was followed. Data were fitted to the following: $[ketol] = \alpha + \beta \exp(-\lambda t)$ unless otherwise noted. [b] $[OH^-]$ determined by titration, or from calculation of dilution with degassed water. [c] [ketol] determined from the mass of ketol added. [d] $[OH^-]$ determined by measurement of buffer pH; initial rate kinetics fit to $[ketol] = \zeta + \eta t$; thence $\lambda = -\eta/\zeta$ (ζ in mM).



Ketol deprotonation is a rapid equilibrium, so that $k_{obs} = k_{5-1}/(1 + K_{5-2}/[OH^-])$. Fitting the data from Table 3 with weighted nonlinear least squares to this equation gives $k_{5-1} = (1.50 \pm 0.09) \times 10^{-5}\ s^{-1}$, $K_{5-2} = K_w/K_a^{ketol} = (1.4 \pm 0.1) \times 10^{-2}$ M, and $K_a^{ketol} = (6.5 \pm 0.5) \times 10^{-13}\ M^{-1}$ ($pK_a = 12.19 \pm 0.04$). Therefore, since $k_{2-1} = k_{5-1}/K_{5-2}$ the second-order rate constant for base-catalyzed retroaldol of the ketol is $(9.7 \pm 1.0) \times 10^{-4}\ M^{-1}\ s^{-1}$.

Kinetics and Equilibria for Ketol Formation and Dehydration. Ketol and enone formation were followed in the forward direction by mixing trifluoroacetophenone and acetone in aqueous base or buffer and following the appearance of products by HPLC. Trifluoroacetophenone was difficult to quantify because of severe peak tailing in the HPLC. This is presumably because of the ketone−hydrate equilibrium, and the best separations are obtained at lower temperatures where this equilibration is slowed. Elevated temperatures (to 40 °C) resulted in more tail than peak while ice temperature gave a tail that did not severely affect the quantitation of the ketol. Early method development with methanol−water eluent with stock solutions of ketone in either water or methanol showed what appeared to be hemiacetal formation and breakdown on

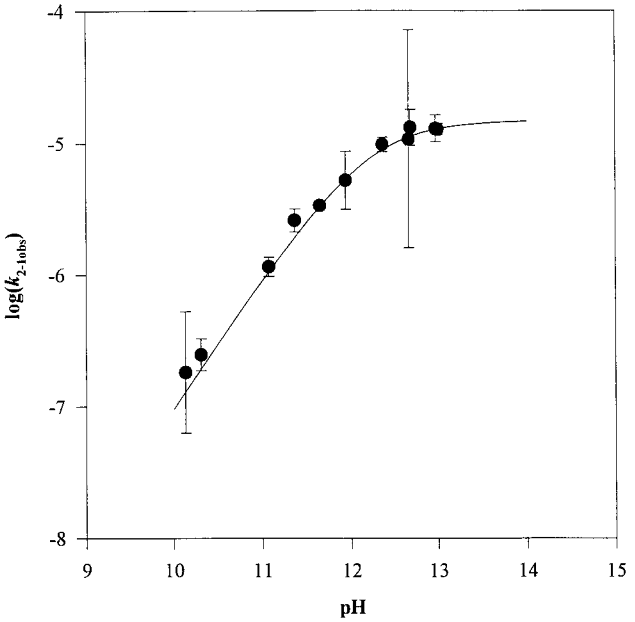


Figure 2. pH dependence of apparent first-order rate constants for retroaldol cleavage of 1,1,1-trifluoro-2-hydroxy-2-phenyl-4-pentanone (**2**).

the column. The ratios of peaks and magnitude of absorbance between the peaks were dependent on the composition of both injection solvent and eluent. Acetonitrile−water mixtures showed promise so that the earlier system was abandoned, but its peculiarities support the hydration explanation for tailing.

It seemed imprudent to rely on the peak areas or peak heights from trifluoroacetophenone because of peak tailing. The equilibrium concentration of trifluoroacetophenone was taken as its initial concentration, determined by mass used, minus the concentration of ketol present, as determined by HPLC. This undoubtedly introduces error, but that error can be estimated. The trifluoroacetophenone peak was followed and agreed approximately with the calculated concentration.Trifluoroacetophenone also undergoes slow haloform cleavage with a half-life of 160 h in 0.1 M hydroxide solution.[14] This effect is ignored in these calculations. Acetone condenses with itself to give diacetone alcohol and mesityl oxide. The HPLC showed the presence of side products including acetone self-condensation products, identified by comparison to authentic samples, which were ignored in the quantitation. Calculations of the effect of self-aldol on the acetone concentration based on known rates and equilibrium constants[12,15] showed the effect would only be a few percent. This effect is ignored in the calculations.

First-order growth of the ketol peak was observed and followed for several half-lives. Nonlinear least squares was used to determine both the apparent rate constants and the equilibrium concentration of ketol. Only the equilibrium concentration is of interest in this treatment. The apparent equilibrium constant, defined as $K_{\text{app}} = [\text{ketol}]_{\text{total}}/([\text{TFA}]_{\text{total}}[\text{acetone}])$, is pH dependent because the pK_a's of both the trifluoroacetophenone hydrate and the ketol are in the pH range studied. Following Scheme 1, the theoretical pH equilibrium profile should follow:

$$K_{\text{app}} = K_{1-2}(1 + K_{5-2}[\text{OH}^-])/(1 + K_{1-6} + K_{1-7}[\text{OH}^-]) \quad (1)$$

where $K_{1-6} = 77.6$ and $K_{1-7} = 7.76 \times 10^5\ \text{M}^{-1}$ as determined by Stewart,[16,17] and $K_{5-2} = K_w/K_a = (1.4 \pm 0.1) \times 10^{-2}$ M as determined above. The results of the formation reactions are summarized in Table 4. K_{1-2} was determined for each experiment by correcting K_{app} for hydration and pH effects, and the weighted mean of the individual experiments is $K_{1-2} = (2.657 \pm 0.003) \times 10^3\ \text{M}^{-1}$. K_{app} as a function of pH is shown in Figure 3, along with the theoretical line.

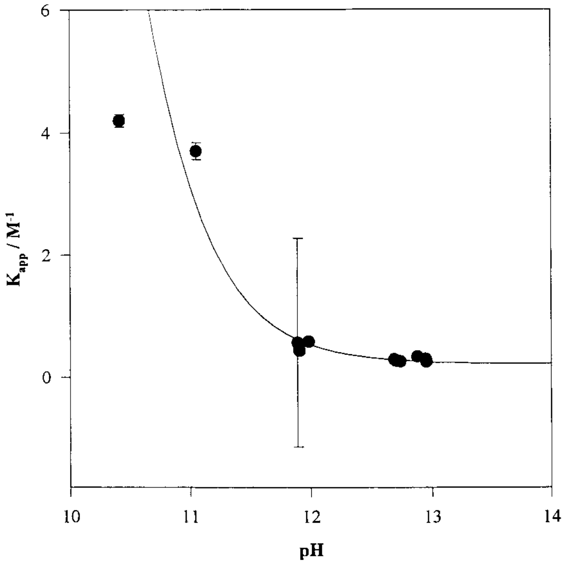


Figure 3. Apparent equilibrium constant as a function of pH for the aldol reaction of acetone with trifluoroacetophenone.

The point at the lowest pH in the aldol formation equilibrium profile shows a very significant deviation from the line. The HPLC data showed a possible decrease in the trifluoroacetophenone concentration that had not occurred in other runs. If the TFA concentration estimated by inspection of the HPLC results is used to calculate the observed equilibrium constant, the point falls much closer to the line. To avoid inconsistency, this was not done, but it seems likely that there are systematic errors for this point.

The approach to equilibrium between ketol and enones is expected to be slow except at high pH. At high pH, however, the equilibrium is shifted in favor of the ketol by its conversion to ketolate. As a result, detection of the enones was very difficult, and our estimates of enone concentration at equilibrium are correspondingly imprecise. The best compromise was a hydroxide concentration near 0.05 M. HPLC analysis of equilibrated solutions did not resolve the peaks from the two enones so that a hybrid calibration constant calculated by using the measured calibration constants for the two enones and the isomerization equilibrium constant was used.

In this way the dehydration equilibrium constants were determined: $K_{2-3} = (4.3 \pm 0.4) \times 10^{-3}$ and $K_{2-4} = (1.1 \pm 0.1) \times 10^{-4}$. The rate and equilibrium constants determined for the hydroxide-catalyzed reactions in the aldol condensation of acetone with trifluoroacetophenone are summarized in Table 5.

Discussion

With the aldol condensation of acetone with trifluoroacetophenone fully characterized, the ability of the Marcus relation to predict aldol reaction rates and substituent effects on the aldol reaction can be assessed.

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Table 4. Apparent Aldol Formation Constants for the Reaction of Acetone with Trifluoroacetophenone[a]

10^2 [TFA]^b (M)	[OH$^-$]^b (M)	10^3[ketol]$_e$^{c}	10^2[TFA]$_e$^{d} (M)	[acetone]$_e$^{d}	pH^e	K_{app}^{f} (M^{-1})	10^{-3} K_{calc}^{g} (M^{-1})
2.050 ± 0.002	0.1	5.518 ± 0.039	1.498	1.076	12.87	0.342 ± 0.029	3.40 ± 0.28
1.007 ± 0.002	0.1	2.320 ± 0.016	0.775	0.998	12.94	0.300 ± 0.019	3.06 ± 0.19
1.021 ± 0.002	0.1	0.710 ± 0.009	0.950	0.291	12.95	0.256 ± 0.001	2.62 ± 0.01
1.020 ± 0.002	0.1	0.257 ± 0.009	0.994	0.098	12.95	0.264 ± 0.000	2.698 ± 0.003
1.016 ± 0.002	0.06	2.317 ± 0.024	0.784	0.998	12.68	0.296 ± 0.023	2.69 ± 0.21
0.528 ± 0.002	0.06	0.602 ± 0.007	0.467	0.490	12.73	0.263 ± 0.004	2.45 ± 0.04
1.012 ± 0.002	0.06	0.763 ± 0.011	0.936	0.291	12.69	0.281 ± 0.001	2.56 ± 0.01
1.020 ± 0.002	0.06	0.268 ± 0.004	0.993	0.099	12.70	0.271 ± 0.000	2.481 ± 0.001
1.020 ± 0.002	0.02	3.18 ± 0.01	0.702	0.997	11.90	0.453 ± 0.032	1.88 ± 0.13
1.011 ± 0.002	0.02	3.66 ± 0.69	0.645	0.996	11.89	0.6 ± 1.7	2.32 ± 6.95
1.126 ± 0.002	0.02	1.26 ± 0.05	1.000	0.289	11.91	0.434 ± 0.005	1.81 ± 0.02
1.013 ± 0.002	0.02	0.515 ± 0.003	0.962	0.091	11.98	0.587 ± 0.000	2.728 ± 0.001
0.505 ± 0.002	0.00113	3.36 ± 0.13	0.169	0.538	11.05	3.70 ± 0.14	3.29 ± 0.23
0.510 ± 0.002	0.00026	3.53 ± 0.14	0.157	0.537	10.41	5.47 ± 0.06	1.484 ± 0.016
							av 2.656 ± 0.034

[a] In aqueous hydroxide or buffer solution at 25.0 °C; ionic strength maintained at 0.1 M with KCl; analysis by HPLC. [b] Concentration as added to reaction flask. [c] Equilibrium concentration of ketol determined by HPLC analysis. [d] Concentration corrected for formation of ketol. [e] pH calculated from hydroxide concentration corrected for consumption by TFA hydrate and ketol. [f] [ketol]$_e$/([TFA]$_e$[acetone]$_e$). [g] K_{1-2} calculated from eq 2.

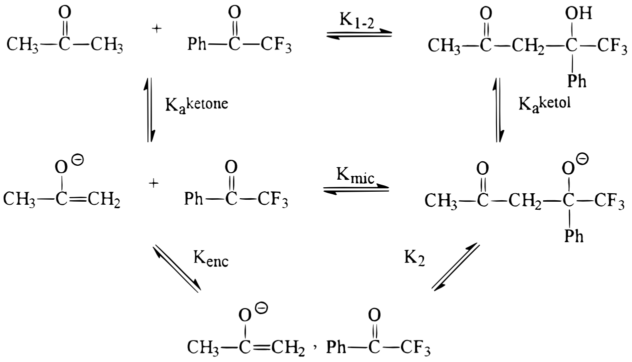
Table 5. Summary of Rate and Equilibrium Constants for the Hydroxide-Catalyzed Aldol Condensation of Acetone with Trifluoroacetophenone

constant	value
K_{1-2}^{a}	$(2.66 \pm 0.03) \times 10^3$ M^{-1}
k_{1-2}^{b}	2.75 ± 0.25 M^{-2} s^{-1}
k_{2-1}^{c}	$(1.03 \pm 0.09) \times 10^{-3}$ M^{-1} s^{-1}
K_{2-3}^{d}	$(4.3 \pm 0.4) \times 10^{-3}$
k_{2-3}^{e}	$(3.5 \pm 0.3) \times 10^{-7}$ M^{-1} s^{-1}
k_{3-2}^{f}	$(8.09 \pm 0.06) \times 10^{-5}$ M^{-1} s^{-1}
K_{2-4}^{d}	$(1.09 \pm 0.10) \times 10^{-4}$
k_{2-4}^{e}	$(2.3 \pm 1.0) \times 10^{-10}$ M^{-1} s^{-1}
k_{4-2}^{f}	$(2.1 \pm 0.9) \times 10^{-6}$ M^{-1} s^{-1}
K_{3-4}^{g}	$(2.55 \pm 0.07) \times 10^{-2}$
k_{3-4}^{h}	$(4.83 \pm 0.15) \times 10^{-2}$ M^{-1} s^{-1}
k_{4-3}^{h}	(1.89 ± 0.03) M^{-1} s^{-1}
K_{5-2}^{i}	$(1.44 \pm 0.11) \times 10^{-2}$ M^{-1}
other constants	
K_a^{ketol}^{j}	$(6.9 \pm 0.5) \times 10^{-13}$ M^{-1}
$k_{3-4} + k_{4-3}$^{k}	(1.94 ± 0.03) M^{-1} s^{-1}

[a] Determined from aldol formation reactions. [b] Calculated from $k_{1-2} = k_{2-1} \times K_{1-2}$. [c] Determined from hydroxide-catalyzed retroaldol. [d] Determined by equilibrium concentration in aldol formation. [e] Calculated from $k_{2-3} = k_{3-2} \times K_{2-3}$; $k_{2-4} = k_{4-2} \times K_{2-4}$. [f] Calculated from the observed hydration rate constant with $k_{3-2} = k_{obs}/(2(1 + K_{3-4}))$; $k_{4-2} = k_{obs}/(2(1 + K_{4-3}))$. [g] Determined from HPLC analysis of enone equilibration. [h] Determined from UV and HPLC studies of isomerization; values calculated by $k_{3-4} = k_{obs}/(1 + 1/K_{3-4})$; $k_{4-3} = k_{obs}/(1 + K_{3-4})$. [i] Determined from the ketol retroaldol pH rate profile. [j] Calculated from $K_a = K_w/K_{5-2}$. [k] Observed second-order rate constant from enone isomerizations.

Table 6 summarizes the predicted [1a] and observed equilibrium and rate constants for the aldol reaction studied, as well as revised predicted rate constants. These were calculated in the same way as the originally predicted[1a] rate constants but using the experimentally determined instead of estimated equilibrium constants. The detailed calculations are summarized in Table S1, and were based on the analysis shown in Scheme 3.

Scheme 3. Thermodynamic Cycles Used To Derive the Equilibirum Constant Needed for the Marcus Analysis of the Aldol Addition of Acetone to Trifluoroacetophenone



The estimated K_{1-2} and ketol pK_a values, as used in the original predictions for the aldol reaction of acetone with trifluoroacetophenone, were both significantly different from those determined in this study. By using the experimentally determined values, the prediction using the Marcus relation is significantly closer to the observed rate constants: within 0.44 log units for the retroaldol rate. There is another significant source of uncertainty in these calculations. The calculated K_{1-2} is very sensitive to the hydration equilibrium constant for TFA and the pK_a of the hydrate. Changing the values of either of these constants results in significant changes in the calculated K_{1-2}. Therefore the uncertainty in K_{1-2} for this reaction is more realistically about 0.5 log units. Despite these uncertainties, both the revised and original estimates gave predictions which were within approximately an order of magnitude.

K_{1-2} is very sensitive to substitution on the electrophile. With acetone as nucleophile, an equilibrium enhancement of 6.14 log units can be achieved by changing from acetophenone to trifluoroacetophenone as electrophile. The rate constant for

Table 6. Comparison of Predicted and Measured Equilibrium and Hydroxide-Catalyzed Rate Constants for the Aldol Reactions[a]

		log(K_{1-2}/M^{-1})^a		log(k_+/M^{-2} s^{-1})^b			log(k_-/M^{-1} s^{-1})^b		
nuc	elec	pred	meas	pred^c	rev^d	meas	pred^c	rev^d	meas
acetone	TFA	2.47	3.42	0.48	0.90	0.44	−1.99	−2.52	−2.99

[a] Equilibrium constant for the formation of neutral ketol from neutral ketone plus neutral ketone. [b] Observable macroscopic rate constant; $v_{forward} = k_+$[HO$^-$][acetone][TFA]$_{free}$.; $v_{reverse} = k_-$[HO$^-$][ketol]$_{neutral}$. [c] Predicted value[1a] based on estimated equilibrium constants, and an average value for the intrinsic barrier. [d] Revised predicted values are estimated rate constants based on the aldol formation constants determined in this work, including the kinetic pK_a for the ketol, and an average value for the intrinsic barrier.[1a]

aldol addition is also very sensitive to substituents in the carbonyl electrophile. The enhancement in log k_{mic} on going from acetophenone to trifluoroacetophenone is 3.90 log units.

Although trifluoroacetophenone is far more reactive in terms of the microscopic rate constant, it is actually less reactive in terms of the observable behavior under normal synthetic conditions because so much of the total trifluoroacetophenone is tied up as the carbonyl hydrate anion. In terms of the free ketones the rate ratio is $2.75/(3.41 \times 10^{-4}) = 8065$; in terms of the total concentration of ketone (free, hydrated, or as the hydrate anion) at 0.1 M HO^- the rate ratio is $(2.96 \times 10^{-6})/(3.41 \times 10^{-5}) = 0.0866$. The calculation for total ketone concentration used the apparent pseudo-second-order rate constants for 0.1 M HO^-.

This work demonstrates that large substituent effects can be found for the aldol reaction when the nature of the carbonyl electrophile is changed. This is in accord with the normal behavior of carbonyl compounds toward nucleophilic addition.[20]

We have also demonstrated that it is possible to predict the rate constant for an unknown aldol addition, even when it differs very considerably in reactivity from the model compounds. The prediction was based on the rates and equilibrium constants for the reactions of CH_2O, CH_3CHO, PhCHO, and CH_3COCH_3 as electrophiles with CH_3CHO, CH_3COCH_3, and $PhCOCH_3$ as nucleophiles, and represents a predicted rate enhancement of 4 orders of magnitude over the reaction of acetone with acetophenone. This is a further demonstration of the utility of the Marcus relation for correlation and prediction of rate constants for organic reactions, and in particular for synthetically useful reactions such as the aldol condensation.

Tools for making organic chemistry a more predictive science are now at hand, and further developments of these methods should have significant benefits both to the science and to its applications.

Experimental Section

Materials. Solvents and salts were BDH reagent grade unless otherwise noted. All other chemicals were from Aldrich. THF was dried by refluxing over sodium, and distilling. Acetone was spectrophotometric grade and was used without further purification.

Methods. Least-squares analysis was carried out with FORTRAN programs developed in this lab using the methods of Bevington[21] and Deming.[22] Linear fits used weighted values for both independent and dependent variables. Nonlinear fitting assumed that the independent variable was free from error, but used weighted dependent variables.

Extensive modifications were made to the nonlinear least-squares programs in the course of this work. Provision was made for the imposition of constraints on any parameter(s). This allowed parameters not well-defined by the data to be constrained to be close to independently determined values so that a better fit to the other parameters could be obtained. The method used is described by Deming.[24]

The program used to simultaneously fit multiple species in multiple experiments uses functions of the individual microscopic rate constants to determine observable rate constants and preexponential terms for the change in concentration/integration of each species. This allows the determination of both rate constants in an equilibrium, for example, where otherwise three separate calculations would be required: calculation of the observed rate constant, calculation of the equilibrium constant, and the determination of the individual microscopic rate constants from the observed rate and equilibrium constants. Simultaneous fitting is a particular advantage when considering a cyclic equilibrium where the observable preexponentials and rate constants are complicated functions of the individual rate constants. Simultaneous fitting also allows each set of data to act as a constraint on the others, which results in much better fits when some of the data are of poor quality.

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Supporting Information Available: Preparation and spectroscopic data for compounds **2**, **3**, and **4**; general methods and kinetics procedures; table of detailed Marcus relation calculations of rate constants for the aldol reactions (9 pages, print/PDF). See any current masthead page for ordering information and Web access instructions.

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[18] On the basis of the reported rate constant for acetone plus acetophenone,[11] the pK_a for acetone,[19] and the rate constant for the reaction of acetone plus trifluoroacetophenone, Table 5, log k_{mic} = log k_{obs} + pK_a(acetone) − 14.00.

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