

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE UNIVERSITY OF DELAWARE]

The Cyanide Ion Catalyzed Cleavage of Aromatic α -Diketones

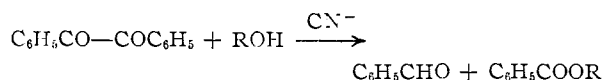
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A kinetic study of the cleavage of aromatic α -diketones in the presence of cyanide ion has been made using a spectrophotometric method. The cleavage of benzil and several mono- and disubstituted benzils were followed in methanol, ethanol and 1-propanol solvents. The effects of varying initial concentrations of reactants, benzaldehyde, lithium chloride, methoxide ion and water were studied. The activation energy and entropy of activation for cleavage of benzil were calculated from the cleavage rates at temperatures near 5, 15 and 30°. A mechanism is postulated for the reaction and a rate expression derived which is in agreement with the observed experimental results.

Introduction

Benzil, in an alcoholic solution of cyanide ion, is rapidly cleaved into benzaldehyde and an ester of benzoic acid.



This reaction was first reported by Jourdan¹ in 1883. Dakin and Harington² also reported the cleavage of benzil as well as anisil, *m*-dinitrobenzil, piperil and furil in alcoholic ammonium cyanide solutions. The products isolated from the cleavage of benzil were benzamide and benzaldehyde. Cleavage of the benzil monoximes,³ benzoin and several substituted benzoin⁴ by cyanide ion has also been reported. Weiss⁵ mentions the cleavage of benzil by cyanide ion as a means of separating mixtures of benzil and benzoin.

A study of the products of the cleavage of benzil and a number of mono- and disubstituted benzils has been completed in this Laboratory.⁶ The products of the cleavage reaction were found to consist of equimolar concentrations of aldehyde and ester. The more electron-releasing substituent was in most cases associated with the ester fragment. The objective of the present study was to ascertain the mechanistic factors which control the rate of the cleavage reaction and the role of the catalyst, cyanide ion, in this highly specific reaction (which at first glance appeared to be related to the effect of the hydroxide ion in the benzil-benzilic acid rearrangement⁷).

Experimental

Starting Materials.—Potassium cyanide (Baker and Adamson, A.C.S. Reagent Grade) was dried under vacuum at 100° for 24 hours and stored in a vacuum desiccator over Drierite until needed. Solutions of the KCN in anhydrous solvents were freshly prepared before each series of rate determinations. In no case was a solution more than one day old used. The concentration of cyanide ion was determined by titration against a 0.10 *N* AgNO₃ solution in the presence of ammonia and KI.⁸

Methanol, ethanol and 1-propanol solvents were dried by the method of Lund and Bjerrum⁹ and distilled under an

inert atmosphere directly into air-tight storage containers. Karl Fischer water analyses showed less than 0.01% water in the anhydrous solvents.

Sodium methoxide and magnesium methoxide solutions were prepared by dissolving sodium or magnesium metal in the anhydrous methanol. The concentration of methoxide ion was determined by diluting 10-ml. aliquots with water and titrating with 0.1 *N* HCl to a phenolphthalein end-product.

A commercial grade benzaldehyde was purified by vacuum distillation into glass ampoules. The sealed ampoules were stored in the dark until needed. Unused benzaldehyde remaining in the ampoules was discarded. The crude benzaldehyde was first freed of acidic impurities by washing with 5% Na₂CO₃ solution then dried over CaCl₂ before distillation. A middle fraction boiling at 46–47.5° under 4 mm. pressure was saved for use.

The tetrahydrofuran was a commercial grade solvent purified by refluxing with sodium shot for 48 hours and distillation through a Vigreux column at 66.0–66.5° under atmospheric pressure into a storage container.

Lithium chloride (Mallinckrodt Analytical Reagent) was dried in a vacuum oven for 24 hours at 100° before use.

The benzil and substituted benzils used in this work were prepared as part of a prior study.⁶ A list of the physical constants and absorption maxima of the benzils is given in Table I. Solutions of the desired benzil were made by dissolving an accurately weighed amount of the benzil in the anhydrous solvent. Solutions were prepared daily and stored in the dark during periods between use.

TABLE I
PHYSICAL CONSTANTS AND ABSORPTION MAXIMA OF SUBSTITUTED BENZILS

Benzil	M.p., °C.	Absorption max. used, $m\mu$
Benzil	95.0	375
4-Methoxybenzil	52.0–53.0	375
4-Dimethylaminobenzil	101.0–102.0	460
4-Chlorobenzil	75.0	375
4-Methylbenzil	30.0	370
4- <i>t</i> -Butylbenzil	B.p. 219 (2 mm.)	370
4,4'-Dimethylbenzil	108.0	375
4,4'-Di- <i>t</i> -butylbenzil	104.0–104.5	375
4-Dimethylamino-4'-chlorobenzil	143.5–144.0	460
4-Methoxy-4'-chlorobenzil	128.0	370
4,4'-Dimethoxybenzil	133.0	375

Kinetic Procedure.—The rate of cleavage was followed spectrophotometrically by measuring the decrease in the absorption maxima of the benzil. A list of the absorption maxima of the benzils studied is shown in Table I. A Process and Instruments RS3 recording spectrophotometer was used and the variation in absorbance was continuously charted on the modified Leeds and Northrup Speedomax recorder provided with this instrument. A commercial Corex optical cell was modified so that two separate compartments were present. In this way, solution of each reactant, KCN and benzil, were held separately within the same cell, thermostated to a constant temperature, then mixed just prior to placing the cell in the spectrophotometer. The spectrophotometer cell holder was also thermostated so that the cells re-

- (1) F. Jourdan, *Ber.*, **16**, 659 (1883).
- (2) H. D. Dakin and C. R. Harington, *J. Biol. Chem.*, **55**, 487 (1923).
- (3) A. H. Blatt and R. P. Barnes, *THIS JOURNAL*, **56**, 1148 (1934).
- (4) J. S. Buck and W. S. Ide, *ibid.*, **53**, 1912, 2350, 2784 (1931).
- (5) M. Weiss and M. Appel, *ibid.*, **70**, 3606 (1948).
- (6) J. S. Luloff, Thesis in partial fulfillment of the requirements for the degree of Master of Science, June, 1953.
- (7) F. H. Westheimer, *THIS JOURNAL*, **58**, 2209 (1936).
- (8) H. H. Willard and N. H. Furman, "Elementary Quantitative Analysis," D. Van Nostrand Co., Inc., New York, N. Y., 1940, p. 188.
- (9) H. Lund and J. Bjerrum, *Ber.*, **64**, 210 (1931).

mained at a constant temperature during the reaction period. The recorder was started at the moment the solutions were mixed so that an accurate measure of the total reaction time was known; all but the initial ca. ten seconds of the reaction could be monitored in this fashion.

Pre-determined volumes of each reactant, KCN and benzil, were microbureted into each compartment of the optical cell, then sufficient anhydrous solvent added to either compartment to bring the total volume to 3.20 ml. In this way, the concentration of one reactant could be varied and the other held constant over a series of rate determinations.

The rate law observed in most of the runs readily is derived¹⁰

$$k = \frac{1}{t} \ln \frac{(D_{\infty} - D_0)}{(D_{\infty} - D)}$$

where D_{∞} is the optical density of the solution measured after an infinite time, D_0 is the optical density initially and D is the optical density at any given time. For a given initial concentration of benzil, the term $(D_{\infty} - D_0)$ is constant and a plot of $\ln(D - D_{\infty})$ against time is linear, with a slope equal to the observed rate constant, k_{obs} . The typical rate measurement shown in Fig. 1 demonstrates that the data also may be plotted for purposes of the Guggenheim method¹¹ of obtaining the rate constant of a pseudo first-order reaction.

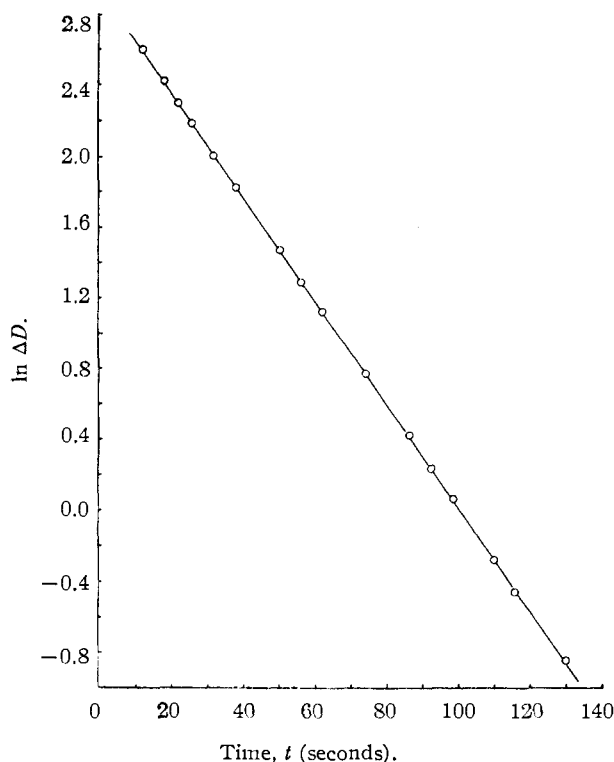


Fig. 1.—Calculation of observed rate constant by Guggenheim method (slope = 0.0295 sec.⁻¹).

Results and Conclusions

Kinetic Order.—The observed kinetics were first order with respect to benzil at each initial benzil concentration. However, a small but reproducible dependence of the rate constant on initial benzil concentration, over a range of initial benzil concentrations, was observed. The data for a series of reactions at varying initial benzil and cyanide ion concentrations are shown in Fig. 2.

Catalysis of the cleavage is demonstrated clearly

(10) A. A. Frost and R. G. Pearson, "Kinetics and Mechanism," John Wiley and Sons, Inc., New York, N. Y., 1953, p. 37.

(11) E. A. Guggenheim, *Phil. Mag.*, **2**, 538 (1926).

in Fig. 2 by the linear dependence of the rate constant on initial cyanide ion concentration for any constant initial benzil concentration.

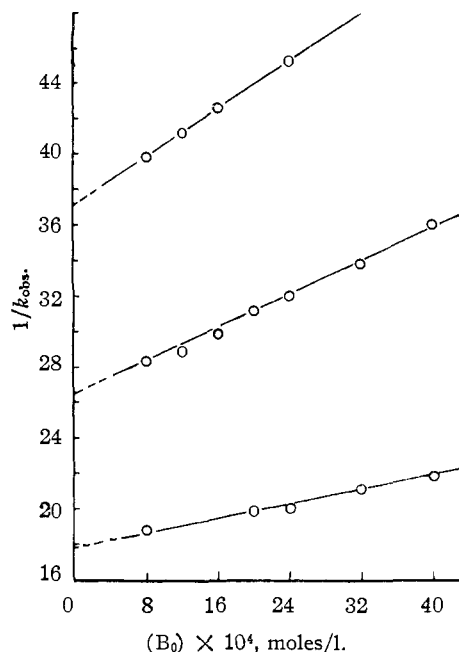


Fig. 2.—Dependence of rate on initial benzil concentration: top, $(\text{CN}_0^-) = 0.0024 M$; middle, $(\text{CN}_0^-) = 0.0032 M$; lower, $(\text{CN}_0^-) = 0.0048 M$.

The decrease in rate with increasing initial benzil concentration suggested the possible presence of an acidic impurity in the benzil which might tend to remove cyanide ion from reaction as HCN (which is not a catalyst for the reaction as will be demonstrated shortly). However, repeated recrystallization of the benzil had no effect on the rate. Also, the formation of an acidic product during the reaction would be expected to lead to a continual change in the concentration of free cyanide ion, again, by formation of HCN. This would be reflected in a changing rate during the reaction and a departure from the generally observed pseudo first-order kinetics.

The Effect of Added Benzoic Acid.—The addition of benzoic acid causes an almost linear decrease in the observed rate constant. When an amount of benzoic acid equivalent to the initial cyanide ion concentration is added, the rate constant is reduced to less than 4% of that in the original reaction composition. No change in the kinetic order of the reaction is to be noted, however.

It has been well established that cyanohydrin formation¹² requires attack by cyanide ion on the carbonyl function. Svirbely and Roth also have produced evidence indicating general base catalysis of this reaction.¹³ From the known dissociation constants of benzoic acid and hydrocyanic acid in aqueous solution, it is apparent that an equivalent of added benzoic acid reduces the cyanide ion concentration to a very small fraction of its original

(12) See reference 15 and references cited therein as well as (a) A. Lapworth, *J. Chem. Soc.*, **83**, 995 (1903); (b) **85**, 1206 (1904).

(13) W. J. Svirbely and J. F. Roth, *THIS JOURNAL*, **75**, 3106 (1953).

magnitude. We may infer from these considerations that the formation of a cyanohydrin intermediate requiring the availability of (free) cyanide ion is an essential step in the mechanism of the cleavage reaction.

Effect of Added Benzaldehyde.—A decrease (ca. 35%) of the rate constant in the presence of an amount of added benzaldehyde equivalent to four to five times the amount formed as product was found. The decrease in rate in the presence of added benzaldehyde can be attributed to the equilibrium formation of a cyanohydrin in which cyanide ion is removed from participation in the cleavage reaction.

The invariance of kinetic order of the cleavage noted upon addition of benzaldehyde supports the view that the cyanohydrin equilibrium must be extremely mobile. The rapidity with which such equilibria are established in alkaline media has also been reported by Stewart and Fontana¹⁴ and Yates and Heidler¹⁵ in their investigations of typical cyanohydrin equilibria.

Influence of Ionic Strength.—The absence of any salt effect is demonstrated by the failure to observe any change in either the rate or the order of reaction on addition of lithium chloride in amounts up to ten times a low, fixed cyanide ion concentration. For a reaction transition state involving a neutral molecule and a negative ion no salt effect would be predicted at the low ionic strengths employed in these studies. This permits the conclusion¹⁶ that the effect of variation in cyanide ion concentration is entirely independent of its neutral salt concentration and is determined by its role as a specific ion catalyst in this reaction.

Effect of Methoxide Ion.—The addition of methoxide ion, as sodium or magnesium methoxide, increased the observed rate as shown in Fig. 3.

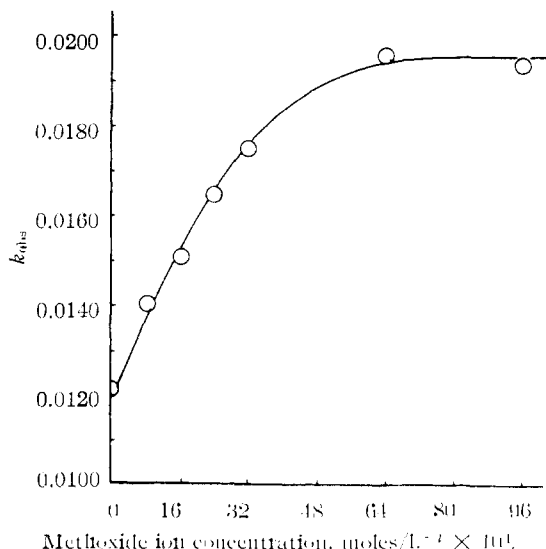


Fig. 3.—Plot of added methoxide ion concentration against observed rate constant in methanol solution at 30.0°: $(CN_0^-) = 0.0016 M$; $(B_0) = 0.0240 M$.

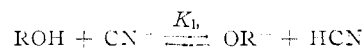
(14) T. Stewart and B. Fontana, *THIS JOURNAL*, **62**, 3281 (1940).

(15) W. F. Yates and P. L. Heidler, *ibid.*, **74**, 4153 (1952).

(16) E. A. Moelwyn-Hughes, "The Kinetics of Reactions in Solutions," Oxford Press, Oxford, England, 1947, p. 97.

At low base concentrations, no variation in kinetic order was observed. At very high base levels, the reaction tended to vary from strict first-order obedience.

These results suggest that methoxide ion increases the rate by a reversal of the solvolysis reaction of cyanide ion. The solvolysis equilibrium can be formulated as



and

$$K_h(ROH) = (OR^-)(HCN)/(CN^-)$$

where K_h is the solvolysis constant. Although no value for the solvolysis constant of cyanide ion in methanol could be found in the literature, it is possible to show that

$$\frac{K_h(\text{MeOH})}{K_h(\text{H}_2\text{O})} = \frac{K_e(\text{MeOH})}{K_e(\text{H}_2\text{O})}$$

where $K_e(\text{MeOH})$ and $K_e(\text{H}_2\text{O})$ are the acidity constants measured by Hine and Hine.¹⁷ Thus, the solvolysis constant of cyanide ion in methanol, $K_h(\text{MeOH}) = 9.25 \times 10^{-5}$ mole/l., can be calculated from that in water, $K_h(\text{H}_2\text{O}) = 2.79 \times 10^{-5}$ mole/l.,¹⁸ assuming that to a first approximation there is no change in the activity coefficients of extremely dilute solutions of the reactants in either solvent. For a given initial cyanide ion concentration (CN_0^-) , and added methoxide ion concentration (OMe^-) , the hydrogen cyanide concentration at equilibrium can be calculated from

$$K_h(\text{MeOH}) = \frac{[(OMe^-) + (HCN)](HCN)}{(CN_0^-) - (HCN)}$$

Assuming that (HCN) is small with respect to the added (OMe^-)

$$K_h(\text{MeOH}) = \frac{(OMe^-)(HCN)}{(CN_0^-) - (HCN)}$$

whereby

$$(HCN) = \frac{K_h(\text{MeOH})(CN_0^-)}{K_h(\text{MeOH}) + (OMe^-)}$$

The corrected cyanide ion concentration (CN_a^-) is obtained at each methoxide ion concentration by subtracting the calculated (HCN) from (CN_0^-) .¹⁹

For each added methoxide ion concentration shown in Table II at least four rate measurements were made in which the initial benzil concentration was varied. These rates were graphically extrapolated to zero benzil concentration to obtain the limiting rate, k' . The apparent constancy of the second-order rate constant k'' over a significant variation in initial methoxide and cyanide ion concentrations clearly defines the role of added base.

Solvents Effects.—The differences in the observed rate constants when measured in anhydrous methanol, ethanol and 1-propanol were small but

(17) J. Hine and M. Hine, *THIS JOURNAL*, **74**, 5266 (1952).

(18) R. W. Harman and F. P. Woxley, *Trans. Faraday Soc.*, **20**, 502 (1925).

(19) Although (CNa^-) was calculated by allowing for the formation of HCN from (CN^-) by hydrolysis in a reaction solution containing no carbonyl and the (HCN) in our rate equation refers to the actual concentration in a reaction solution, we may substitute (CNa^-) for $(CN_0^-) - (HCN)$ since the rate constants have been extrapolated to zero benzil concentration; see Fig. 2 and discussion in later sections of this report.

TABLE II
EXTRAPOLATED FIRST-ORDER RATE CONSTANTS CORRECTED
FOR SOLVENT HYDROLYSIS OF CYANIDE ION IN ANHYDROUS
METHANOL AT 30.0°

Initial cyanide ion concn. (CN_0^-), moles/liter	Added methoxide ion concn., mole/l.	Corrected cyanide ion concn. (CN_a^-), mole/liter	$k',^a$ sec. ⁻¹	$k'',^a$ 1./m.-sec.
1.60×10^{-3}	12.6×10^{-4}	1.78×10^{-2}	14.1
1.60	0.0008	14.6	1.98	13.6
1.60	.0016	15.2	2.04	13.4
1.60	.0024	15.4	2.12	13.8
1.60	.0032	15.6	2.20	14.1

Av. 13.8 ± 0.3

^a Where k' is the limiting value of the observed rate constant (k_{obs}) as (B_0) approaches zero, and $k'' = k' / (\text{CN}_a^-)$. Each value of k' is determined by an extrapolation from at least four determinations of k_{obs} at varying (B_0).

TYPICAL SERIES AT CONSTANT (B_0) AND (CN_0^-) AS PLOTTED IN FIG. 3

Methoxide ion concn. mole/liter	k_{obs} , sec. ⁻¹
....	0.0122
0.0008	.0141
.0015	.0151
.0024	.0166
.0032	.0175
.0064	.0196
.0096	.0193

consistent and well outside the experimental error of the measurements. In order to resolve the cause of this variation, water and tetrahydrofuran were (separately) used as diluents of the alcoholic solvents and the effects of these additions on the rate constant were noted. A variation in medium dielectric by a factor of almost two was accomplished by such dilutions.

Neither diluent had an effect on the rate constant in methanol (though in some runs the water was present in the amount of up to 31 mole per cent.) indicating that general solvent effects due to dielectric and polar properties of the medium are absent in this reaction. However, the results with ethanol and 1-propanol had a somewhat different character. Though additions of moderate amounts of tetrahydrofuran produced no rate change, the reaction proved to be very sensitive to dilution of either of these alcohols with water. In aqueous ethanol and 1-propanol solutions the order of reaction was no longer constant. The instantaneous rates of reaction decreased markedly throughout the course of reaction and the rate of decrease was most pronounced in solution containing the greatest proportions of water. Furthermore, this response to the amount of added water was steepest in the case of 1-propanol as is evident from a plot of the ratio of the instantaneous observed rate constants in the presence of water, k_w , at 50% reaction versus the observed rate constants in the anhydrous solvent, k_0 , as shown in Fig. 4.

There are, conceivably, two (apparent) influences of solvent at work in this reaction. (1) Solvent acidity controls the solvolysis of cyanide ion, and consequently the available cyanide ion catalyst concentration. (2) Solvent nucleophilicity³⁸ determines the nature of the product and, therefore, the extent to which an alcohol competes with water in the product-forming step in a mixed solvent medium. The operation of this latter factor can

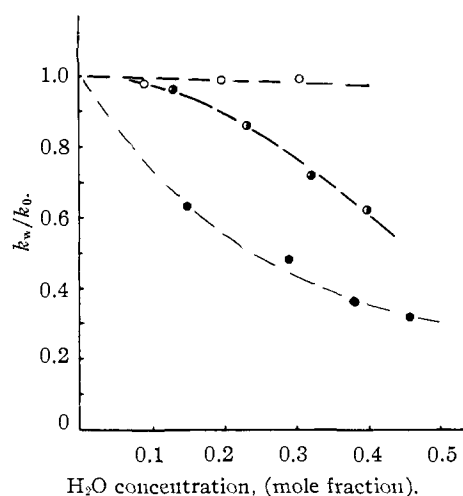


Fig. 4.—Effect of water where k_w/k_0 is the ratio of the observed rate constant in the presence of added water (k_w) at 50% reaction to the observed rate constant in anhydrous solvent at 30.0° (k_0): aqueous methanol solutions, O; aqueous ethanol solutions, ◐; aqueous 1-propanol solutions, ●.

be seen from the data illustrated in Fig. 4 which demonstrate clearly that 1-propanol is considerably less nucleophilic than water and competes very poorly in the product-forming step. Ethanol apparently represents some improvement in this regard and methanol which is more nucleophilic than water can tolerate 31 mole per cent. (possibly more) without evidencing the rate-retarding formation of any benzoic acid. The presence of ammonia (a reagent of greater nucleophilicity) when ammonium cyanide is the cleavage reagent results in formation of benzamide as a predominant product.²

As for the operation of the first factor, it is to be expected that the more acidic solvent,¹⁷ methanol, would afford the lowest available concentration of cyanide ion, and this is evidently the case. The limiting rate constant, k' , in each of the alcoholic solvents used are shown in Table III. Therein, it will be noted that at identical initial cyanide ion concentrations the k' in anhydrous methanol is smaller than that in the ethanol or 1-propanol. Furthermore, the second-order constant, k'' , computed on the basis of the corrected cyanide concentration (over an approximately three-fold range of CN_0^-) and corresponding to an almost threefold variation in k' is independent of the nature of the alcoholic solvent well within experimental accuracy. This confirms also the inference drawn above that the solvent enters the reaction only in a non-rate-determining step.

The lack of response to change in solvent dielectric is a general property of reactions in which the transition state is of the same charge character as the reactant (or a stable intermediate formed by the reactants).²⁰ An attractive mechanism of reaction consistent with these and the above inferences may be discussed in terms of an energy-reaction coordinate diagram. The reactants (cyanide ion and benzil) readily form a stable intermediate anion on the path to the transition state. The elongation of the central carbon-carbon bond in

(20) See reference 10, p. 122 *et seq.*

range 0.8–1.0. Therefore, the last term in the denominator (of the right member) of eq. 14 is always a great deal smaller than the value of (B) and never exceeds 0.2 (B). For almost all the course of reaction this term is negligible with respect to the other denominator terms and, consequently, the first-order rate constant, k_{obs} , may be expressed quite simply as

$$k_{obs} = \frac{k_2 K_1 K_4 (\text{CN}_0^- - \text{HCN})}{K_4 + (B_0) - (\text{CN}_0^-) + (\text{CN}^-) + (\text{HCN})} \quad (15)$$

On extrapolation to zero initial benzil concentration, the condition $(\text{CN}_0^-) = (\text{CN}^-) + (\text{HCN})$ is valid and eq. 15 then reduces to the form

$$k' = k_2 K_1 [(\text{CN}_0^-) - (\text{HCN})] \quad (16)$$

where k' is the extrapolated value of the observed rate constant and the term $[(\text{CN}_0^-) - (\text{HCN})]$ is equivalent to the corrected cyanide ion concentration (CN_a^-) discussed previously; see Table II. The value of $k_2 K_1$ found by this method was approximately 13.7; compare the values of k'' in Tables II and III.

The experimental rate data has been found to be entirely in agreement with the predictions of eq. 15 and 16 by plotting the data in several alternate ways. For example, eq. 15 may be written in the form

$$\frac{1}{k_{obs}} = \frac{1}{(\text{CN}_0^-) - (\text{HCN})} \left(\frac{1}{k_2 K_1} + \frac{B_0}{k_2 K_1 K_4} + \frac{(\text{CN}^-) + (\text{HCN}) - (\text{CN}_0^-)}{k_2 K_1 K_4} \right) \quad (17)$$

Under the reaction conditions readily accessible to study $(B_0) \gg (\text{CN}_0^-)$ and the concentrations of uncomplexed cyanide, (CN^-) and (HCN) , are also very small. Thus, several terms of eq. 17 involving these quantities may be assumed to be relatively negligible and eq. 17 reduces to the approximate expression

$$\frac{1}{k_{obs}} = \frac{\alpha}{\text{CN}_0^-} - \gamma \quad (18)$$

where the term γ represents the small, virtually constant contribution of the last term in the expansion of eq. 17. A plot of $1/k_{obs}$ versus $1/\text{CN}_0^-$ for the specific reaction conditions is linear and the slope, $\alpha = (1/k_2 K_1) + ((B_0)/k_2 K_1 K_4)$ may be obtained. The variation of α with (B_0) according to the derived relation

$$(B_0) = k_2 K_1 K_4 \alpha - K_4 \quad (19)$$

is also linear for values of the ordinate representing more than a threefold variation in (B_0) . The values of K_4 and k'' (i.e., $k_2 K_1$) were obtained from the slope and intercept of this plot. The terms of eq. 15 may also be rearranged into the form

$$\frac{K_4 + (B_0)}{(\text{CN}_0^-)} = \frac{k_2 K_1 K_4}{k_{obs}} + 1 \quad (20)$$

A plot of $(K_4 + (B_0))/(\text{CN}_0^-)$, using the value of $K_4 = 0.11$ obtained by application of eq. 19, versus $1/k_{obs}$ for a large number of runs involving variations in both (B_0) and (CN_0^-) again gives a good straight line of slope $k_2 K_1 K_4$ and consequently affords an additional determination of k'' . The values of k'' from these plots of eq. 19 and 20 are approximately 20% less than the values determined directly by application of corrections for cyanide

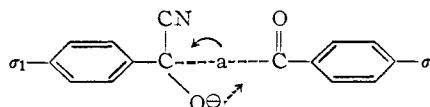
hydrolysis to the observed rate constant; see Tables II and III. This difference is, of course, not unexpected in view of the approximations used in obtaining the derived relations 18, 19 and 20.

The excellent fit of the data to all the above relations reduces the possibility of accidental correspondence of the observed rate data to the eq. 15 originally derived on the basis of the mechanism of the cleavage reaction proposed above.

The Effect of Substituents on the Rate of Cleavage.—Clearly, in a complex reaction a linear free energy relationship, expressing substituent effects, must depend on the electronic factors that determine the over-all rate by their contributions to all the steps prior to and including the rate-determining step of reaction. Accordingly, the magnitude and sign of ρ in the Hammett equation has often been used as an indication of the electronic factors operating in the mechanism of a complex reaction.²³ In the present case it is realized readily that the over-all ρ constant may be expressed as a sum of terms; that is

$$\log \frac{k_{obs}}{k_{obs}^0} = \log \frac{K_1}{K_1^0} + \log \frac{k_2}{k_2^0} \quad (21)$$

Furthermore, since there are two (substituent) rings affecting the seat(s) of reaction the linear free energy relationship is required to express how these substituent effects are combined in the cleavage reaction of the bond a in



where σ_1 is defined as the substituent which ends up in aldehyde and σ_2 in ester product.

Amongst the many functions attempted the only good approach to a linear relationship obtained was between the sum of the Hammett substituent constant $(\sigma_1 + \sigma_2)$ and the $\log(k''/k_0'')$ as shown in Fig. 5. In this respect the cleavage reaction follows a Hammett equation of the form

$$\log(k/k^0) = \rho \Sigma \sigma \quad (22)$$

discussed by Jaffé²⁴ and by Taft²⁵ to express the effect of multiple substitution and shown by others such as Swain, Stockmayer and Clarke²⁶ to apply even when the effective substituents are attached to different rings conjugated with the seat of reaction. The concordance of our results with an equation of this form would seem to indicate, furthermore, that the ρ observed represents an average value derived of the strictly additive contributions of the ρ values for a rapidly established equilibrium (K_1) and a kinetic step (k_2).

The data from which the Hammett plot, Fig. 5, was drawn are listed in Table III for benzil and Table IV for the substituted benzils.

The value of $\rho = 3.45$ was determined by the

(23) See, for example, H. Kwart and P. S. Frances, *THIS JOURNAL*, **77**, 4907 (1955), and other references cited there in this context.

(24) H. H. Jaffé, *Chem. Revs.*, **53**, 191 (1953).

(25) R. W. Taft, Jr., Chapter in "Steric Effect in Organic Chemistry," edited by M. S. Newman, John Wiley and Sons, Inc., New York, N. Y., 1956, pp. 623–624.

(26) C. G. Swain, W. H. Stockmayer and J. T. Clarke, *THIS JOURNAL*, **72**, 5426 (1950).

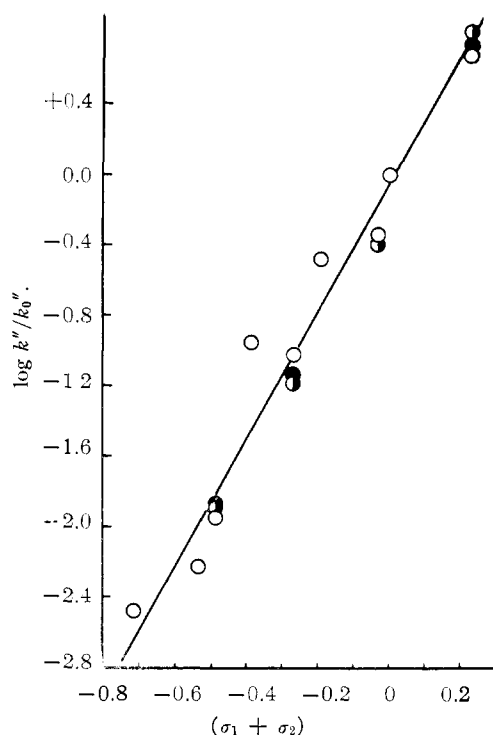


Fig. 5.—Hammett equation plot: O, methanol solvent; ●, 1-propanol; ◐, ethanol.

method of least squares.^{27a} The probable error was 0.18. Most important, the correlation coefficient was 0.976, strongly suggesting the existence of a genuine relation between the variables plotted in Fig. 5.

TABLE IV
CLEAVAGE OF SUBSTITUTED BENZILS AT 30°

Benzils	Corrected cyanide ion concn. (CN ⁻), mole/liter	ROH solvent	k' , ^a sec. ⁻¹	k'' , ^a 1./m.-sec.
4-Chloro	3.20×10^{-4}	MeOH	17.1×10^{-2}	61.6
4-Methoxy	3.20	MeOH	0.32	1.18
4- <i>t</i> -Butyl	3.20	MeOH	1.24	4.49
4-Dimethylamino	12.8	MeOH	0.05	0.04
4-Chloro-4'-methoxy	3.20	MeOH	1.60	5.92
4-Chloro-4'-dimethylamino	3.20	MeOH	0.05	0.19
4,4'-Dimethoxy	32.00	MeOH	0.22	0.08
4,4'-Di- <i>t</i> -butyl	4.20	MeOH	0.054	1.48
4-Chloro	3.20	EtOH	23.0	76.5
4-Methoxy	6.40	EtOH	0.61	1.00
4-Chloro-4'-dimethylamino	6.40	EtOH	0.11	0.19
4-Chloro-4'-methoxy	3.20	EtOH	1.73	5.78
4-Chloro	2.40	<i>n</i> -PrOH	19.5	88.5
4-Methoxy	2.40	<i>n</i> -PrOH	0.20	0.88
4-Chloro-4'-dimethylamino	2.40	<i>n</i> -PrOH	.034	0.15

^a The k' is the limiting value of the observed rate constants (k_{obs}) extrapolated to zero benzil concentration and $k'' = k'/(CN_0^-)$. In each case the extrapolation to k' was done graphically based on at least 4 rate measurements at different (B_0) concentrations. It is to be noted also that $k'' = k_2K_1$ from eq. 16.

(27) (a) "Statistical Methods in Research and Product," edited by O. L. Davies, second ed., 1945, Oliver and Boyd, London, pp. 123-124; (b) THIS JOURNAL, p. 136; (c) see reference 24 for a comprehensive listing of ρ values for side chain reactions.

This magnitude of ρ is unusually large for a side chain reaction.^{27c} We have taken this to indicate that both the $\rho(K_1)$ and $\rho(k_2)$ terms contributing have the same positive sign. This is entirely consistent with expectation based on the proposed mechanism of reaction. The displacement of the cyanohydrin (K_1) in the direction of forming (C^-) is, of course, expected to be favored by electron-withdrawing substituents. The positive value of $\rho(k_2)$ confirms the proposed transition state of the cleavage reaction in which the cyanohydrin carbon must bear considerable negative charge (as indicated) and is aided when σ_1 is electron withdrawing. This accords with the conclusion reached (above) on the basis of the observed insensitivity of the cleavage reaction to solvent dielectric. This lack of response of the rate-determining step to the nature of the alcoholic solvent is also noted in Fig. 5 by the fact that all points, regardless of solvent (methanol, ethanol or propanol) are quite closely coincident with the drawn line. Obviously, the nature of R in the transition state exerts very little effect on the breaking of the carbon-carbon bond and the stabilization of the charge resulting.

The absence of a strong electromeric requirement to assist bond (a) breaking in the principal transition state is suggested by two observations; (i) the failure of Brown's constants²⁸ to give a good, consistent, linear relationship; (ii) the failure of electron-releasing substituents to significantly accelerate cleavage as would have been expected if resonance stabilization of positive charge on the σ_2 carbonyl was the single important feature of the principal transition state.

The results obtained by analysis of the products of cleavage of all the benzils investigated (Table IV) correlate well with this conclusion and with the proposed mechanism. Thus, in each instance where σ_1 was more positive than σ_2 , the expected (σ_1) aldehyde and (σ_2) ester were the sole products obtained. This is in agreement with the mechanism in that the carbonyl linked to the more electron-deficient ring will be the preferred locus of cyanide ion attack forming (C^-) in equilibrium K_1 . The one exception is the case of the mono-chlorobenzil which gives almost an equimolar mixture of all four possible cleavage products.⁶ This exception would appear to indicate that the $\rho(K_1)$ and $\rho(k_2)$ terms make almost equal contributions to the over-all ρ of reaction. The chloro substituent exerts its accelerating effect equally well in both possible positions; as σ_1 by increasing the equilibrium concentration of (C^-), as σ_2 by directly increasing the ease of cleavage of the central carbon-carbon bond in the transition state.²⁹ The net result, therefore, can be approximated by a model in which both substituents are in the same ring and exerting their effect independently, as concluded by Jaffé for several Hammett series obeying the relationship in eq. 22.

Still another aspect of the substituent effects on

(28) H. C. Brown and Y. Okamoto, THIS JOURNAL, **79**, 1913 (1957).

(29) Obviously the chlorine as σ_2 could also increase the electrophilicity of the unsubstituted benzoyl carbon (to cyanide ion attack) by transmission of its inductive effect through the vicinal carbonyl group.

the cleavage reaction calls for comment here. When the 4,4'-dichlorobenzil was prepared it proved to be too insoluble in alcoholic solvents for rate measurement and comparison in a Hammett series. Nonetheless, crude (competitive) rate studies clearly indicated that its cleavage reaction was much faster than all the substituted benzils in Table IV. However, eq. 22, in a sense, is a discontinuous relation, for it was not possible to observe the cleavage reaction with benzils substituted with more electron-attracting groups. Substances such as *p*-nitrobenzil and 9,10-phenanthraquinone formed stable, colored solutions with cyanide ion which were readily reverted³⁰ to the starting diketones. This suggested the possibility that the potentials of certain α -diketones are sufficiently great to oxidize the cyanide ion while being converted into stable semiquinones. Further study on this matter is in progress.

Temperature Effects.—The Arrhenius activation energy for the cleavage of benzil in methanol was determined to be 4.2 kcal./mole from a plot of $\log k''$ vs. $1/T$ using results obtained at 30.0, 14.7 and 4.4° (Table V). The entropy of activation was computed in the usual manner³¹ and found to be about -41.1 e.u., varying only very little with the temperature within the range of measurement.

TABLE V
TEMPERATURE DEPENDENCE OF BENZIL CLEAVAGE IN
METHANOL

Initial cyanide ion concentration = 0.0032 M		
Temp., °C.	k' , sec. ⁻¹	k'' , l./m.-sec.
30.0	3.65×10^{-2}	13.5
14.7	2.51	8.8
4.4	2.08	7.2

From the fact that the rate appears to be independent of the solvent the conclusion might be drawn that very little change in solvation effects is experienced by cyanide ion with the various solvents tested; *i.e.*, cyanide ion regards all these solvents more or less like ROH, where variation in R has a negligible effect.³² Furthermore, a profound change in the extent and nature of the solvation in proceeding from (C⁻) to (E⁻) in the transition state does not seem to occur either under these conditions. Assuming an entropy for the preliminary cyanohydrin equilibrium K_1 to be roughly of the order -16 to -17 e.u.,³³ a decrease in activation entropy of 23-24 e.u. must be accounted for in the rate-determining step (k_2) of the cleavage. Obviously, this does not correspond to the simple picture of a spontaneous dissociation in the transition state which in typical cases is attended by a significant, positive ΔS^\ddagger .³⁴ On the other hand,

(30) These results, described in part in the master's thesis of J. S. Luloff, University of Delaware, June, 1953, will be discussed in detail in a future publication.

(31) S. Glasstone, K. J. Laidler and H. Eyring, "The Theory of Rate Processes," McGraw-Hill Book Co., Inc., New York, N. Y., 1941, p. 197.

(32) For a discussion of solvent effects on the activation parameters, see J. E. Leffler, *J. Org. Chem.*, **20**, 1202 (1955).

(33) Estimated from data of J. W. Baker and M. L. Hemming, *J. Chem. Soc.*, 191 (1942), on the formation of benzaldehyde cyanohydrin in alcohol solution.

(34) See, for examples, A. T. Blomquist and I. A. Bernstein, *THIS JOURNAL*, **73**, 5546 (1951), and A. T. Blomquist and A. J. Euselli, *ibid.*, **73**, 3883 (1951).

solvent electrostriction effects, which may not differ greatly in going from methanol to propanol, could very well accommodate a negative ΔS^\ddagger of the magnitude estimated for the k_2 step. This would mean that, contrary to the implication of the insensitivity of rate to ROH, the solvent does indeed play a role exclusive of its dielectric properties.

Role of Cyanide Ion as a Specific Catalyst.—Several extraordinary circumstances determine the unique role of cyanide ion as a specific reagent for benzil cleavage. Thus, it is especially well suited sterically for attack at even the hindered carbonyl carbon. This has been made evident in data discussed by Pauling³⁵ on the shape and the effective atomic radii of the largest atoms of a series of nucleophilic agents. Not only is the cyanide ion one of the smallest of such reagents but its cylindrical shape is particularly advantageous since the bonding angle to the carbonyl carbon is along the axis of the carbon-nitrogen bond.

The readiness with which cyanide bonds to carbonyl can be estimated from measurement by Swain and Scott³⁶ and by Hawthorne, Hammond and Graybill³⁷ comparing its nucleophilicity with that of other anions in alkyl halide substitutions.³⁸ The cyanide ion appears to be one of the strongest nucleophilic agents known, exceeded only by a very few (and much larger) anions like thiosulfate. From another viewpoint, the specificity of cyanide here is related to the very large intrinsic electronegativity^{35b} of the nitrile group in the anion (C⁻). Thus, the formation of (C⁻) is the result of the nucleophilic character of the cyanide ion; the decomposition of (C⁻) is the result of the electron-withdrawing power of the nitrile group and the stability of the anionic product (E⁻) conferred by resonance with the nitrile group. This latter effect is not unrelated to the origin of specific catalysis by cyanide ion in the benzoin condensation where an intermediate carbonion similar to (E⁻) has been postulated.³⁹

The hydroxide ion, amongst other nucleophilic reagents we have tried to substitute for cyanide in the cleavage reaction, fails because of the lower nucleophilicity and (even more importantly) because of its inability to contribute sufficiently to bond breaking either by induction and/or stabilization of

(35) (a) L. Pauling, "Nature of the Chemical Bond," Cornell University Press, Ithaca, N. Y., 1948, p. 75; (b) also a discussion of other contributing factors in reference 26, p. 616, *et seq.*

(36) C. G. Swain and C. B. Scott, *THIS JOURNAL*, **75**, 141, 247 (1953).

(37) M. F. Hawthorne, G. S. Hammond and B. M. Graybill, *ibid.*, **77**, 486 (1955).

(38) We use the term nucleophilicity with reference to a measure of the ability of cyanide ion to bond to the carbonyl carbon and with exactly the same significance with which many authors have used the term in considering displacements and solvolysis of halide ion from carbonyl in substrates like benzoyl halides, carbamyl halides and analogous substrates like sulfonyl halides. Among current contributions to *THIS JOURNAL* employing this usage see for example reference 32 and H. K. Hall, Jr., *ibid.*, **77**, 5993 (1955); **78**, 1450 (1956). The fact that the reaction center may be a trigonal carbon, or that an equilibrium occurs between the attacking nucleophilic agent and the carbonyl center forming an intermediate addition product prior to the rate-determining step has not restricted the application of the term nucleophilic, as a referee has contended.

(39) A. Lapworth, *J. Chem. Soc.*, **83**, 995 (1903); **85**, 1206 (1904); G. Bredig and E. Stern, *Z. Elektrochem.*, **10**, 582 (1904); E. Stern, *Z. physik. Chem.*, **50**, 513 (1905). However, see also the comments of K. B. Wiberg, *THIS JOURNAL*, **76**, 5371 (1954).

the anionic product corresponding to (E⁻). However, one very promising substitute for cyanide ion is presently being investigated in these laboratories, namely, the nitrite ion. This reagent appears to possess the dimensions and geometry necessary for easy attack at the carbonyl as well as a strong inductive effect (as a group covalently bonded to carbon) capable of assisting bond breaking in the anionic intermediate analogous to (C⁻).

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[CONTRIBUTION FROM THE SCHOOL OF CHEMISTRY OF THE UNIVERSITY OF MINNESOTA]

Reaction of Diazo Compounds with Nitroolefins. V. The Orientation of Addition of Disubstituted Diazo Compounds to Nitroolefins¹

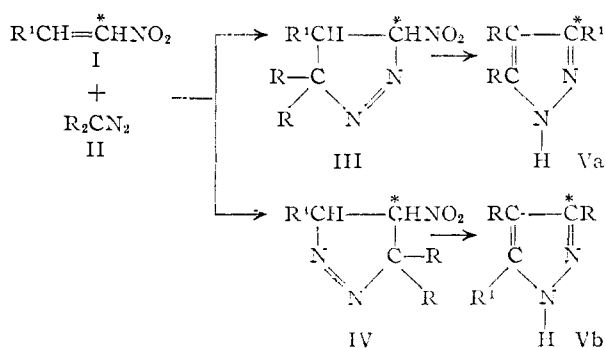
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It has been shown, by radio tracer studies, that disubstituted diazomethane adds to nitroolefins of the type RCH=CHNO₂ to give pyrazolines in which the diazonitrogen atom becomes attached to the β-carbon atom of the nitroolefin. This is opposite to the orientation generally observed for additions involving diazomethane or monosubstituted diazomethane. The pyrazoles, obtained in quantitative yield from these pyrazolines, are thus formed by a single migration of substituent during loss of nitrous acid.

In the preceding articles of this series⁴⁻⁶ the reaction of diazo compounds with nitroolefins was described, and mechanisms for the conversion of the resulting 3-nitropyrazolines into pyrazoles, by loss of the elements of nitrous acid, were discussed.

Reactions involving disubstituted diazo compounds were of particular interest to us, since loss of the elements of nitrous acid from the intermediate pyrazolines was accompanied by migration of groups to give pyrazoles of type V (Va = Vb unless pyrazole ring is tagged).



These pyrazoline intermediates could have either structure III or IV; consequently the derived pyrazole could result from either a single migration of R from IV, or a concerted twofold migration of groups from III.⁴ No direct evidence bearing on these alternative routes has been offered; however, Parham and Hasek⁴ have suggested the

course I → III → V by virtue of the fact that diazomethane and diazoacetic ester generally add to nitroolefins and other activated olefins^{5,6} to give products in which the diazo linkage becomes attached to the α-carbon of the olefin (products such as III). Two possible adducts were, however, reported from the reaction of diazoacetic ester and phenylpropionic ester⁷; consequently, the possibility remains that disubstituted diazo compounds add to activated olefins to give products in which the diazo linkage becomes attached to the β-carbon atom of the olefin (products such as IV) and the above reaction sequence is I → IV → V. This paper describes studies relative to the orientation of addition of disubstituted diazo compounds to nitroolefins, and to the reaction sequence leading to V.

Tautomeric pyrazoles of type Va and Vb, in which the carbon atoms are not tagged, are known to be rapidly interconverted, and are generally represented by a single structure. Inspection of the above formula, however, reveals that a decision between the single or twofold migration (or between III or IV) can be made provided: (a) the α-carbon atom of the nitroolefin is tagged, and (b) the pyrazole V can be suitably degraded to determine the fate of the radioactive carbon.

The synthetic and degradative schemes used in this work, both for tagged and untagged experiments, are outlined in the series of equations.

The yield of VI, from *p*-benzyloxybenzaldehyde and nitromethane, was 20–25%, 55–65% and 80–83%, respectively, when methyl, ethyl and isopropyl alcohol were employed as solvents. When a benzene solution of VI and diphenyldiazomethane was allowed to stand for five weeks, a crystalline nitropyrazoline was obtained in 40% yield. This product (VIIa or VIIb) melted at 130.5–131.5°, and there was no evidence for the formation of an isomeric pyrazoline.

(7) K. von Auwers and O. Ungemach, *Ber.*, **66B**, 1205 (1933).

(1) Supported in part by the Smith, Kline and French Research Foundation and by the Greater University Fund of the University of Minnesota.

(2) From the Ph.D. Thesis of Carl Serres, Jr., University of Minnesota, 1956.

(3) Monsanto Chemical Fellow, 1955–1956; Procter and Gamble Summer Fellow 1955; E. I. du Pont de Nemours Summer Fellow 1956.

(4) W. E. Parham and W. R. Hasek, *THIS JOURNAL*, **76**, 799 (1951).

(5) W. E. Parham and J. L. Bleasdale, *ibid.*, **73**, 4664 (1951).

(6) W. E. Parham and J. L. Bleasdale, *ibid.*, **72**, 3843 (1950).