

Dichotomous Salt Effects in the Hydrophobic Acceleration of the Benzoin Condensation

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Abstract: The effects of inorganic salts on the rate of the aqueous cyanide-catalyzed benzoin condensation are studied. Some salts, such as LiCl, are found to increase the reaction rate, while others, such as LiClO₄, decrease it. Additionally, salt effects are found to exist in organic solvents. The divergent effects are postulated to result from a compact, hydrophobic transition state.

Some salts such as Na₂SO₄ or KCl tend to salt organic compounds out of water, decreasing their solubility, while others such as NaI or KClO₄ can show a salting-in effect.¹ Such salt effects can be used to diagnose hydrophobic interactions between reagents in transition states, so they could be powerful tools for understanding reaction mechanisms. In spite of this there are very few reports of rate studies utilizing contrasting salting-out/in effects. Bunton has reported an example in an S_N2 reaction,² and we have reported that both the rate and endo/exo selectivity of certain Diels-Alder reactions are affected in opposite ways by lithium chloride (salting out) and guanidinium chloride (salting in).³⁻⁵

In the classic and well-studied benzoin condensation (eq 1), the kinetics are second order in benzaldehyde and first order in the cyanide catalyst; at constant catalyst concentration they are pseudo



second order in benzaldehyde. We now report that the rate of the cyanide-catalyzed aqueous benzoin condensation is affected both positively and negatively by various salts, consistent with salting-out and salting-in properties. Furthermore, related salt effects seem to operate in certain polar organic solvents. The results are consistent with hydrophobic packing of the benzaldehyde reactants in the transition state.

Experimental Section

Instrumentation. Kinetics were followed by HPLC analysis of samples, using an IBM 9533 HPLC pump and 9522 UV detector (254 nm), monitored with a Spectraphysics 4270 integrator. An IBM C-18 phase column at room temperature was used with eluant consisting of 60:40 (v/v) MeOH/H₂O pumped at 1.0 mL/min. Typical retention times were 5.5 min for benzaldehyde and 6.7 min for benzoin. A Beckman DU-8 spectrophotometer was used in Beer's law studies, and NMR spectroscopy was done with a Varian Model VXR200, using D₂O solvent with an external reference of tetramethylsilane.

Materials. Salts were reagent-grade anhydrous and were used without further purification. Benzaldehyde was distilled immediately before use and was >99.5% pure by HPLC. Water was distilled-deionized and was saturated with argon before use. Organic solvents were deaerated with argon and then degassed by two freeze-pump-thaw cycles. DMSO was Aldrich anhydrous; ethylene glycol was obtained from Fisher and was dried over 3-Å molecular sieves; formamide was Fisher brand, used as supplied.

Kinetics Measurements. Reactions were run on a 1-mL scale in glass vials with septa under argon atmosphere and were incubated at 65 °C. Each experiment was run at least three times at a given set of conditions; the errors listed are standard deviations. Initially [PhCHO] was 41 mM and [KCN] was 23 mM in the aqueous and ethanol reactions and 60 and

Table I. Effects of Salts (5.0 M) and Cyclodextrins on the Rate of the Benzoin Condensation of Benzaldehyde in H₂O

salt	10 ⁴ k ₂ , ^a M ⁻¹ min ⁻¹	salt	10 ⁴ k ₂ , ^a M ⁻¹ min ⁻¹
no salt	123 ± 31	CsCl	153 ± 28
LiCl	470 ± 75	CsI	228 ± 32
LiBr	166 ± 17	β-CD, 5 mM	45 ± 9
LiClO ₄	36 ± 3	β-CD, 10 mM	88 ± 19
LiI	24 ± 7	γ-CD, 5 mM	217 ± 19
KCl	351 ± 71	γ-CD, 10 mM	274 ± 7

^a Pseudo-second-order (in benzaldehyde) rate constants for the benzoin condensation in the presence of 23 mM KCN.

30 mM, respectively, for the reactions run in other solvents.

Aliquots were periodically removed and injected onto the HPLC. The ratio of benzoin to benzoin was generally used to determine benzoin yield at a given time. The increase in benzoin peak area at constant injection volume was also followed in a few cases, with similar results. Plotting 1/[PhCHO] - 1/[PhCHO]₀ versus time gave straight lines whose slopes were taken as the pseudo-second-order rate constant (the CN⁻ concentration does not vary). The early data in a run generally gave a good linear fit (correlation ≥ 0.99) when treated by second-order methods; however, downward curvature was sometimes noticeable at longer reaction times. This was apparently due to air leakage through worn septa. The identity of the peak assigned to benzoin was independently confirmed by isolation after a kinetic run.

Results and Discussion

Aqueous Solution Effects. Figure 1 illustrates the salt effects in water. At 5.0 M concentration, LiCl increases the second-order rate constant (as compared with the case without added salt) by a factor of 3.8, while LiClO₄ decreases it by 3.0-fold. The results of tests using several different salts at 5 M are presented in Table I. From these studies, LiCl and KCl strongly accelerate the reaction, while LiBr, CsCl, and CsI weakly accelerate it; LiClO₄ and LiI markedly slow the benzoin condensation. Guanidinium chloride at high concentration affected the acidity of the medium, so it could not be used.

Paired with lithium cation, the anions can be ranked Cl⁻ > Br⁻ > ClO₄⁻ ≈ I⁻ in order of decreasing rate. In other studies of salting-out/in phenomena the anions nearly always display this order.^{2,8,9} The cation series is less conclusive. Paired with chloride anion, the ordering here is Li⁺ > K⁺ > Cs⁺. While this is the order in which salts decrease the solubility of benzoic acid¹ and *o*-nitroaniline in H₂O,⁶ cation ordering often varies considerably from case to case.^{1,9} Cesium iodide in our study gave (surprisingly) a weak acceleration.

Salting-in agents decrease the hydrophobic effect by breaking up ordered water structure.^{1,7-10} Salting-out agents stabilize water structure and thus give the opposite result. As in the Diels-Alder reaction,^{3-5,11} we attribute our salt effects to a transition state in

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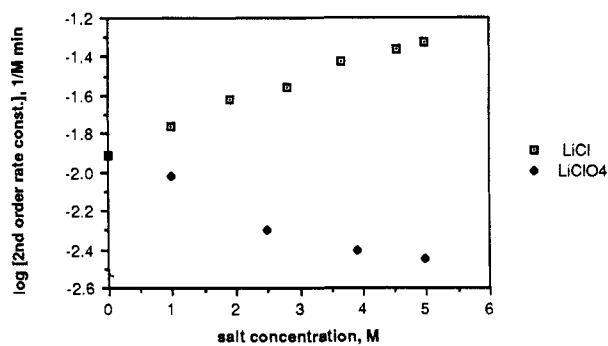
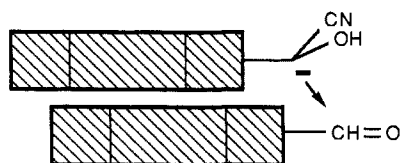


Figure 1. Effects of added LiCl and LiClO₄ on the pseudo-second-order (in benzaldehyde) rate constant for the cyanide-catalyzed benzoin condensation with 23 mM KCN at 65 °C.

which the hydrophobic reactants can be in close association (eq 2), although we cannot rule out small contributions by ion-solute



interaction, especially for the cations.⁹ When the phenyl rings are in direct face-to-face contact, the cyanohydrin anion (as it rehybridizes in the transition state) is aligned at the proper angle for attack on the carbonyl group.¹² This stacking association is stabilized in the presence of salting-out agents such as LiCl, while LiClO₄ and other salting-in agents decrease the extent of this hydrophobic effect. In ethanol solution, where stacking effects should be greatly reduced, the reaction run with no additives is ~200 times slower than in water.

Further evidence for close packing of the aromatic rings comes from our kinetic experiments with cyclodextrins. It has been shown that γ -cyclodextrin (γ -CD) can bind two aromatic rings at a time, most probably in the stacked orientation.¹³ We find (Table I) that 5 mM γ -CD enhances the reaction rate as expected. The smaller β -CD can bind only one aromatic ring, so it inhibits the reaction.

Solubility studies support the idea that the observed aqueous effects are the result of changes in the activity coefficient of benzaldehyde. We find that at 20 °C benzaldehyde is soluble in water to 60 mM; in 5 M LiCl the benzaldehyde solubility is reduced to 27 mM, while in 5 M LiClO₄ it is increased to 100

Table II. Salt Effects on the Rate of Benzoin Condensation of Benzaldehyde in Organic Solvents

solvent	salt	concn, M	10 ⁴ k ₂ , ^a M ⁻¹ min ⁻¹
ethylene glycol	none		50 ± 18
	LiCl	1.0	38 ± 4
	LiClO ₄	1.0	31 ± 1
formamide	none		177 ± 13
	LiCl	2.0	101 ± 19
	LiClO ₄	2.0	44 ± 2
DMSO	none		5850 ± 430
	LiCl	1.0	1780 ± 130
	LiClO ₄	1.0	1810 ± 90

^a Pseudo-second-order (in benzaldehyde) rate constants for the benzoin condensation in the presence of 30 mM KCN.

mM. To explain the rate effects, the hydrophobically stacked transition state must show smaller activity coefficient effects per phenyl group.

Beer's law plots in water alone and with these salts show no large deviation from linearity up to the saturation point. Proton magnetic resonance studies in D₂O show small shifts in the aromatic resonances in the presence of 5 M salts; interestingly, the HOD resonance is affected more strongly, supporting the idea that water structure is an important factor.

Organic Solvents. Nonaqueous polar solvents dissolve LiCl and LiClO₄ to an appreciable extent. We have examined the benzoin condensation in ethylene glycol, in formamide, and in dimethyl sulfoxide (DMSO). The salts affect the reaction rate in these media as well (Table II). In contrast with the results in water, we found that both salts *slowed* the reaction. However, in formamide LiClO₄ showed the stronger effect, suggesting that the perchlorate anion is a "salting-in" ion even in formamide. The very large rate in DMSO, almost 50 times that in H₂O, probably reflects the ability of DMSO to activate CN⁻ by solvating metal cations.

To our knowledge salting-out and salting-in contrasting effects have not been previously examined in purely organic solvents. If such effects are operating here, we must postulate that they are overwhelmed by cation effects on the activity coefficient of CN⁻ through coordination or ion pairing. We are currently examining hydrocarbon solubilities and Diels-Alder reactions in such solvents, in which the salt effects may more closely parallel those in water.

Our results further demonstrate hydrophobic effects on organic reaction rates. The diagnostic but rarely used salting out/in tests should be generally helpful in establishing the reason that some reactions, such as the benzoin condensation and Diels-Alder additions, are much faster in water than in common organic solvents. In appropriate cases these tests give unique evidence about transition-state structure.

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