Kinetics of the Thiazolium Ion-Catalyzed Benzoin Condensation

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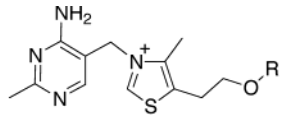
The formation of benzoin (Ph-CHOH-CO-Ph) from two molecules of benzaldehyde, catalyzed by 3-benzyl-5-(2-hydroxyethyl)-4-methylthiazolium bromide in methanol buffered with Et_3N/Et_3NH^+-Cl^- has been studied. Initial-rate studies at various concentrations of PhCHO (0.1−1.7 M) showed that the reaction is close to being first order in PhCHO. Following the reaction in deuteriomethanol, ^{1}H NMR spectroscopy allowed rate constants for all three kinetically significant steps to be determined. These show that all three steps are partially rate-determining. A normal deuterium kinetic isotope effect for the overall reaction ($k_H/k_D \approx 3.4$) is observed using PhCDO, and a large inverse solvent isotope effect ($k_D/k_H \approx 5.9$) is observed using deuteriomethanol, consistent with the kinetic scheme presented here.

Introduction

It has been known since 1943 that thiamin (**1**) and

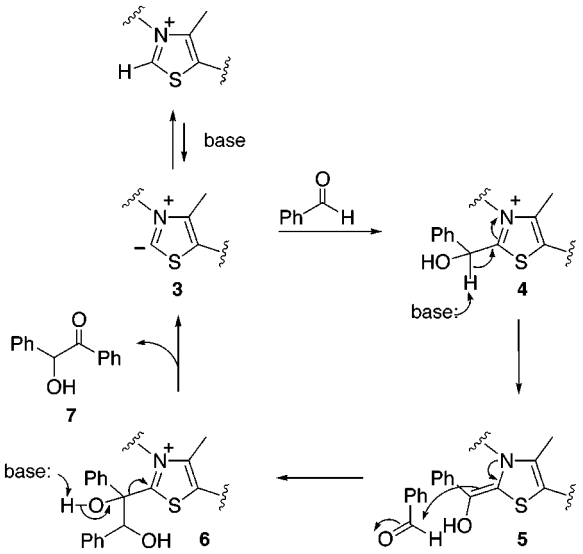


1 R = H, Thiamin
2 R = $P_2O_6^{3-}$, Thiamin diphosphate

related thiazolium salts can catalyze the benzoin condensation in the presence of mild base.[1] The mechanism that is generally accepted (Scheme 1) was first proposed by Breslow[2] and is analogous to the mechanism of the cyanide-catalyzed reaction proposed in 1903 by Lapworth.[3] Although alternative mechanisms have been proposed, these have been effectively ruled out by spectroscopic and kinetic studies.[4,5] The mechanisms of enzymic reactions that use thiamin diphosphate (**2**) as a coenzyme are believed to be similar.

The cyanide-catalyzed benzoin condensation has been studied in great detail, and rate constants for all the kinetically significant steps have been available since 1971.[6] It is surprising, therefore, that the same is not true for the thiazolium salt-catalyzed reaction, even though the latter is more synthetically useful because it works with enolizable and non-enolizable aldehydes and the catalyst can be made asymmetric.[7] The kinetics of

Scheme 1. Mechanism of the Thiazolium Salt-Catalyzed Benzoin Condensation



the overall reaction have been studied several times with different thiazolium salts under different conditions, but there is disagreement as to whether the reaction is second order with respect to PhCHO[8−10] or first order[11] or some combination of the two.[12,13]

We present here a more thorough investigation of the kinetics of the thiazolium salt-catalyzed benzoin condensation than has previously been reported. Both initial-rate studies at low catalyst concentrations and ^{1}H NMR studies at stoichiometric catalyst concentrations have been used, and these have allowed the rate constants of all kinetically significant steps to be determined.

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Results

Initial-Rate Studies at Low Catalyst Concentration. The majority of the previous studies of the kinetics of the thiazolium salt-catalyzed benzoin condensation[8−10,12,13] have followed the reaction over time, starting with a fixed concentration of benzaldehyde. They have then attempted to fit first- or second-order rate equations to the data. We feel this approach is unacceptable for several reasons.

(a) The order of the reaction may change with the changing concentration of PhCHO. Application of steady-state kinetics to the mechanism of Scheme 1 gives a rate equation of the form

$$\text{rate} = \frac{k_{cat}[\text{PhCHO}]^2[\text{catalyst}][\text{base}]}{a + b[\text{PhCHO}] + c[\text{PhCHO}]^2} \qquad (1)$$

where *a*, *b*, and *c* are constants made up of all the rate constants of the individual steps and the concentrations of the base and its conjugate acid. It can be seen from this equation that the rate could show a sigmoid dependence on [PhCHO]: At very low [PhCHO], the term *a* will be the only significant one in the denominator, and the rate will be proportional to [PhCHO]^2; at a sufficiently high [PhCHO], the term *c*[PhCHO]^2 will be the significant one, and so the rate will be independent of [PhCHO]; and between these two extremes, there should be a region where the reaction is first order with respect to [PhCHO]. This middle region may be short or long depending on whether *b* is large or small with respect to *a* and *c*.

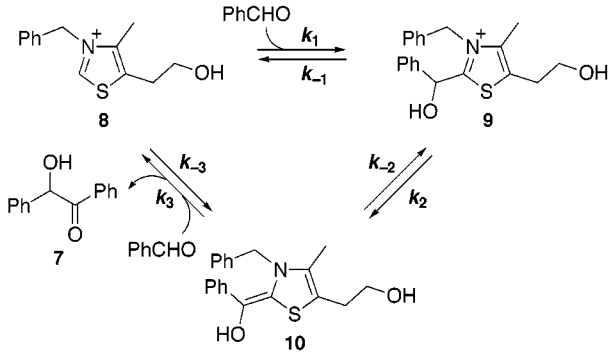
(b) The catalyst may not be entirely stable over the course of the reaction. Our experience with thiazolium salts is that in some cases the reactions tend to stop before reaching completion, and relatively high levels of catalyst are required to obtain reasonable yields.[7]

(c) The reaction may be slowed by side-products. One known side-product, resulting from aerial oxidation of enamine **5** (the "active-aldehyde" intermediate), is benzoic acid.[5] This would protonate some of the base used and thus slow the reaction. Even a relatively small amount of $Et_3NH^+Cl^-$ is known to cause a marked decrease in rate when Et_3N is used as the base.[12]

(d) The equations used for the progress of second- and first-order reactions assume that the reaction is irreversible. While the equilibrium is known to favor benzoin, it is also known that the reverse reaction can be observed,[11] and thus, this assumption is not valid.

The above difficulties in following the reaction over an extended period are not unique to thiazolium salt-catalyzed reactions. Enzymic reactions show all the same problems, and it is for this reason that studies of enzyme kinetics are always based on initial rates measured at various concentrations of substrate. It was decided, therefore, to conduct an initial-rate study on the benzoin reaction. There has been one previous report of an initial-rate study, but this was applied to complex macrocyclic thiazolium salts containing a cavity for binding the substrate.[11] With these substrates, sigmoid kinetics were observed.[17] It was particularly interesting, therefore, to find out whether a simple thiazolium salt shows similar sigmoid kinetics (as it could do, according to eq 1) or more straightforward first- or second-order kinetics, as other authors have claimed.

Scheme 2. Catalyst and Kinetic Model Used in This Work



The catalyst chosen for this study was the most readily available one, previously used by many other research groups, 3-benzyl-5-(2-hydroxyethyl)-4-methylthiazolium bromide (**8**) (Scheme 2). This is commercially available but in this study was made by the simple alkylation of the corresponding thiazole with benzyl bromide.[15] The solvent chosen was methanol, again the most commonly used solvent, with Et_3N as the base buffered with $Et_3NH^+Cl^-$. Other workers have used a [Et_3N]:[$Et_3NH^+Cl^-$] ratio of 9:1,[10,13] but a ratio of 2:1 was chosen for this study to give a better buffer capacity. A temperature of 50 °C was chosen in accordance with other studies.[8,9,18,19]

Two methods were used to follow the reaction, UV absorbance at 320 nm and reverse-phase HPLC. Both methods gave essentially the same rates. In common with other workers,[5,12,13] we observed no dimerization of the catalyst (which gives an interfering UV absorbance)[8] provided benzaldehyde was present. The HPLC method, though slower, has the advantage that possible side-products, such as benzaldehyde dimethyl acetal and methyl benzoate,[5] could be detected and would not contribute to the measurement of benzoin produced. No traces of these side-products could be detected (occasionally, a very small amount of benzoic acid could be detected, but this seems to have been present in the starting benzaldehyde and did not increase during the reaction).

The initial rates were measured for benzaldehyde concentrations ranging from 0.086 to 1.74 M, with the concentration of catalyst kept constant at 0.03 M. As can be seen from Figure 1, the initial rate essentially increases linearly with [PhCHO] over this whole range.

We conclude that under our experimental conditions the reaction is essentially first order with respect to PhCHO. It is tempting to conclude that previous studies that found the reaction to be second order in PhCHO were wrong due to the factors outlined in b−d. All three of these factors would tend to make a first-order reaction appear more like a second-order reaction because of a

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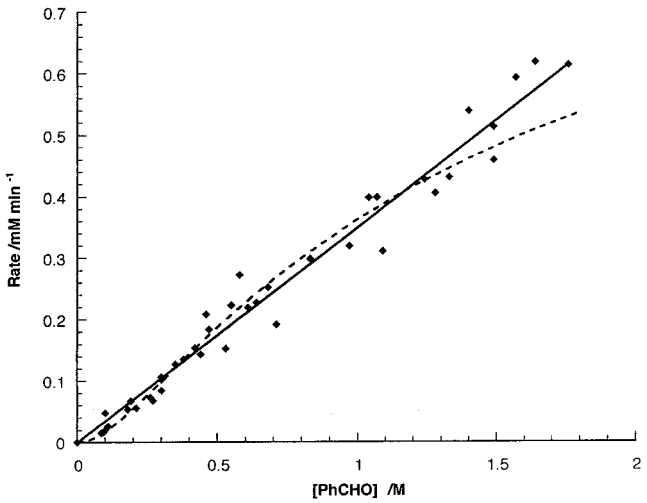


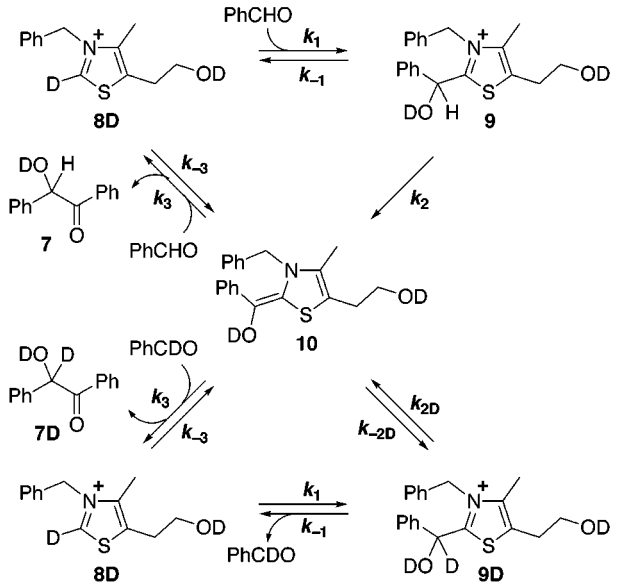
Figure 1. Rate of benzoin formation at different concentrations of PhCHO. The solid line (—) is the best fit of the first-order equation, rate = k[PhCHO]. The dashed line (– –) is the calculated rate using $k_1 = 0.14$ M^{-1} min^{-1}, $k_2 = 0.035$ min^{-1}, $k_{-1} = 0.025$ min^{-1}, $k_{-3} = 0.01$ M^{-1} min^{-1}, and $k_3/k_{-2} = 1$ M^{-1}.

slowing of the rate toward the end of the reaction that is not simply due to the decreased [PhCHO]. However, one should note that some of the previous studies used DMSO[10] or water/DMSO[9] as solvent instead of methanol, while others used unbuffered Et_3N.[8,12] Indeed, it has been claimed that the reaction is second order in PhCHO when Et_3N alone is used but first order when $Et_3NH^+Cl^-$ is added.[12]

^{1}H NMR Studies at Stoichiometric Catalyst Concentrations. There are three reasonably simple scenarios that could account for the observed, essentially first order, dependence with respect to [PhCHO]. The first is that attack of the ylide **3** on the first benzaldehyde molecule to form the 2-(α-hydroxybenzyl)thiazolium salt (HBT) **4** is the rate-determining step. The second is that deprotonation of HBT **4** is rate-determining, and formation of HBT is a rapid equilibrium that favors starting materials (so that the concentration of HBT is proportional to [PhCHO]). The third possibility is that the attack of the enamine **5** on the second benzaldehyde molecule is rate-determining, and the first step is a rapid equilibrium that favors products (so that the catalyst is present almost entirely as HBT). Interconversion between the thiazolium salt and the ylide **3** is very rapid under these conditions and need not be considered as a separate step in our kinetic scheme (Scheme 2). We reasoned that it would be possible to distinguish between the three possibilities by ^{1}H NMR spectroscopy (provided that separate signals for the free catalyst and the adduct could be identified) and by studying deuterium isotope effects.

The ^{1}H NMR experiments were conducted in deuteriomethanol with $Et_3N/Et_3NH^+Cl^-$ at a probe temperature of 27 °C, using approximately equal concentrations of catalyst **8** and PhCHO (0.3 M). Both benzaldehyde and benzoin show singlets well-separated from other signals in this mixture, at δ 9.99 and 6.13, respectively, but these cannot be used to reliably measure the concentrations of these compounds because exchange of the aldehydic hydrogen atom can occur, by reversal of steps 2 and 1, and then, incorporation of PhCDO into benzoin leads to

Scheme 3. Kinetic Model for the Benzoin Condensation in CD_3OD[a]



[a] Reprotonation of the active aldehyde intermediate **10** leads to the deuterated HBT **9D** rather than to **9**. This step has a primary deuterium isotope effect associated with it.

deuterated product also (see Scheme 3). Instead, the doublets for the aromatic protons ortho to the carbonyl groups in benzaldehyde and benzoin, at δ 7.90 and 7.95, respectively, were used to quantify these compounds while the singlets at δ 9.99 and 6.13 were used to measure the extent of deuteration.

Immediately after the start of the reaction, a new set of signals began to appear, which corresponded to those reported for HBT **9**.[20] These appear at δ 6.80 (2H, d, J = 8 Hz, *o*-Hs on one of the phenyl groups),[21] 6.39 (1H, s, α-H), 5.60 and 5.78 (each 1H, d, J = 17 Hz, N^+CH_2), and 2.26 (3H, s, 4-Me). The doublet at δ 6.80 and the singlet for the 4-methyl group at δ 2.26 were used to measure the concentration of the HBT **9**, and the singlet at δ 6.39 was used to assess its level of deuteration. The 4-methyl group of the free catalyst **8** at δ 2.46 was used to measure its concentration. The last ^{1}H NMR spectrum, taken after 150 min, is shown in Figure 2. It can be seen that the compounds mentioned above are the only significant components and that the signals are all well-resolved, including those of the free thiazolium salt **8**, which indicates that there has been no significant degradation of the catalyst.

No signals were observed for the enamine **10**, implying that one or more of the reactions of this compound are fast as compared to the reaction that forms it. Similarly, no signals attributable to the benzoin adduct (as **6**) were observed, and so the kinetic models (Schemes 2 and 3) have been simplified by treating the formation of benzoin **7** from enamine **10** as a single step.

The integrals of the various peaks in the spectrum were converted into concentrations by taking the sum of the concentrations of free thiazolium salt **8** and HBT **9**

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(21) This is probably the N-benzyl group because 2-(α-hydroxybenzyl)thiamin **11** does not show a similar doublet upfield of the other aromatic protons, but 6′-H on the pyrimidine ring is shifted 1.4 ppm upfield relative to its position in thiamin.

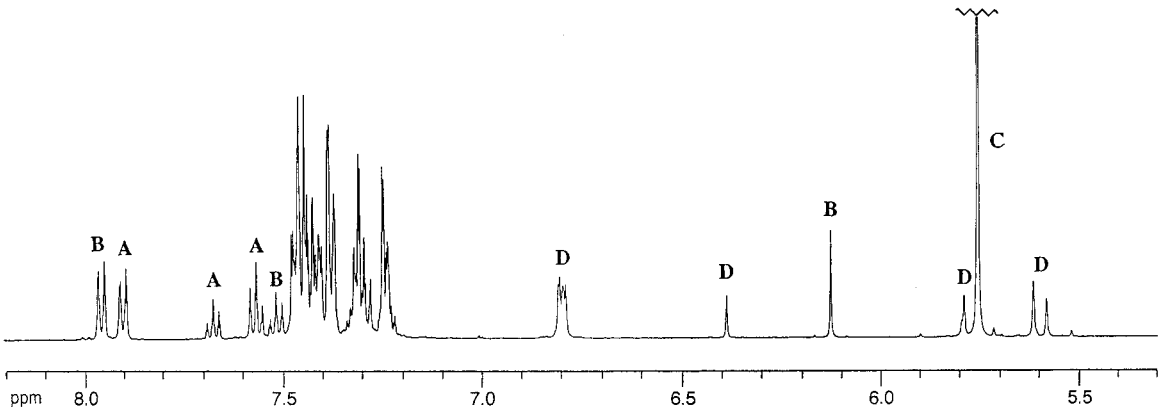


Figure 2. Part of the ^{1}H NMR spectrum of the reaction mixture for the benzoin condensation of PhCHO in CD_3OD taken after 150 min of reaction. Relevant peaks are marked as follows: A, benzaldehyde; B, benzoin; C, catalyst **8**; and D, HBT **9**.

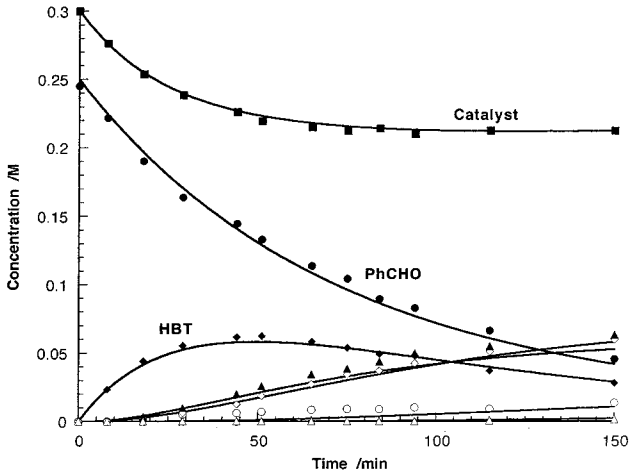


Figure 3. Concentration of the components of the benzoin condensation of PhCHO in CD_3OD plotted against time: ■, free catalyst **8**; ●, PhCHO; ◆, HBT **9**; ◇, deuterated HBT **9D**; ▲, benzoin; ○, PhCDO; △, deuterated benzoin. All concentrations were measured by NMR spectroscopy. The lines are the concentrations calculated by the kinetic simulation using the rate constants shown in Table 1.

to be equal to the known initial thiazolium salt concentration. All other concentrations were calculated relative to this value using the ratios of the relevant integrals. Spectra were recorded at intervals over 2.5 h, and the results are shown graphically in Figure 3. It is immediately apparent that none of the three simple kinetic scenarios presented above are correct; formation of the HBT is not a rapid preequilibrium, nor is it the slow rate-determining step. The other important point to notice is that the rate of accumulation of the deuterated HBT **9D** is very similar to that of benzoin **7**. This implies that, at this concentration of PhCHO and in deuteriomethanol as the solvent, enamine **10** gets partitioned almost equally between going on to benzoin and returning to HBT.

A kinetic simulation of these data was performed using a standard spreadsheet with 300 steps of 1 min each. The various rate constants were adjusted to get the best fit to the data, as judged by the RMS deviation from the experimental data. The resulting calculated curves, the solid lines shown in Figure 3, fit the data well. It should be noted that a substantial deuterium isotope effect on the deprotonation/reprotonation step (k_2 and k_{-2}) was required to reproduce the observed accumulation of the deuterated HBT **9D** at the expense of the undeuterated form **9**. The rate constants from the simulation that gave the curves shown were as follows: $k_1 = 0.046\ M^{-1}\ min^{-1}$, $k_{-1} = 0.0043\ min^{-1}$, $k_2 = 0.0192\ min^{-1}$, $k_3/k_{-2} = 1\ M^{-1}$, $k_{-3} = 0.001\ M^{-1}\ min^{-1}$, and k_H/k_D for $k_2 = 6.5$ (Scheme 2). All secondary isotope effects were assumed to be negligible. The values of k_{-3} and k_H/k_D should not be taken as particularly accurate because small changes to these had little effect on the resulting curves. However, the other values are reasonably reliable (±10%) because each affects different parts of the resulting curves. Thus, the value of k_1 is determined by the initial rate of loss of PhCHO and increase of HBT; the value of k_2 is determined by the subsequent rate of formation of benzoin plus deuterated HBT; the value of k_3/k_{-2D} is determined by the ratio of benzoin to deuterated HBT; and the value of k_{-1} is determined by the rate of formation of PhCDO from the deuterated HBT.

To confirm these results, three further experiments were performed under the same conditions but using (i) CH_3OH in place of CD_3OD, (ii) PhCDO in place of PhCHO, and (iii) both CH_3OH and PhCDO. The experiments using CH_3OH as the solvent were followed by reverse-phase HPLC, which detected benzaldehyde and benzoin but not the free catalyst **8** or the HBT **9**. However, the concentration of HBT at time t could be assumed to be equal to the "missing" benzaldehyde, i.e., $[HBT]_t = [PhCHO]_0 - [PhCHO]_t - 2[benzoin]_t$. The concentration of free catalyst is then given by $[catalyst]_t = [catalyst]_0 - [HBT]_t$. The reaction with PhCDO in CD_3OD was followed by ^{1}H NMR as before. The results of these time-course experiments are shown in Figures 4−6, and the derived rate constants are given in Table 1.

It can be seen from Table 1 that the derived rate constants are similar in all four experiments except that (i) the rate constants k_1, k_{-1}, and k_2 are approximately twice as fast in the experiments in CD_3OD as in the experiments in CH_3OH, presumably the result of a solvent isotope effect and (ii) the deuterium isotope effect of 6.5 on step 2 is not relevant in the experiment which has no deuterium in the solvent or reagent.

Figure 7 shows a graph of benzoin produced vs time for all four experiments. The rate of benzoin production is reasonably constant after an initial lag (while HBT accumulates) and before the PhCHO is nearly all consumed. From the slopes of these almost linear regions of

Table 1. Rate Constants That Gave the Best Fit to the Experimental Data Calculated Using a Simulation Based on the Kinetic Model Shown in Scheme 3

solvent	aldehyde	[aldehyde], M	[catalyst], M	k_1, M^{-1} min^{-1}	k_{-1}, min^{-1}	k_2, min^{-1}	k_3/k_{-2}, M^{-1}	k_{-3}, M^{-1} min^{-1}	k_H/k_D on step 2	RMS deviation
CD_3OD	PhCHO	0.25	0.3	0.046	0.0043	0.0192	1.0	0.001	6.5	0.003 82
CH_3OH	PhCHO	0.36[a]	0.3[a]	0.028	0.0025	0.0070	1.0	0.001		0.004 50
CH_3OH	PhCDO	0.28	0.3	0.026	0.0023	0.0090	1.0	0.001	6.5	0.005 23
CD_3OD	PhCDO	0.235	0.3	0.051	0.0044	0.0200	1.0	0.001	6.5	0.004 95

[a] A repeat of this experiment at slightly higher concentrations of PhCHO (0.45 M) and catalyst (0.4 M) gave very similar rate constants.

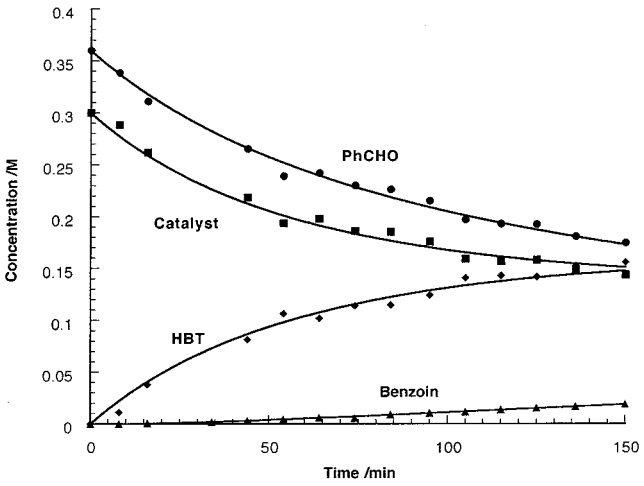


Figure 4. Concentration of the components of the benzoin condensation of PhCHO in CH_3OH plotted against time: ■, free catalyst **8**; ●, benzaldehyde; ◆, HBT **9**; ▲, benzoin. The concentrations of benzaldehyde and benzoin were measured by HPLC; the other concentrations were obtained by subtraction as described in the text. The lines are the concentrations calculated by the kinetic simulation using the rate constants shown in Table 1.

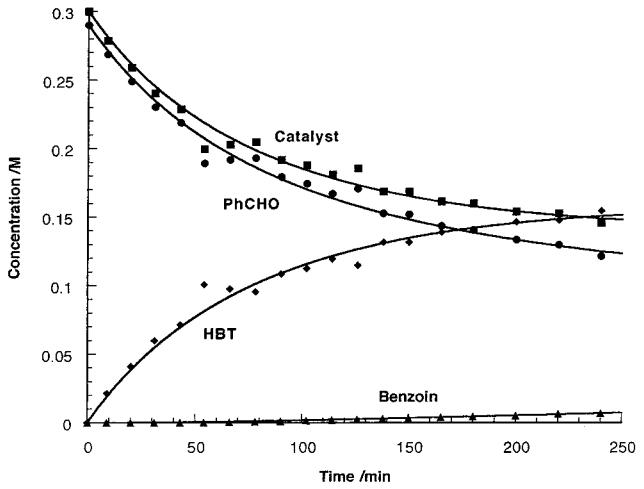


Figure 5. Concentration of the components of the benzoin condensation of PhCDO in CH_3OH plotted against time: ■, free catalyst **8**; ●, benzaldehyde; ◆, HBT **9**; ▲, benzoin. The concentrations of benzaldehyde and benzoin were measured by HPLC; the other concentrations were obtained by subtraction as described in the text. The lines are the concentrations calculated by the kinetic simulation using the rate constants shown in Table 1.

each graph, deuterium kinetic isotope effects on the overall reaction rate have been calculated. The substrate isotope effect (PhCHO vs PhCDO) was approximately 3.4 (average of the two values in the different solvents after correcting for the differing starting concentrations),

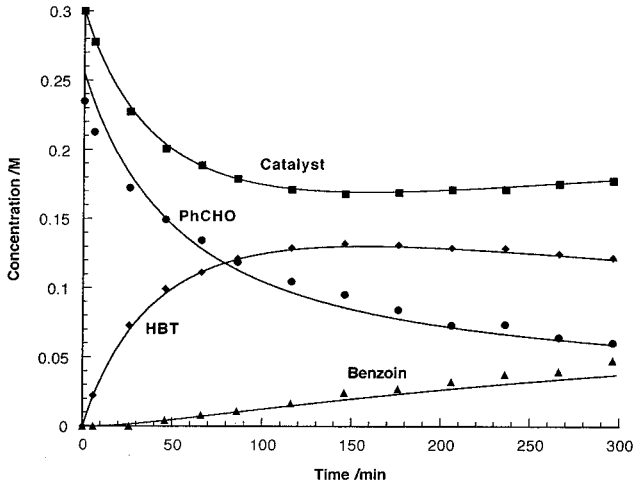


Figure 6. Concentration of the components of the benzoin condensation of PhCDO in CD_3OD plotted against time: ■, free catalyst **8**; ●, PhCDO; ◆, deuterated HBT **9D**; ▲, deuterated benzoin. All concentrations were measured by NMR spectroscopy. The lines are the concentrations calculated by the kinetic simulation using the rate constants shown in Table 1.

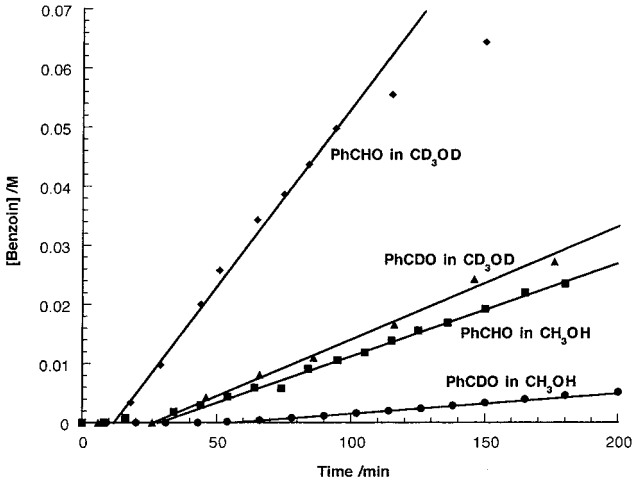


Figure 7. Formation of benzoin plotted against time for the four experiments (see Figures 3−6).

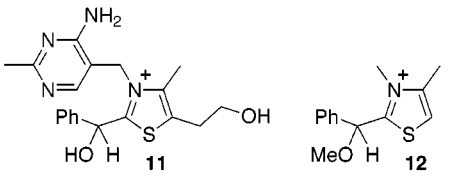
whereas the inverse solvent isotope effect (CD_3OD vs CH_3OH) was approximately 5.9 (average of the two values for the different aldehydes). Taken together, these two isotope effects mean that the rate of reaction of PhCHO in CD_3OD is 20× faster than that of PhCDO in CH_3OH.

The large inverse solvent isotope effect is the result of slowing down the reprotonation of enamine **10**, i.e., k_{-2}. This means that more of the enamine goes forward to form benzoin and less goes back to HBT **7**. This result confirms the conclusion that both the k_2 and the k_3 steps

are partially rate-determining; therefore, the overall rate of reaction is sensitive to the partition ratio, k_3/k_{-2}, for the enamine.

Discussion

The rate constants derived here are consistent with (and extend) a study of 2-(α-hydroxybenzyl)thiamin **11** that was made many years ago.[19] In that work, it was



found that in 0.6 M Tris buffer at pH 8.1 at 50 °C exchange of the α-proton (k_2) occurred with a half-life of ca. 24 min and that reversion to thiamin had a half-life of 115 min, giving a ratio of ca. 5:1 (cf. our ratio of 9:1). In the presence of 0.15 M PhCHO (solvent MeOH−H_2O, 1:3), benzoin was produced at an initial rate that would have given a half-life of 86 min (though deviation from first-order kinetics was noted before this half-life was reached). This is 3.5× slower than the deprotonation step, implying partitioning of the enamine intermediate in a ratio of 2.5:1 in favor of reprotonation to give **11**. When the buffer strength was halved to 0.3 M, the rate of benzoin production also halved, suggesting general base catalysis in the deprotonation step. Our observed partition ratio at this [PhCHO] is ca. 7:1 using a buffer strength of 0.16 M.

Another more recent study looked at the base-catalyzed oxidation of HBT **9** by quinones.[20] This reaction involves a rapid oxidation of the enamine **10** by the quinone and is zero order in oxidant, the rate-determining step being the deprotonation of the HBT.[22] This study used sodium acetate/acetic acid buffers in methanol and also observed general base catalysis. The measured rate of the general base-catalyzed reaction was ca. 2.5×10^{-4} [AcO^-][HBT] M s^{-1}. Thus, at the same concentration of base as we used, 0.106 M, the acetate-catalyzed reaction is ca. 5× slower than the Et_3N-catalyzed deprotonation that we measured. This is consistent with the higher pK_a of Et_3NH^+ as compared with AcOH (in methanol, the pK_a of AcOH is 9.44,[23] whereas the pK_a of Et_3NH^+ is expected to be similar to its value in water, 11.0).

Our results are also consistent with a study of the deprotonation of the 2-(α-methoxybenzyl)-3,4-dimethylthiazolium ion **12** by hydroxide.[24] This found that deprotonation occurred at ca. 1.1 min^{-1} at pH 14. Our deprotonation rate is much slower, but we are using a much weaker base. In water, Et_3NH^+ has a pK_a of 11.0, and so the 2:1 mixture of Et_3N/Et_3NH^+ that we used would have a pH of 11.3. At this pH, the rate of deprotonation of **12** would be 0.0022 s^{-1}, 5.5× slower than the deprotonation of **9** that we measured. A deuterium isotope effect on this step of ca. 6 was measured[24] and was also consistent with our findings.

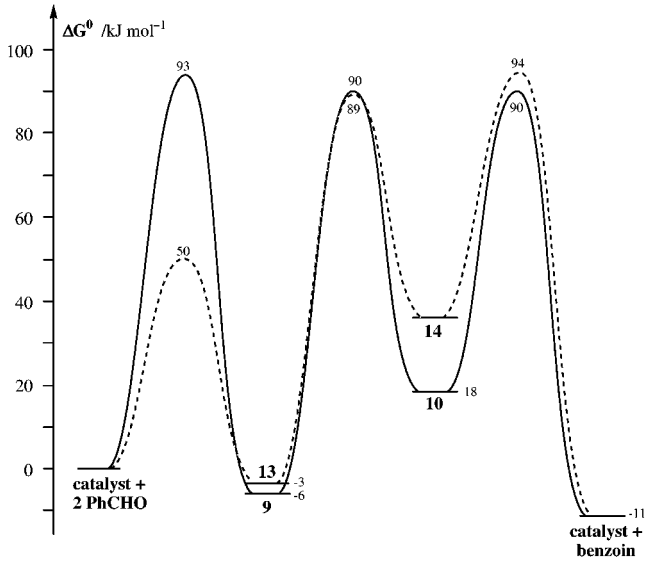


Figure 8. Free-energy profile for the thiazolium-catalyzed (—) and cyanide-catalyzed (− −) benzoin condensations at 27 °C and [PhCHO] = 1 M. The free energies for each reaction are given relative to the energy of its starting materials. The data for the cyanide-catalyzed reaction are calculated from ref 6. The relative free energy of the carbanion **14** is not known, and this intermediate has been put in an arbitrary position in this figure for illustrative purposes only.

One question that remains to be answered is whether the essentially first-order kinetics that we observed at low [catalyst] are consistent with the rate constants from the kinetic simulations. To allow for the difference in temperature (50 °C instead of 27 °C), larger values for the rate constants were assumed. For the associative steps (k_1 and k_2), the rate constants were increased by a factor of 5, whereas for the dissociative step (k_{-1}) the rate constant was increased by a factor of 10. The ratio k_3/k_{-2} was left unchanged because both are associative steps. The rates of benzoin formation over the period of 5−55 min were then calculated using the kinetic simulation. The resulting curve for variation in rate with [PhCHO] is given in Figure 1 (− −). This curve fits our data well at low [PhCHO] but seems to slightly underestimate the rate at [PhCHO] > 1.5 M. One reason for this may be that at these high concentrations of PhCHO the concentration of the solvent, methanol, is significantly reduced. This may slow the reprotonation of the enamine **10** and hence promote formation of benzoin.

The rate constants derived from the kinetic simulations allow free energies of activation to be calculated using the Eyring equation. The resulting free-energy profile is shown in Figure 8. The energy of the enamine **10** has been calculated to be ca. 24 kJ mol^{-1} above that of HBT **9** from the reported estimates[24,25] for the pK_a of HBT of 15.5 along with the effective pH of 11.3. As there are two bimolecular steps in the kinetic scheme, a standard state for [PhCHO] must be adopted, and this has been set at 1 M. At this concentration, the rates of the forward and back reactions from the enamine **10** are almost exactly equal to each other, and the transition states for these

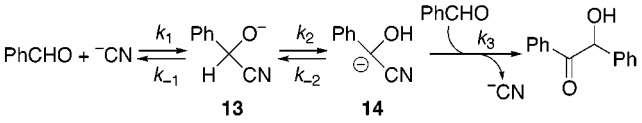
(22) The authors in ref 20 came to a different conclusion: Deprotonation is rapid, and the reaction is zero order in quinone because of formation of a tight complex between enamine **10** and the quinone followed by slow electron transfer. This conclusion is contradicted, however, by the general base catalysis that they observed.

(23) Schowen, R. L.; Latham, K. S. *J. Am. Chem. Soc.* **1967**, *89*, 4677−4683.

(24) Barletta, G. L.; Zou, Y.; Huskey, W. P.; Jordan, F. *J. Am. Chem. Soc.* **1997**, *119*, 2356−2362.

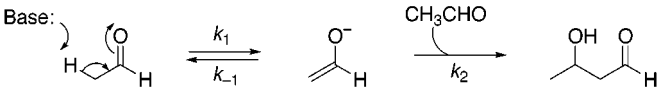
(25) Washabaugh, M. W.; Stivers, J. T.; Hickey, K. A. *J. Am. Chem. Soc.* **1994**, *116*, 7094−7097.

Scheme 4. Kinetic Model for the Cyanide-Catalyzed Benzoin Condensation[a]



[a] See the free-energy profile in Figure 8.

Scheme 5. Kinetic Model for the Base-Catalyzed Aldol Condensation



steps are just lower than that for the first step, formation of HBT. All three steps are therefore partially rate-determining. At lower concentrations of PhCHO, both the first and third steps (k_1 and k_3) become slower, whereas the second step (k_2) remains unchanged and so becomes slightly less rate-determining than the other two steps.

Also shown in Figure 8 for comparison are the corresponding free energies for the cyanide-catalyzed benzoin condensation from ref 6. It can be seen that the initial step, formation of the cyanohydrin anion **13** (see Scheme 4), is much faster than formation of HBT under our conditions but that the remaining two steps have transition states of very similar energy in the cyanide- and thiazolium salt-catalyzed reactions. The partitioning of the carbanion **14** favors return to the cyanohydrin **13** over the forward reaction by a factor of 7.5, even at [PhCHO] = 1 M (it was pointed out, however,[6] that the reverse reaction involves removal of a proton from the solvent methanol, which is at a much higher concentration; if the concentrations of PhCHO and methanol were equal, then reaction of carbanion **14** with the PhCHO would be slightly favored).

The situation that we have revealed here for the benzoin condensation is rather similar to that for the base-catalyzed aldol condensation of acetaldehyde (Scheme 5).[26] At high [CH_3CHO], the C−C bond-forming step is fast, and so the deprotonation is rate-determining, the reaction is first order with respect to CH_3CHO, and general base catalysis is observed. At low [CH_3CHO], on the other hand, the C−C bond-forming step is slow as compared with reprotonation of the enolate, and so the reaction is second order with respect to CH_3CHO, and only specific base catalysis is observed. In D_2O, a substantial isotope effect on k_{-1} was found, implying that at low [CH_3CHO] the overall forward reaction would initially be much faster in D_2O than in H_2O, just as we have observed for the benzoin condensation.

Conclusions

A method has been developed for determining the rate constants of all the kinetically significant steps of the thiazolium salt-catalyzed benzoin condensation. With the most commonly used catalyst **8**, no step is fully rate-determining; instead, all three steps are partially rate-determining for [PhCHO] in the range 0.1−1.7 M. The resulting kinetics cannot accurately be described as either first or second order, but as it happens, the variation of rate with [PhCHO] is fairly close to first order in this range. The overall reaction is ca. 6-fold faster in deuteriomethanol than in normal methanol, due largely to a large isotope effect slowing down the reprotonation of enamine **10**.

Comparison of our data with other data in the literature has been complicated by the variety of different conditions used in the past. It is hoped that the conditions used here will become standard ones for measuring catalysis by thiazolium salts so that in the future more meaningful comparisons will be possible.

It is generally believed that over the course of time enzymes have evolved to become more efficient by lowering the activation energy of the various steps of a reaction in such a way as to make all the activation energies similar in size.[27] It is of interest, therefore, that this already appears to be the case for nonenzymic catalysis by thiazolium salts, and this may have been a factor in the selection of the thiazolium salt, thiamin diphosphate, as an enzymic cofactor in the early days of evolution.

Experimental Section

General Directions. Methanol (HPLC grade from BDH) was degassed by being bubbled with argon for 20 min prior to use. Benzaldehyde was washed with 10% aqueous sodium carbonate solution followed by saturated aqueous sodium sulfite solution. It was then dried over magnesium sulfate and distilled in vacuo.[14] α-D-Benzaldehyde was distilled in vacuo before use. Triethylamine was distilled at atmospheric pressure before use. 3-Benzyl-5-(2-hydroxyethyl)-4-methylthiazolium bromide was made by reaction of the thiazole with benzyl bromide.[15] It was recrystallized twice from acetonitrile and dried under vacuum, mp 109−110 °C (lit[16] 109−110 °C). Triethylamine hydrochloride, dimethyl terephthalate, and d_4-methanol were all obtained commercially and were not further purified. HPLC was performed on a Hypersil H5MOS reverse-phase column (25 cm × 4.6 mm) eluted with MeOH/H_2O (6:4) at a flow rate of 1 mL/min; detection was by UV at 254 nm.

Kinetic Studies at Catalytic Concentrations of Thiazolium Salt. Method 1. Methanolic solutions were prepared under argon containing buffer (0.27 M Et_3N and 0.13 M Et_3N·HCl) and benzaldehyde (≤1.5 M). Aliquots (2 mL) of each solution were mixed. A separate solution of 3-benzyl-5-(2-hydroxyethyl)-4-methylthiazolium bromide (0.15 M) in MeOH was prepared. All solutions were prewarmed to 50 °C in a thermostated water bath, and the reactions were then initiated by injecting 1 mL of the catalyst solution into each buffered solution of aldehyde. At frequent time intervals, samples were taken from the reaction mixtures and placed in a 1-mm UV cell, and their absorbances (A_t) at 320 nm were recorded. By making the assumption that the concentration of HBT in this case is negligible, the concentration of benzoin present at the time of each measurement can be calculated using the following equation:

$$A_t = 0.1[([\mathrm{PhCHO}]_o - 2[\mathrm{benzoin}])\epsilon_{\mathrm{PhCHO}} + [\mathrm{benzoin}]\epsilon_{\mathrm{benzoin}}]$$

where $[\mathrm{PhCHO}]_o$ = initial concentration of benzaldehyde (M). $\epsilon_{\mathrm{PhCHO}}$ is 28.7 at 320 nm, and $\epsilon_{\mathrm{benzoin}}$ is 273.6.

For higher initial benzaldehyde concentrations (>1.5 M), measured aliquots (50−100 μL) were taken from the reaction mixture and diluted with methanol (2.5 mL), and their UV absorbance was measured in a 10-mm cell. Appropriate adjustments were made to the above equation.

Method 2. Reaction mixtures were prepared and initiated as in method 1. At frequent time intervals, a sample (typically 20 μL) was removed, diluted with methanol (1.5 mL), and

(26) Bell, R. P.; Smith, M. J. *J. Chem. Soc.* **1958**, 1691−1698.

(27) Albery, W. J.; Knowles, J. R. *Angew. Chem., Int. Ed. Engl.* **1977**, *16*, 285−293.

analyzed by HPLC. It was found that for an equimolar solution of PhCHO and benzoin, the peak height for benzoin was 1.30× higher than that for PhCHO. Assuming the concentration of HBT is negligible, then $[PhCHO]_o = [PhCHO] + 2[benzoin]$, and the concentration of PhCHO and benzoin can be obtained from the relative peak heights of the HPLC trace using the equations:

$$[PhCHO] = 1.30A[PhCHO]_o/(1.30A + 2B)$$

and

$$[benzoin] = B[PhCHO]_o/(1.30A + 2B)$$

where A = PhCHO peak height, and B = benzoin peak height.

Kinetic Studies at Stoicheiometric Concentrations of Thiazolium Salt. Method 3. A solution of Et_3N (0.106 M), $Et_3N{\cdot}HCl$ (0.053 M), and 3-benzyl-5-(2-hydroxyethyl)-4-methylthiazolium bromide (0.3 M) in d_4-methanol (0.75 mL) was prepared under argon in an NMR tube fit with a gastight septum. The reaction was then initiated by the addition of either benzaldehyde or α-D-benzaldehyde (225 μmol). The tube was briefly shaken to ensure complete mixing and then immediately placed in a 500-MHz NMR spectrometer with the probe temperature set at 27 °C. The ^1H NMR spectrum of the reaction mixture was recorded at approximately 15-min intervals for several hours. The proportions of benzaldehyde, benzoin, catalyst, and HBT present at each time were estimated by comparing the relative sizes of relevant integrals (see earlier sections and Figure 2) and converted to concentrations using the known initial concentrations of the catalyst.

Method 4. A solution was prepared under argon containing Et_3N (0.106 M), $Et_3N{\cdot}HCl$ (0.053 M), and 3-benzyl-4-methyl-5-(2-hydroxyethyl)thiazolium bromide (0.3 M) in methanol. The solution also contained dimethyl terephthalate (0.03 M) as an internal standard. The solution was prewarmed to 27 °C, and reaction was then initiated by the injection of either benzaldehyde or α-D-benzaldehyde (to give a 0.3 M solution). At frequent time intervals, a sample (20 μL) was removed, diluted with methanol (1.5 mL), and analyzed by HPLC. The peak heights for benzaldehyde and benzoin were scaled using the reference peak (dimethyl terephthalate) to avoid sampling errors and then converted to concentrations using previously measured calibration curves.

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