The Mechanism of the Benzoin Condensation[1,2]

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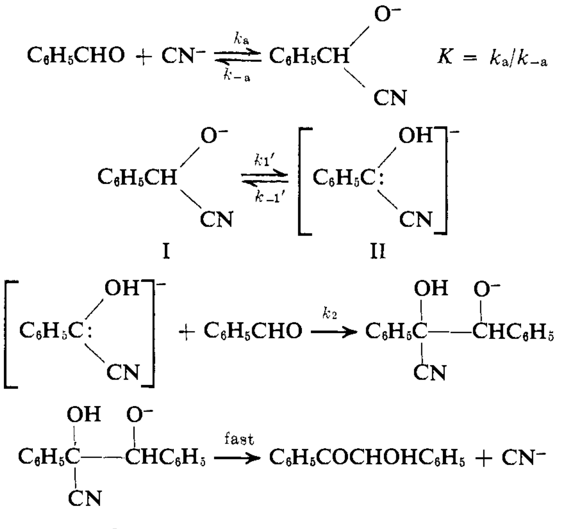
Abstract: The benzoin condensation in methanol at 44–66° proceeds by addition of cyanide ion to benzaldehyde ($\Delta G^* \sim 12$ kcal/mol, $\Delta G°_{298} = -0.74 \pm 0.04$ kcal/mol, $\Delta H° = -9.9 \pm 0.2$ kcal/mol, $\Delta S° = -30.6 \pm 0.6$ eu), conversion of the adduct to a cyanocarbanion ($\Delta G^*_{298} = 21.31 \pm 0.02$ kcal/mol, $\Delta H^* = 10 \pm 0.5$ kcal/mol, $\Delta S^* = -38 \pm 3$ eu, relative to original reactants, $k_H/k_D = 4.3$ at 25° for C_6H_5CHO *vs.* C_6H_5CDO), and condensation of the carbanion with benzaldehyde ($\Delta G^*_{298} = 22.5 \pm 0.1$ kcal/mol, $\Delta H^* = 10 \pm 2$ kcal/mol, $\Delta S^* = -42 \pm 4$ eu, relative to original reactants). The scheme is essentially that of Lapworth, proposed over 65 years ago.

The benzoin condensation (eq 1) is of interest to biochemists as a model for certain carbon–carbon bond formation reactions in which the catalytic entity is the thiazolium function of thiamine pyrophosphate rather than cyanide ion.[4] The condensation has long

$$2C_6H_5CHO \xrightarrow{CN^-} C_6H_5CHOHCOC_6H_5 \qquad (1)$$

provided physical-organic chemistry with an excellent example of specific catalysis[5] and, perhaps for that reason, was one of the early organic reactions subjected to kinetic study[6–9] at the beginning of this century. Lapworth,[6,7] using his own demonstration that cyanohydrin formation is rapid relative to the condensation and the evidence of Bredig and Stern[8,9] that the reaction is kinetically second order in benzaldehyde and first order in cyanide ion, proposed the mechanism of Scheme I, in which the k_2 step was taken as rate determining. This mechanism satisfies the kinetic requirements as well as explaining the specificity for the cyanide catalyst (and the activity of the thiazolium species), since a successful catalyst must possess not only nucleophilic reactivity (eq 2) but the ability to stabilize an adjacent negative charge in the "active aldehyde" intermediate II formed in eq 3.

Scheme I



$$C_6H_5CHO + CN^- \underset{k_{-a}}{\overset{k_a}{\rightleftharpoons}} C_6H_5CH\begin{matrix}O^-\\CN\end{matrix} \qquad K = k_a/k_{-a} \qquad (2)$$

$$\underset{\text{I}}{C_6H_5CH\begin{matrix}O^-\\CN\end{matrix}} \underset{k_{-1}'}{\overset{k_1'}{\rightleftharpoons}} \underset{\text{II}}{\left[C_6H_5\ddot{C}\begin{matrix}OH\\CN\end{matrix}\right]^-} \qquad (3)$$

$$\left[C_6H_5\ddot{C}\begin{matrix}OH\\CN\end{matrix}\right]^- + C_6H_5CHO \xrightarrow{k_2} C_6H_5\overset{OH}{\underset{CN}{C}}-\overset{O^-}{C}HC_6H_5 \qquad (4)$$

$$C_6H_5\overset{OH}{\underset{CN}{C}}-\overset{O^-}{C}HC_6H_5 \xrightarrow{\text{fast}} C_6H_5COCHOHC_6H_5 + CN^- \qquad (5)$$

Wiberg,[10,11] in his pioneering investigations of kinetic isotope effects, found some apparent inconsistencies with the mechanism of Scheme I. Since eq 4 is taken as rate determining (it or a later step being demanded by the kinetics), previous steps should be rapid and reversible. Thus reaction of C_6H_5CHO in a solvent deuterated in an exchangeable position should lead to rapid formation of C_6H_5CDO (rapid, reversible formation of II with reprotonation of carbon by solvent) and its subsequent condensation. Correspondingly, C_6H_5CDO in protiated solvent should lose its label rapidly in comparison to condensation. Such was not found; in fact, in 66% ethanol-water, containing 52% deuterium in exchangeable positions, the condensation and exchange rates were approximately equal. As Wiberg noted,[10] this was "clearly at variance" with the predictions of the Lapworth mechanism. A subsequent study,[11] employing a more highly deuterated solvent, reinforced this view.

Because of the considerable importance of this reaction, we undertook to establish the mechanism in quantitative detail. Our strategy was to examine the components of the Lapworth mechanism step by step, as follows. (a) The forward *rate* of eq 2 may be found from the cyanide ion induced broadening of the aldehydic proton absorption in the nmr. (b) The *equilibrium* data for eq 2 are available from the instantaneous decrease in intensity of the n–π^* ultraviolet absorption of the aldehydic carbonyl group, produced by cyanide ion. (c) The *rate* of formation of the carbanion II, from *protiated reactant in protiated solvent*, can be found by measuring k_D, the rate of loss of deuterium from C_6H_5CDO, and k_T, the rate of loss of tritium from C_6H_5CTO. The desired rate constant k_H is then calculated from the Swain-Schaad equation[12] (eq 6). (d) The

$$k_H/k_T = (k_H/k_D)^{1.44} \qquad (6)$$

rate of benzoin formation is provided by an ultraviolet analytical technique. Scheme I is then tested by comparison of its integrated, steady-state rate equation

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(1) This research was supported by the University of Kansas General Research Fund, the National Aeronautics and Space Agency (University of Kansas Institutional Grant), and by the National Science Foundation and the National Institutes of Health.

(2) Further information may be found in J. P. Kuebrich, Ph.D. Thesis in Chemistry, University of Kansas, 1968.

(3) Holder of a Research Career Development Award of the National Institute of General Medical Sciences.

(4) R. Breslow, *Ciba Found. Study Group (Pap.)*, No. 11, 65 (1961).

(5) J. Hine, "Physical Organic Chemistry," 2nd ed, McGraw-Hill, New York, N. Y., 1962, p 264.

(6) A. J. Lapworth, *J. Chem. Soc.*, 83, 995 (1903).

(7) A. J. Lapworth, *ibid.*, 85, 1206 (1904).

(8) H. G. Bredig and E. Stern, *Z. Elektrochem.*, 10, 582 (1904).

(9) E. Stern, *Z. Phys. Chem.*, 50, 513 (1905).

(10) K. B. Wiberg, *J. Amer. Chem. Soc.*, 76, 5371 (1954).

(11) K. B. Wiberg, *ibid.*, 77, 5988 (1955).

(12) C. G. Swain, E. C. Stivers, J. F. Reuwers, and L. J. Schaad, *ibid.*, 80, 5885 (1958).

Table I. Rate Constants and Activation Parameters for Isotope Exchange of Benzaldehyde, Benzaldehyde-*d*, and Benzaldehyde-*t* with Solvent Protium in Methanol[a]

Substrate	10^3k_{ex}, M^{-1} sec^{-1} (T, °C)	ΔG^*_{298}, kcal/mol	ΔH^*, kcal/mol	ΔS^*, eu
C_6H_5CTO[d]	0.82 (44.8); 1.04 (49.8); 1.39 (55.6); 1.90 (59.3); 2.00 (60.9); 2.09 (60.9)[b]	22.58 ± 0.03	12.3 ± 0.5	−35 ± 2
C_6H_5CDO	1.16 (41.7); 2.76 (57.2); 3.95 (64) [1.14 (41.7); 2.32 (57.2); 3.70 (64)][c]	22.19 ± 0.01	11.6 ± 0.5	−35 ± 2
C_6H_5CHO[e]	4.73 (44.6); 6.39 (50); 7.54 (54.8); 9.86 (60.9); 10.2 (61.5); 12.3 (66)	21.31 ± 0.01	10 ± 0.5	−38 ± 3

[a] Standard deviations in k_{ex} never exceeded ±5%. Temperatures are accurate to ±0.2° and precise to ±0.1°. Standard states for activation parameters are 1 M for solutes and pure liquid for methanol. [b] Determined in sealed ampoules. [c] From increase in CH absorption, measured simultaneously with decrease in CD absorption (preceding rate constants). [d] Further data in Table IV. [e] Calculated from eq 9 using preceding data at temperatures of interest for the condensation reaction.

(containing K and k_1', both of which are known from above, and k_2/k_{-1}', which is the only unknown) with the data for aldehyde concentration *vs.* time. If a fit is possible, it will determine k_2/k_{-1}'.

Results

All reactions were carried out with potassium cyanide catalyst in absolute methanol as solvent.

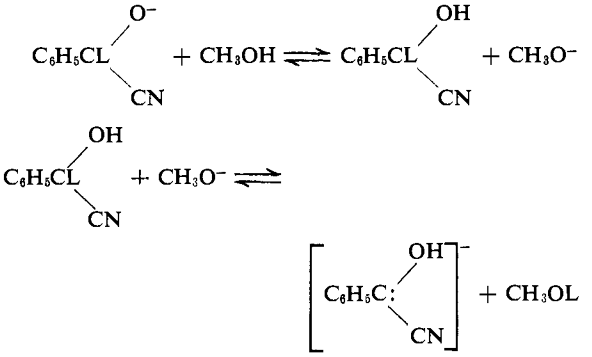
Broadening of the Aldehydic Proton Nmr Signal by Cyanide Ion. Addition of potassium cyanide to methanol solutions of benzaldehyde (about 0.8 M) in concentrations of 1–10 × 10^{-4} M produced a dramatic broadening of the aldehydic proton absorption at 580 Hz downfield of tetramethylsilane, attributable to rapid chemical exchange[13] with the cyanide adduct (eq 2). From the dependence of line width on cyanide concentration,[14] the rate constant k_a is calculated to be 16 ± 1 × 10^3 M^{-1} sec^{-1} at 34°.

Equilibrium Addition of Cyanide Ion to Benzaldehyde. A very rapid decrease in the absorption at 320 nm of methanolic solutions of benzaldehyde was noted on addition of cyanide ion, presumably due to adduct formation (eq 2). When measurements were carried out in 0.0285 M sodium methoxide solutions, to assure that the cyanohydrin was ionized, equilibrium constants (temperatures in degrees Celsius in parentheses) could be calculated according to eq 7 to be: 13.39 ± 0.32

$$K = [C_6H_5CHOCN]^-/[C_6H_5CHO][CN^-] \qquad (7)$$

(3.8); 8.33 ± 0.05 (10.5); 4.09 ± 0.05 (22.5)M^{-1}. These yield the thermodynamic quantities (1 M standard states): $\Delta G°_{298} = -0.74 \pm 0.04$ kcal/mol; $\Delta H° = -9.9 \pm 0.2$ kcal/mol; $\Delta S° = -30.6 \pm 0.6$ eu.

Cyanide-Catalyzed Isotope Exchange of C_6H_5CLO with Methanol. The loss of isotopic label from C_6H_5CDO and from C_6H_5CTO is catalyzed by cyanide ion, presumably *via* addition (eq 2), neutralization of the adduct (eq 8a), and hydrogen transfer (eq 8b). Reversal of eq 8b will of course introduce unlabeled hydrogen from the solvent pool. Deuterium exchange, followed by an infrared technique in which disappearance of the 2105-cm^{-1} CD band and appearance of the 2816-cm^{-1} CH band were simultaneously monitored *vs.* the aromatic CH absorption at 3076 cm^{-1} as standard, and tritium exchange, measured by scintillation counting, gave good first-order kinetics over the time periods studied. The reactions were also first order in cyanide ion concentration, yielding the second-order rate constants shown in Table I.



$$C_6H_5CL(O^-)(CN) + CH_3OH \rightleftharpoons C_6H_5CL(OH)(CN) + CH_3O^- \qquad (8a)$$

$$C_6H_5CL(OH)(CN) + CH_3O^- \rightleftharpoons [C_6H_5C{:}(OH)(CN)]^- + CH_3OL \qquad (8b)$$

For purposes of treating the benzoin condensation kinetics, it is desirable to have the rate constant for protium–protium exchange, *i.e.*, $Kk_1' = k_1$ (see eq 2 and 3). From the deuterium and tritium exchange rate constants and a rearranged form (eq 9) of the Swain–Schaad equation (eq 6)[12,15] the requisite values are obtained and are also given in Table I. Activation parameters calculated from the Eyring equation (eq 10) are included in Table I as well.

$$k_H = k_D^{3.27}/k_T^{2.27} \qquad (9)$$

$$k = (\mathrm{k}T/h)\exp\left\{-\frac{\Delta H^*}{RT} + \frac{\Delta S^*}{R}\right\} \qquad (10)$$

Kinetics of the Benzoin Condensation. The mechanism of Scheme I can be reformulated as in eq 11, where A refers to *free* benzaldehyde and C to *free* cyanide ion. Here $k_1 = Kk_1'$, II is the "active aldehyde," as in eq 3, and P means benzoin. The steady-state assumption is made for II to yield eq 12, where A still refers to free benzaldehyde but C_0 to stoichiometric (total added) cyanide ion; K is the equilibrium constant

$$2A + C \underset{k_{-1}'}{\overset{k_1}{\rightleftharpoons}} II + A \xrightarrow{k_2} P + C \qquad (11)$$

$$-d[A]/dt = k_1[C_0][A]^2/(K[A]^2 + (K\alpha + 1)[A] + \alpha) \qquad (12)$$

for adduct formation (eq 2) and $\alpha \equiv k_{-1}'/k_2$. The

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(13) E. F. Caldin, "Fast Reactions in Solution," Wiley, New York, N. Y., 1964, p 215.

(14) Detailed experiments in buffered solutions by Dr. K. L. Chellappa have confirmed this value; Dr. Chellappa's studies will shortly be published.

(15) The theoretical value[12] of 1.44 in eq 6 has been amply confirmed in succeeding years by experiments in which tritium and deuterium proton-transfer rates are both measurable.[16]

(16) E. S. Lewis and J. K. Robinson, *J. Amer. Chem. Soc.*, 90, 4337 (1968).

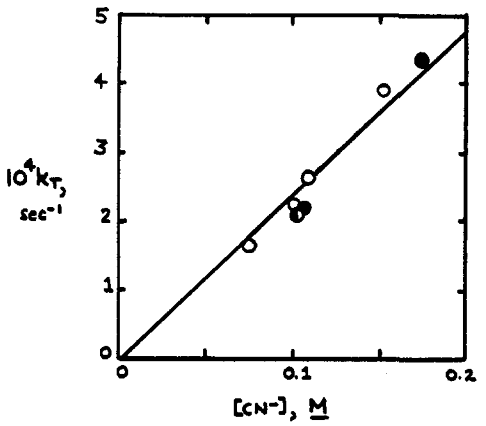

Figure 1. First-order rate constants for cyanide-catalyzed detritiation of C_6H_5CTO, as a function of cyanide concentration, in CH_3OH (open circles), CH_3OD (filled circles), and 50% CH_3OH–50% CH_3OD (half-filled circle).

integrated form of this equation (eq 13), in which all quantities with the exception of α are independently determined, was employed to find the value of α by iterative curve fitting. Aldehyde concentrations, determined by ultraviolet spectroscopic analysis, experimental observation times, and times calculated from eq 13 are shown for typical experiments in Table II.

Table II. Typical Kinetic Data for the Cyanide-Catalyzed Benzoin Condensation of Benzaldehyde in Methanol[a]

Temp, °C	Absorbance	[Benzoin], M	[Benzaldehyde], M	t_{exp}, min	t_{calcd}, min
44.6	0.217	0.000	0.390	0	0
	0.297	0.018	0.353	101	109
	0.379	0.037	0.315	240	244
	0.430	0.049	0.292	345	341
	0.489	0.062	0.265	481	460
[KCN] = 0.1080 M; K = 1.24 M^{-1}; α = 7.5 M^{-1}					
50.0	0.116	0.000	0.209	0	0
	0.133	0.004	0.202	38	40
	0.170	0.012	0.185	154	155
	0.217	0.023	0.163	334	326
	0.241	0.029	0.152	436	434
[KCN] = 0.1059 M; K = 0.99 M^{-1}; α = 7.5 M^{-1}					
54.8	0.221	0.000	0.398	0	0
	0.244	0.005	0.388	28	13
	0.335	0.026	0.346	70	69
	0.444	0.051	0.290	160	166
	0.526	0.070	0.259	250	239
	0.620	0.091	0.216	378	367
[KCN] = 0.1181 M; K = 0.75 M^{-1}; α = 7.5 M^{-1}					

[a] Temperatures are precise to ±0.1° and accurate to ±0.2°. Concentrations of all species are total, stoichiometric values. K is defined by eq 7 and α by eq 12.

$$k_1C_0t = K\{[A]_0 - [A]\} + (K\alpha + 1)\ln\frac{[A]_0}{[A]} + \alpha\{[A]^{-1} - [A]_0^{-1}\} \quad (13)$$

At all temperatures, a single value of $\alpha = 7.5 \pm 0.5$ M^{-1} described the data. A summary of the condensation data is given in Table III.

Table III.[a] Summary of Kinetic Data for the Benzoin Condensation in Methanol

Temp, °C	[C_6H_5-CHO]$_0$, M	[KCN], M	K, M^{-1}	α
44.6	0.390	0.1080	1.24	7.5
50.0	0.394	0.1066	0.99	7.5
50.0	0.209	0.1059	0.99	7.5
50.0	0.306	0.1049	0.99	7.5
50.0	0.296	0.1126	0.99	7.5
50.0	0.392	0.1126	0.99	7.5
50.0	0.197	0.1066	0.99	7.5
50.0	0.394	0.1059	0.99	7.5
54.8	0.394	0.1181	0.75	7.5
60.9	0.305	0.1002	0.58	7.5
60.9	0.393	0.1002	0.58	7.5
61.5	0.399	0.0508	0.57	7.5
61.5	0.398	0.1017	0.57	7.5
66.0	0.305	0.1072	0.47	7.5
66.0	0.391	0.1072	0.47	7.5

[a] See Table II for definitions of symbols and comments.

Solvent Isotope Effect on Carbanion Formation. Table IV shows first-order rate constants k_{ex} for loss of tritium from C_6H_5CTO in methanol, methanol-d, and mixtures of the two at 62°. Figure 1 exhibits a plot of k_{ex} *vs.* cyanide concentration; since all data are described by the second-order rate constant, $k_T = 2.4 \pm 0.2 \times 10^{-3}\ M^{-1}\ sec^{-1}$. Thus $k_{CH_3OH}/k_{CH_3OD} = 1.0 \pm 0.1$. To ascertain whether the lack of solvent isotope effect might originate in cancellation of a transition-state effect by a reactant solvation isotope effect, the isotopic fraction factor[17] for potassium cyanide was measured by the Gold–Kresge–Allred method.[18] No change (to within ±0.1 Hz) in the chemical shift of the proton in either methanol or 93:7 (v/v) CH_3OD–CH_3OH was observable on addition of potassium cyanide up to mole fractions of 0.006 (by comparison, sodium methoxide at a mole fraction of 0.005 causes a 7.25-Hz change in the proton chemical shift). This means that the isotopic fractionation factor for potassium cyanide is unity to well within the 10% precision of the solvent isotope effect so that it is not cancelling any transition-state isotope effect. The transition state, to the same precision, must be equally stable in the light and heavy solvents.

Table IV. Rate Constants for Cyanide Ion Catalyzed Tritium Loss from Benzaldehyde-t at 62.0 ± 0.2°

Solvent	[CN$^-$], M	10^4k_{ex}, sec^{-1}
CH_3OH	0.075	1.65
CH_3OH	0.101	2.26
CH_3OH	0.109	2.65
CH_3OH	0.152	3.92
CH_2OH (50%), CH_3OD (50%)	0.103	2.10
CH_3OD	0.107	2.20
CH_3OD	0.173	4.36

Discussion

Addition of Cyanide Ion to Benzaldehyde. The rapidity of the addition of cyanide ion to the benzaldehyde carbonyl group is expected; ΔG^* is about 12

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(17) A. J. Kresge, *Pure Appl. Chem.*, **8**, 243 (1964).

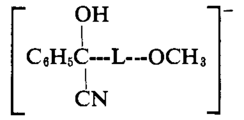
(18) (a) V. Gold, *Proc. Chem. Soc.*, 141 (1963); (b) A. J. Kresge and A. L. Allred, *J. Amer. Chem. Soc.*, **85**, 1541 (1963).

kcal/mol at 34°. The stability of intermediate I, on the other hand, is rather greater than has usually been assumed. It has customarily been taken to be a steady-state, low-concentration species, while the equilibrium constant of about 1 M^{-1} for its formation at 50° means that (at initial concentration of 0.3 M aldehyde and 0.1 M cyanide ion) as much as 7% of the aldehyde and 20% of the cyanide ion are present as adduct. This must be taken account of in the kinetic treatment.

The thermodynamics of formation of I is quite rational. The decrease in enthalpy of 9.9 kcal/mol probably corresponds to the formation of a new carbon–carbon σ bond, in exchange for a weaker CO π bond, together with the exothermic solvation of the basic alkoxide center of I rather than cyanide ion, which appears not to interact strongly with the protic solvent (no effect on the chemical shift of the hydroxyl proton). The same factors should both contribute to a negative change in entropy, the new bond formation converting translational to vibrational degrees of freedom while the "freezing" of solvent around the alkoxide center will also reduce the total randomness, giving a total loss of about 31 eu.

Formation of the "Active-Aldehyde" Carbanion II. According to the formulation of eq 8, II is presumed to form *via* the activation process of eq 14. Several types

$\mathrm{C_6H_5CLO + CN^- + CH_3OH \longrightarrow}$



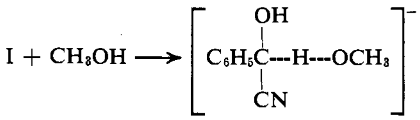
$$\left[\mathrm{C_6H_5}\underset{\mathrm{CN}}{\overset{\mathrm{OH}}{\mathrm{C}}}\text{---}\mathrm{L}\text{---}\mathrm{OCH_3}\right]^- \qquad (14)$$

III

of evidence are pertinent to structure III for the activated complex of the carbanion-forming sequence.

(a) If the transferring hydrogen ion L is not extremely asymmetrically disposed, III implies a kinetic isotope effect.[19–21] Extrapolating the data of Table I to 25°, we find $k_H/k_D = 4.3 \pm 0.4$.

(b) The activation parameters for formation of III ($\Delta H^* = 10$ kcal/mol, $\Delta S^* = -38$ eu) are unsurprising *per se* but may fruitfully be combined with the thermodynamics of formation of adduct I ($\Delta H° = -9.9$ kcal/mol, $\Delta S° = -30.6$ eu) to find for reactions of the adduct (eq 15) the values $\Delta H^* = 19.9 \pm 0.7$ kcal/mol, $\Delta S^* = -7 \pm 3$ eu. The entropy change, in particular,



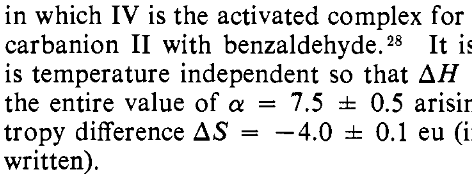
$$\mathrm{I + CH_3OH \longrightarrow} \left[\mathrm{C_6H_5}\underset{\mathrm{CN}}{\overset{\mathrm{OH}}{\mathrm{C}}}\text{---}\mathrm{H}\text{---}\mathrm{OCH_3}\right]^- \qquad (15)$$

is much more suggestive of the bimolecular process involving solvent binding than of, say, a 1,2 shift of the proton of I from C to O to yield II.

(c) If the CH_3O moiety in III were equivalent to a methoxide ion (reactant-like transition state for proton transfer with OL bond order of zero), then the exchange reaction should proceed more rapidly in CH_3OH than in CH_3OD by a factor of about 1.7. This estimate is obtained by using More O'Ferrall's isotopic fractionation factor ϕ of 0.76 for methoxide ion[22] (showing that CH_3OH occupies a solvation site of methoxide preferentially over CH_3OD by a factor of $(0.76)^{-1} = 1.3$) and by assuming that one lone pair of the transition-state CH_3O is bound to the transferring proton, while the other two lone pairs bind solvent molecules. The transition state should then be stabler relative to reactants in the preferred solvent CH_3OH by a factor of $(1.3)^2 = 1.7$. Furthermore, our demonstration that $\phi = 1$ for cyanide ion means that (under the usual assumption that $\phi = 1$ for the uncharged reactant species) no modification of the estimate is introduced by reactant solvation.

A product-like transition state (OL bond order of unity) has the CH_3O in an effective CH_3OL state which is exactly like the reactant CH_3OH (if the rule of the geometric mean[23] holds) so that $k_{ex}^{CH_3OH}/k_{ex}^{CH_3OD} = 1$. For intermediate transition states of OL bond order x, presumably[24,25] $k_{ex}^{CH_3OH}/k_{ex}^{CH_3OD} = (1.7)^{1-x}$. Our observation that $k_{ex}^{CH_3OH}/k_{ex}^{CH_3OD} = 1 \pm 0.1$ is consistent with OL bond orders x from 0.83 to 1. Now the CH and CD stretching frequencies of the reactant benzaldehyde (2816 and 2105 cm^{-1}, respectively) indicate a maximum kinetic isotope effect[26] at L of 5.6 for eq 14, under the usual assumptions.[19,21,25] The large isotope effect of 4.3 observed for this apparently asymmetric transition state seems to suggest that a plot of k_H/k_D *vs.* x for this reaction has a rather broad maximum, perhaps for the reason given by Willi and Wolfsberg[27] (a sharp activation barrier) or perhaps for the reason given by More O'Ferrall and Kouba[21] (conversion of tetrahedral C–L in I, with two high-frequency bends and a stretch, to CH_3OL in the product with a high-frequency bend, a stretch, and a low-frequency torsion gives abnormally large isotope effects for product-like transition states).

Reaction of Carbanion II with Benzaldehyde. The fit of the data for aldehyde disappearance (or benzoin appearance) with time is fully consistent with Scheme I. The interesting datum obtained from the fit is $\alpha = k_{-1}'/k_2$, with α^{-1} being the equilibrium constant for eq 16,



$$\left[\mathrm{C_6H_5}\underset{\mathrm{CN}}{\overset{\mathrm{OH}}{\mathrm{C}}}\text{---}\mathrm{H}\text{---}\mathrm{OCH_3}\right]^- + \mathrm{C_6H_5CHO} \longrightarrow \left[\mathrm{C_6H_5}\underset{\mathrm{CN}}{\overset{\mathrm{OH}}{\mathrm{C}}}\text{- - -}\underset{\mathrm{C_6H_5}}{\overset{\mathrm{H}}{\mathrm{C}}}\overset{\text{- - -}}{=}\mathrm{O}\right]^- + \mathrm{CH_3OH} \qquad (16)$$

IV

in which IV is the activated complex for reaction of the carbanion II with benzaldehyde.[28] It is found that α is temperature independent so that $\Delta H = 0$ for eq 16, the entire value of $\alpha = 7.5 \pm 0.5$ arising from an entropy difference $\Delta S = -4.0 \pm 0.1$ eu (in the direction written).

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(19) F. H. Westheimer, *Chem. Rev.*, **61**, 265 (1961).

(20) J. Bigeleisen, *Pure Appl. Chem.*, **8**, 217 (1964).

(21) R. A. More O'Ferrall and J. Kouba, *J. Chem. Soc. B*, 985 (1967).

(22) R. A. More O'Ferrall, *Chem. Commun.*, 114 (1969).

(23) V. Gold, *Trans. Faraday Soc.*, **64**, 2770 (1968); W. J. Albery and M. H. Davies, *ibid.*, **65**, 1059 (1969).

(24) V. Gold, *ibid.*, **56**, 255 (1960).

(25) R. L. Schowen, *Progr. Phys. Org. Chem.*, in press.

(26) The vibration frequencies of benzaldehyde rather than I should be used because the rate constants k_{ex} refer to the process of eq 14.

(27) A. V. Willi and M. Wolfsberg, *Chem. Ind. (London)*, 2097 (1964).

(28) $k_{-1}' = (kT/h)K_{-1}'$ where K_{-1}' is the (defective) equilibrium constant for the activation process II + CH_3OH → III and $k_2 = k(T/h)K_2$ where K_2 is the (defective) equilibrium constant for II + C_6H_5CHO → IV. Thus $k_2/k_{-1}' = \alpha^{-1}$ is the (doubly defective) equilibrium constant for III + C_6H_5CHO → IV + CH_3OH. *Cf.* J. L. Kurz, *J. Amer. Chem. Soc.*, **85**, 987 (1963).

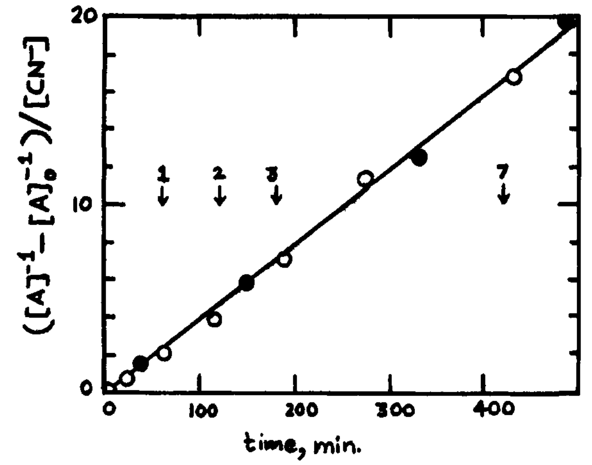


Figure 2. Plot of the integrated second-order rate law for the benzoin condensation in methanol solution, using *stoichiometric* aldehyde (A) and cyanide concentrations, rather than the true values. The filled circles refer to condensation of C_6H_5CHO, initially 0.2089 *M*, with potassium cyanide initially 0.1059 *M*, at 50.0°. The open circles refer to condensation of C_6H_5CDO, initially 0.3646 *M*, with potassium cyanide initially 0.1018 *M* at 50.9°. The numbered arrows indicate successive half-life times for loss of deuterium from C_6H_5CDO under the same conditions.

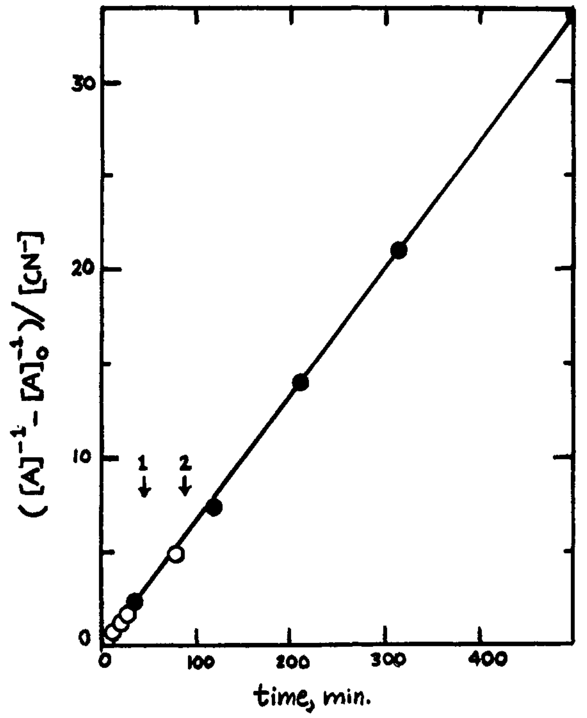


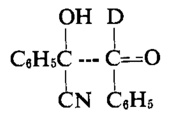
Figure 3. Plot of the integrated second-order rate low for the benzoin condensation in methanol solution, using *stoichiometric* aldehyde (A) and cyanide concentrations, rather than the true values. The filled circles refer to condensation of C_6H_5CHO, initially 0.3928 *M*, with potassium cyanide initially 0.1002 *M*, at 60.9°. The open circles refer to condensation of C_6H_5CDO, initially 0.3461 *M*, with potassium cyanide initially 0.1102 *M*, at 59°. The numbered arrows indicate half-life times for loss of deuterium from C_6H_5CDO under the same conditions.

The two activated complexes III and IV result from a partial binding of the carbanion II to two quite different electrophiles, methanol and benzaldehyde, respectively. The fact that these interactions occur with no enthalpic difference is a further confirmation of the conclusion reached above from the solvent isotope effect that III has a small C–H bond order (*i.e.*, CH_3OH moiety methanol-like). If the same is true of IV, *i.e.*, if it has a small C–C bond order in the forming bond, then the weakness of interaction of the carbanion with the two electrophiles means that the CH_3OH part of III is "methanol-like" and the C_6H_5CHO part of IV is "benzaldehyde-like" and thus eq 16 has $\Delta H = 0$. In fact, the Hammond postulate[29a] and the Swain–Thornton rule[29b] predict that the strongly basic carbanion should react *via* a carbanion-like transition state with either Brønsted acids (CH_3OH) or Lewis acids (C_6H_5CHO). Long ago, Ingold, De Salas, and Wilson[30] showed how the reaction of cyanocarbanions with proton donors could be explained in terms of a carbanion-like transition state (the conjugate base of an α,β-unsaturated nitrile protonated more rapidly at the high charge density α site rather than at the thermodynamically preferred γ position).

The entropic preference of the carbanion for reaction with methanol rather than benzaldehyde is a matter of choice of standard states. The activation parameters are calculated for standard states of 1 *M* for benzaldehyde and pure liquid for methanol. Binding of the benzaldehyde from the more dilute 1 *M* free state represents a greater reduction in randomness than binding of a methanol molecule from the high-concentration pure liquid. If the inherent reactivities were equal and the methanol reactant were monomeric, then α would be 24.7, the molar concentration of pure methanol. The observed value of 7.5 may suggest a reactive aggregate of three–four methanol molecules.

Mechanism of the Benzoin Condensation. The Lapworth mechanism of Scheme I emerges in this study as completely correct; it needs to be observed that the oxyanion I is not a steady-state intermediate, but accumulates in reasonable amounts, and that neither eq 3 nor eq 4 is completely rate determining since $k_{-1}'/k_2 = 7.5$.

Figures 2 and 3 exhibit an interesting characteristic of the reaction. The data for *total* benzaldehyde concentration are plotted there in the appropriate form for a simple second-order reaction. Notice that if these values (not the free aldehyde concentrations) are used, then the second-order plots are quite linear. Furthermore if C_6H_5CDO is used as substrate (filled circles), the same relationship is obeyed, *although exchange is incomplete*. The numbered arrows on the plots mark the times of successive half-lives for loss of label from C_6H_5-CDO. Now at a benzaldehyde concentration of 0.3 *M* (the initial conditions in Figures 2 and 3), $k_1'/k_2 = 25$ so that the activated complex chiefly determining the slope of these plots is IV. The fact that deuterium substitution (IV-*d*) influences the rate to no detectable degree is a further indication of the "looseness" or small C–C bond order in this transition state.



$$\mathrm{C_6H_5\overset{OH}{\underset{CN}{C}}\cdots\overset{D}{\underset{C_6H_5}{C}}{=}O}$$

IV-*d*

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(29) (a) G. S. Hammond, *J. Amer. Chem. Soc.*, 77, 334 (1955); (b) C. G. Swain and E. R. Thornton, *ibid.*, 84, 817 (1962); E. R. Thornton, *ibid.*, 89, 2915 (1967).

(30) C. K. Ingold, E. De Salas, and C. L. Wilson, *J. Chem. Soc.*, 1328 (1936).

The situation may be different in other solvents. Wiberg[10] found a considerable induction period for C_6H_5CDO in 66% ethanol–water at 64°, which Figures 2 and 3 show to be absent in methanol at 50 and 60°. Furthermore, his study of deuterium introduction into benzaldehyde *via* carbanion II in 52 and 93.7% deuterated 66% ethanol–water seemed to indicate only a minimal isotope effect on proton uptake from solvent.[11] Combined with his observation that exchange and condensation were about equal in rate in 52% deuterated medium at 0.8 M aldehyde, this yields a value for k_{-1}'/k_2 of only 1.6. This value does, however, depend on the deduction that there is no isotope effect on the neutralization of I, which in turn depends on a linear extrapolation of the exchange rates from 52 and 93.7% deuterated media to 50 and 100% deuterium levels. The linear extrapolation was perfectly reasonable to make at the time of Wiberg's work in 1955. Since then, it has become clear how complex can be the dependence of reaction rates on the composition of mixed isotopic solvents, so that the linear function can no longer be assumed correct.[17] The situation is even more complicated in the case of a chemically mixed solvent (ethanol and water) which is also isotopically mixed (deuterium and protium), which was one of the reasons we chose to examine the reaction in methanol rather than under conditions directly comparable to those of Wiberg.

Experimental Section

Materials. Benzaldehyde (Fisher Certified Reagent) was distilled at atmospheric pressure. A center cut of the fraction boiling at 179° (lit.[31] bp 179°) was collected and stored under nitrogen in the refrigerator. Immediately prior to preparation of the kinetic solutions, the benzaldehyde was chromatographed on alumina[32] (Alcoa activated alumina, grade F-20) and then vacuum distilled at 35° (0.4 mm). Potassium cyanide (Baker analyzed reagent) was used as obtained to prepare all stock solutions. Nitrogen was bubbled for several hours through the methanol used to dilute the kinetic solutions for spectroscopic readings. Benzoin was prepared from the reaction of benzaldehyde and potassium cyanide in *N,N'*-dimethylformamide.[33] Methanol-*d* was prepared by the heavy-water hydrolysis of dimethyl carbonate.[34]

Labeled Benzaldehydes. Benzaldehyde-*1-t* was prepared by the cyanide-catalyzed cleavage of benzil in a tritiated solvent.[33] Benzaldehyde-*1-d* was prepared either by the cleavage of benzil with potassium cyanide in a deuterated solvent[33] or *via* 2-phenyl-1,3-dithiane according to the method of Seebach, Erickson, and Singh.[35]

The Effect of Cyanide Ion on the Chemical Shift of the Hydroxyl Proton of Methanol. Two series of potassium cyanide solutions were prepared, one using CH_3OH as the solvent, the second using a mixture of CH_3OD and CH_3OH (93:7, v/v). Five solutions, ranging from 0 to 0.15 M in potassium cyanide, were prepared using each solvent. An aliquot of each solution was transferred to an nmr tube. Each sample was allowed to reach thermal equilibrium while in the probe of the Varian HA 100 nmr spectrometer. The chemical shift of the hydrogen of the hydroxyl group relative to the methyl group was read out directly in cycles per second. The methyl group was shown to be a reliable internal standard by a control experiment in which the chemical shift of the hydroxyl proton (δ_H) relative to the methyl group was measured as a function of mole fraction of CH_3O^- ($N_{CH_3O^-}$) in CH_3OH. A plot of δ_H *vs.* $N_{CH_3O^-}$ has a slope of 1360 which is in good agreement with the value 1450 found by More O'Farrell.[22]

Rate of Addition of Cyanide Ion to Benzaldehyde. A series of methanolic solutions containing sodium methoxide (3×10^{-3} M), benzaldehyde (0.7884 M), tetramethylsilane (1% by volume), and potassium cyanide ($2\text{–}10 \times 10^{-4}$ M) were prepared. The half-band width in cycles per second of the aldehydic proton absorption was measured as a function of varying cyanide concentrations. The Varian A-60 nmr was tuned on the TMS signal between each reading and corrections were made in the half-band width of the aldehydic absorption when necessary. All spectra were run at a 0.2-cps sweep time employing a 50-cycle sweep width, a filter band width of 4, and a radiofrequency power level of 0.04 (at which level no saturation was observed).

Spectroscopic Study of the Complexation of Cyanide Ion with Benzaldehyde. A 0.0285 M solution of sodium methoxide in methanol was used to prepare a series of spectroscopic solutions containing benzaldehyde (0.02–0.04 M), half of which also contained potassium cyanide (0.1026 M). A Cary Model 14 spectrophotometer with a thermostated cell holder was used to determine the absorbance at 320 nm of each solution. The free benzaldehyde concentration was calculated for each solution according to Beer's law, assuming no absorbance at 320 nm by the complex. The free cyanide concentration was calculated by subtracting the complex concentration from the total cyanide concentration. The equilibrium constants were determined at three temperatures from 3.8 to 22.5°. The linear plot of log K *vs.* T^{-1} was then extrapolated to obtain equilibrium constants at the temperatures of the kinetic studies. The observed equilibrium constants were invariant to within 3% over a twofold (0.04–0.02 M) range of initial benzaldehyde concentrations.

Deuterium Exchange Kinetics. Kinetic solutions were prepared by combining 5 ml each of stock solutions of benzaldehyde-1-*d* (0.4 M) and potassium cyanide (0.2 M) in methanol in a 10-ml volumetric flask. The reaction vessel was then thermostated in an oil bath and at appropriate intervals a 2-ml aliquot was removed by means of a pipet and added to a separatory funnel containing 10 ml of water and 1 ml of carbon tetrachloride (Matheson Coleman and Bell, spectroquality reagent). The aldehyde was extracted into the CCl_4 layer. A pipet was used to transfer a small amount of the CCl_4 layer to a BaF_2 ir cell (0.01 mm). The ir spectrum was then determined against a CCl_4 blank using a Beckman IR 8 spectrophotometer. The progress of the reaction was monitored by following the decrease in the aldehydic carbon–deuterium absorption at 2105 cm^{-1}. The aromatic carbon–hydrogen absorption at 3076 cm^{-1} was used as an internal standard and all absorptions at 2105 cm^{-1} were proportionately adjusted. The rate of appearance of the aldehydic carbon–hydrogen absorption at 2816 cm^{-1} was simultaneously observed. The stock solutions prepared were stored in the refrigerator. No aldehyde solution over 2 days old was used. Benzaldehyde-*1-d* prepared by both of the previously described methods gave essentially the same results. The first-order rate constants were calculated using a program which causes the GE 625 computer to calculate the observed first-order rate constants by a least-squares regression treatment of the integrated first-order rate law.

Tritium Exchange Kinetics. The solutions for kinetics were prepared as above, using benzaldehyde-*1-t* instead of benzaldehyde-*1-d*. The reaction vessel was thermostated in an oil bath and at appropriate time intervals a 1-ml aliquot was transferred by means of a pipet to a separatory funnel containing 5 ml of xylene and 5 ml of water. The aldehyde was extracted into the xylene layer. After drying over calcium chloride, a 4-ml aliquot of the xylene extract was added to 15 ml of scintillation solution. The activity of the sample was determined using a Beckman liquid scintillation system. The first-order rate constants were obtained in the same manner as described for benzaldehyde-*1-d*.

Benzaldehyde is a very strong quencher in scintillation counting. However, this complication could be dealt with by having the primary scintillator present in greater concentration than the aldehyde. For these studies the amount of benzaldehyde in the scintillation flask, assuming complete extraction of the aldehyde into xylene, would not be greater than 0.16 mmol. A xylene scintillation solution containing 1.1×10^{-1} M PPO (2,5-diphenyloxazole, Packard scintillation grade) and $2.8 \times 10^{-3}M$ POPOP (1,4-bis-2-(4-methyl-5-phenyloxazolyl), Packard scintillation grade) was used which would have an amount of primary scintillator (PPO) in 15 ml of not less than 1.65 mmol.

Condensation Kinetics. The glass kinetic reaction vessel consisted of a lower portion, having an approximate volume of 15 ml, sealed at one end and with a ground glass inner joint at the other, and an upper portion with a ground glass outer joint at each end and a vacuum stopcock in the middle. Two milliliters each of the benzaldehyde and cyanide solutions were pipetted into the lower

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[31] N. A. Lange, Ed., "Handbook of Chemistry," 9th ed, Handbook Publishers, Sandusky, Ohio, 1956, p 420.

[32] B. A. Marshall and W. Waters, *J. Chem. Soc.*, 1579 (1961).

[33] J. L. Kuebrich and R. L. Schowen, to be published.

[34] A. Streitwieser, L. Verbit, and P. Stang, *J. Org. Chem.*, **29**, 3706 (1964).

[35] D. Seebach, B. W. Erickson, and G. Singh, *J. Org. Chem.*, **31**, 4304 (1966).

portion of the vessel. The two pieces were then secured by means of a copper wire and the vessel was degassed on a vacuum manifold. After all samples had been degassed they were placed in an oil bath. At appropriate time intervals a reaction vessel was removed, allowed to cool to room temperature, and was then opened inside a Glove Bag having a nitrogen atmosphere. A 1-ml aliquot of the sample was then diluted to 51 ml with methanol for spectroscopic reading. The progress of the reaction was monitored by following the increase in absorbance at 320 nm using a Cary Model 14 spectrophotometer. Both benzaldehyde and benzoin absorb at this wavelength, but by use of the equation

$$A_t = 28.37([\text{Ald}]_0 - 2X) + 279.80(X)$$

where A_t is absorbance measured at any time, 28.37 is the molar extinction coefficient of benzaldehyde at 320 nm (determined in control experiments), 279.80 is the molar extinction coefficient of benzoin at 320 nm (also determined by us), $[\text{Ald}]_0$ is the initial aldehyde concentration, and X is the concentration of benzoin; the concentration of benzoin can be calculated at any time. The total absorbance and that of both species obeyed Beer's law. The condensation rate constants were calculated on the basis of the free aldehyde concentration as described above.

Yield of Benzoin from the Reaction of Benzaldehyde with Potassium Cyanide in Methanol. Benzaldehyde (5 ml, 49.3 mmol) was added to 100 ml of methanol containing potassium cyanide (0.65 g, 10 mmol) in a 250-ml three-necked round-bottomed flask fitted with a condensor and a gas inlet tube. The reaction was allowed to continue for 30 hr at reflux temperatures under a nitrogen atmosphere. The reaction solution was allowed to cool to room temperature, acidified with concentrated hydrochloric acid, and taken to dryness on the rotatory evaporator. The organic material was taken up in acetone, filtered, and again taken to dryness on a rotatory evaporator. A brownish solid weighing 4.5 g and melting at 121–130° was isolated. A small amount of this recrystallized from glacial acetic acid to give benzoin (crude yield = 21.2 mm, 86%).[36,37]

Acknowledgments. It is a pleasure to thank Professor J. K. Lee for his advice. We are grateful to Professor K. B. Wiberg (Yale University) for his kindness in introducing Dr. Lupes to the rest of us.

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(36) H. Gilman, Ed.-in-Chief, "Organic Syntheses," Collect. Vol. I, 2nd ed, Wiley, New York, N. Y., 1942, p 94.

(37) A. Lachman, *J. Amer. Chem. Soc.*, 46, 709 (1924).

Chemistry of the Active-Aldehyde Intermediate[1]

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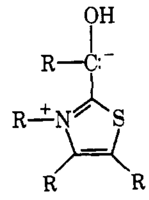
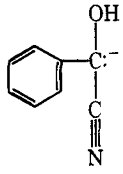
Contribution from the Department of Chemistry,
University of Kansas, Lawrence, Kansas 66044. *Received June 20, 1970*

Abstract: The reaction of benzil with cyanide ion gives an α-benzoyloxycyanocarbanion, a useful model for the α-hydroxycarbanion intermediates ("active aldehyde") of the benzoin condensation and thiamine action in biological systems. As predicted from indications that transition-state binding between these nucleophiles and their electrophilic partners was quite weak, a reasonably unselective behavior and consequently rich chemistry were observed under conditions of varying electrophilicity.

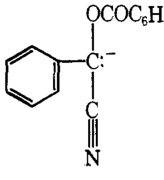
Resonance-stabilized α-hydroxycarbanions (I) are important in biological systems involving thiamine action,[3] where they have acquired the cognomen "active aldehyde" because, if they are formed from aldehydes, the normally electrophilic carbon of the latter becomes activated to a nucleophilic center in I. The cyanocarbanion II is formed in the benzoin condensation[4] and is a good model for studying the chemical behavior of "active aldehyde." Our investigation of the benzoin condensation in methanol led us to the belief that the reactions of II with the two electrophiles of significance in that system, *viz.*, the Brønsted acid methanol and the Lewis acid benzaldehyde, both proceed through "loose" transition states. By this is meant that the transition-state bond between the carbanionic carbon and the electrophile is quite weak, so that the structure of both moieties of the transition state remains little changed from their reactant condition. Among the implications of this proposal are a lack of selectivity of II (and by extension I) in its reactions with electrophiles, since the effects on free energy by structure in the electrophilic portion of the transition state will merely duplicate such effects in the reactant state and thus will be lost from the free energy of activation.



I



II



III

To explore this proposition for validity, we desired to examine the reactions of II under conditions of variable electrophilicity. The mobility of its hydroxyl proton introduced such practical difficulty, however, that we decided instead on the employment of the acyl derivative III. This species can be generated from benzil under a wide variety of conditions.[5–9] Kwart and Baevsky[6] have made plausible the mechanism of eq 1 for its generation.

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(2) Holder of a Research Career Development Award of the National Institute of General Medical Sciences.

(3) T. C. Bruice and S. J. Benkovic, "Bioorganic Mechanisms," Vol. 2, W. A. Benjamin, New York, N. Y., 1966, Chapter 8.

(4) J. P. Kuebrich, R. L. Schowen, M.-s. Wang, and M. E. Lupes, *J. Amer. Chem. Soc.*, 93, 1214 (1971).

(5) F. Jourdan, *Ber.*, 16, 659 (1883).

(6) H. Kwart and M. Baevsky, *J. Amer. Chem. Soc.*, 80, 580 (1958).

(7) W. Dilthey and P. Scheidt, *J. Prakt. Chem.*, 142, 125 (1935).

(8) H. D. Darking and C. R. Harrington, *J. Biol. Chem.*, 55, 485 (1923).

(9) J. C. Trisler and J. L. Frye, *J. Org. Chem.*, 30, 306 (1965).