933. *Proximity Effects in the Amine-catalysed Addition of Ethyl Cyanoacetate to Substituted Benzaldehydes (Knoevenagel Reaction).*

By C. HEITLER.

The kinetics of the Knoevenagel reaction between ethyl cyanoacetate and a number of substituted benzaldehydes have been studied by an ebulliometric method. For *meta*- and *para*-substituted compounds the kinetics fit the Hammett equation with a coefficient of correlation of 0·99, and a standard deviation corresponding to $\pm 10\%$ of the reaction rate constants. The Hammett polar reaction constant was $+1{\cdot}52$, in agreement with the accepted mechanism for these reactions. *ortho*-Substituted compounds reacted at rates which could be made to fit the same equation if it was assumed that the substituents in this position exerted only their inductive effect and the σ'-values of Roberts and Moreland were used in place of the Hammett values. An explanation of this result is suggested in terms of hydrogen bonding for the halogen and methoxy-substituents and of steric suppression of resonance for the nitro-group.

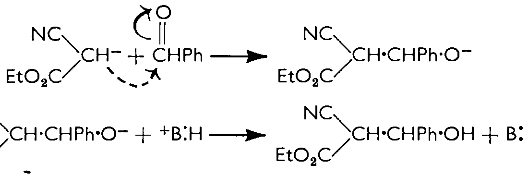
THE kinetics of the Knoevenagel reaction[1] between substituted benzaldehydes and active methylene compounds have not been extensively studied. Pratt and Werbler[2] investigated the reaction between benzaldehyde and various active methylene compounds including ethyl cyanoacetate and diethyl malonate, varying mainly the active-methylene reactant. Their technique was to follow the formation of water when the reaction was carried out in boiling benzene:

$$\mathrm{Ph{\cdot}CHO + CH_2XY \xrightarrow[1]{} HO{\cdot}CHPh{\cdot}CHXY \xrightarrow[2]{} Ph{\cdot}CH{=}CXY + H_2O}$$

They therefore studied the final dehydration whose rate probably bears a complicated relation to that of the first stage. The present work indicates that dehydration takes place at a negligible rate relative to addition, when the reaction is carried out in boiling ethanol, although for some structures, at sufficiently low catalyst concentrations, dehydration could become the fastest step.

The Knoevenagel addition of ethyl cyanoacetate to a series of substituted benzaldehydes has now been studied in boiling 2% ethanolic triethylamine, by using Heitler's method.[3] These reactions followed a second-order kinetic law. The accepted mechanism is illustrated.[4] The reaction should therefore be facilitated by factors which produce an electron deficit on the functional carbon atom.

$$\mathrm{CN{\cdot}CH_2{\cdot}CO_2Et + B\!: \longrightarrow {}^{-}CH(CN){\cdot}CO_2Et + {}^{+}B\!:\!H}$$



The effect of a substituent on the reaction velocity may be divided into the following contributions: (1) An inductive effect, which may be $\pm I$. (2) Resonance interactions: (*a*) with the ring—a resonance polar effect, contributing to the electron availability or deficit at the different positions on the ring, $\pm M$; (*b*) with the functional group. Conjugation with the functional group is weak at the saturated transition stage. It has been

---

[1] Cope, Hoffman, Wychoff, and Harderbergh, *J. Amer. Chem. Soc.*, 1941, **63**, 3452.

[2] Pratt and Werbler, *J. Amer. Chem. Soc.*, 1950, **72**, 4683.

[3] Heitler, *Chem. and Ind.*, 1952, 875.

[4] " Steric Effects in Organic Chemistry," ed. M. S. Newman, Wiley and Sons, New York, 1956, Chapter 13.

calculated that the resonance energy of conjugation of a carbonyl group with a phenyl group is roughly 5·5 kcal. mole^{-1}, and the present results indicate that this is not greatly altered by any of the substituents investigated.[4] (3) Steric or proximity effects, which can alter either the interaction of the substituent with the ring, or affect the coupling of the carbonyl group with the aromatic system, $\pm P$. Factor (2*a*) can be further subdivided into a direct influence exerted from the *ortho*- and *para*-positions, and a resonance inductive effect $\pm M_i$, exerted from the *meta*-position by virtue of the charges induced *ortho* to the functional group.

The observed rate constants for a number of substituted benzaldehydes are given in Table 1. The rate at which the *ortho*-substituted compounds react are all anomalous in the light of the electronic effects to be expected. Halogeno- and methoxy-aldehydes, when *ortho*-substituted, react faster than relative to the *meta*- and *para*-substituted compounds, while the reverse is true of the nitro-aldehydes. The halogen and methoxy-groups have lone pairs of electrons available for conjugation with the rest of the molecule, and this would be expected to reduce the reaction rate of *ortho*- or *para*-substituted relative to *meta*-substituted compounds. The nitro-group accepts a pair of electrons from the ring on conjugation, and this should result in faster reaction of the *o*- than of the *m*-nitro-isomer. It seems that conjugation of these substituents is for some reason reduced in the *ortho*-position.

TABLE 1.

Second-order rate constants (l. mole^{-1} min.$^{-1}$) for reaction of $R{\cdot}C_6H_4{\cdot}CHO$ with $NC{\cdot}CH_2{\cdot}CO_2Et$ [both (0·236 ± 0·01)M] in absolute alcohol containing 2% by vol. of triethylamine, at 78·8—78·4° (0·4° fall during the reaction).

	ortho		*meta*		*para*	
Subst.	*k*	k/k_H	*k*	k/k_H	*k*	k/k_H
(H)	1·48	1·0	1·48	1·0	1·48	1·0
OMe	3·10	2·1	2·69	1·82	0·49	0·33
Br	8·20	5·54	5·41	3·66	3·43	2·32
Cl	8·91	6·05	4·70	3·17	3·27	2·28
F	10·0	6·80	—	—	1·78	1·20
NO_2	13·65	9·23	18·70	13·35	22·0	14·9
Me	1·33	0·89	—	—	1·06	0·71

The rates determined for the *meta*- and *para*-substituted compounds fit the Hammett equation[5] very closely (Fig. 1). Assuming that the inductive and resonance contributions to the electron density at the reaction centre are additive,[4] we may write: $\rho\sigma(para) = f(I + M)$; $\rho\sigma(meta) = f(I + M_i)$. The *ortho*-substituents do not normally obey the Hammett equation, but we can write:

$$\log k_x/k_H(ortho) = f(I + M + P).$$

An independent assessment of f(*I*) would enable f(*M*), f(M_i), and f($M + P$) to be evaluated, the latter on the assumption that the same ρ applies to the *ortho*-substituted compounds.

The σ'-values of Roberts and Moreland[6] provide a measure of f(*I*); these values, based on the classical dissociation constants of substituted bicyclo[2,2,2]octane-1-carboxylic acids, are reasonably free from conjugative effects. (One may assume that the inductive effect, as measured by σ', is inherent in the group and independent of its position in the ring.) Hence:

$$\left.\begin{aligned} \sigma_p - \sigma' &= f(M)/\rho \\ \sigma_m - \sigma' &= f(M_i)/\rho \\ \sigma_o - \sigma' &= f(M + P)/\rho \end{aligned}\right\} = \frac{(\log k_x/k_H)}{\rho} - \sigma'$$

---

[5] Hammett, "Physical Organic Chemistry," McGraw-Hill Book Co., New York, 1940, p. 186; Joffe, *Chem. Rev.*, 1953, **53**, 191.

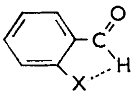
[6] Roberts and Moreland, jun., *J. Amer. Chem. Soc.*, 1953, **75**, 2167.

Table 2 indicates that $f(M + P)$ is zero within the experimental error for all the substituents studied. This result, that the proximity effect just cancels the resonance effects for these six *ortho*-substituted aldehydes, cannot be attributed to chance equivalence of the two effects. Rather it appears that in the *ortho*-positions the resonance of these substituents with the ring has been suppressed. The behaviour of methoxy- and halogen substituents may be accounted for by the localising influence of the aldehydic hydrogen on the lone electron pairs of these substituents, *i.e.*, as a result of hydrogen bonding (cf. A). Hydrogen bonding, although possible, cannot explain the suppression of the resonance (with the ring) of the nitro-group—it would assist the movement of electrons towards the nitro-groups (cf. B). It is possible that the carbonyl and the nitro-group interfere because of their bulk, and this distortion of bond angles or twisting of the groups reduces the ability of both groups to conjugate with the ring. An alternative, but less probable, hypothesis is that the *ortho*-substituents induce formation of a keten-like structure (C), which becomes the reactive species, a mechanism resembling that of the alcoholysis of *ortho*-substituted benzoyl chlorides.[4]

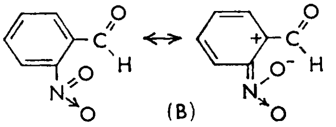
TABLE 2.

$$\frac{\log (k_x/k_{\mathrm{H}})}{\rho} - \sigma'.$$

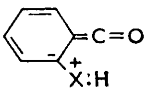
Subst.	OMe	F	Cl	Br	NO_2	Me
$f(M)$ (*para*)	-0.55	-0.44	-0.21	-0.21	$+0.14$	-0.04
$f(M_{\mathrm{I}})$ (*meta*)	-0.06	-0.18	-0.14	-0.08	$+0.10$	-0.02
$f(M + P)$ (*ortho*)	$+0.02$	$+0.05$	$+0.04$	$+0.04$	$+0.01$	$+0.02$
σ'	$+0.23$	$+0.50$	$+0.47$	$+0.45$	$+0.63$	-0.05



(A)



(B)



(C)

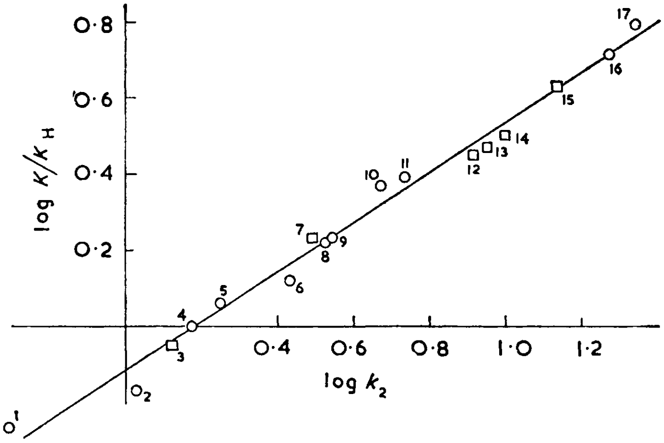


FIG. 1. Plots of log k_2 against log K/K_{H}: ○, against σ (*meta, para*); ☐, against σ' (*ortho*).

1, *p*-MeO. 2, *p*-Me. 3, *o*-Me. 4, *H*. 5, *p*-F. 6, *m*-MeO. 7, *o*-MeO. 8, *p*-Cl. 9, *p*-Br. 10, *m*-Cl. 11, *m*-Br. 12, *o*-Br. 13, *o*-Cl. 14, *o*-F. 15, *o*-NO_2. 16, *m*-NO_2. 17, *p*-NO_2.

The values of log k_x are plotted against σ and σ' in Fig. 1 for the seventeen compounds examined. The correlation coefficient is 0·99, indicating an excellent fit with the Hammett equation,[5] and it is noteworthy that when the σ'-values are used for the *ortho*-substituents these fit the curve without altering the correlation or the standard deviation of the log k_x values ($\pm$0·048 log unit).

It is evident that in order satisfactorily to explain the behaviour of the *ortho*-substituents in this reaction a wide series of compounds must be studied, in particular, those with substituents as free as possible from resonance effects. Not many such compounds are commercially available, so that further work awaits the synthesis of suitable *ortho*-substituted benzaldehydes.

EXPERIMENTAL

A pair of ebulliometers,[7] E_1 and E_2, were employed in opposite arms of a Wheatstone bridge circuit. E_2 was a reference ebulliometer, filled with dry ethanol containing 2% of polyethylene glycol to give a stable boiling temperature; its function was to compensate changes in barometric pressure during a reaction. The ebulliometer E_1 contained the reaction mixture.

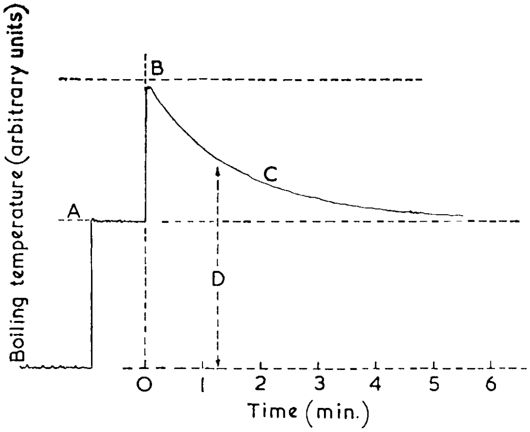


FIG. 2. Chart. A = Elevation on addition of ethyl cyanoacetate. B = Elevation after addition of aldehyde. C = Boiling-temperature trace during progress of reaction.

The output from the bridge was fed to a Honeywell-Brown D.C. microvoltmeter, the chart speed of which could be varied between 5 sec. and 10 min. per inch.

The ebulliometer E_1 was filled with dry ethanol (10 ml.) containing 2% by volume of triethylamine. When a steady base-line was established on the chart (Fig. 2), sufficient aldehyde was added to produce an elevation in boiling temperature corresponding to 64 divisions on the chart. The chart was then set in motion at a convenient speed. When boiling once more proceeded steadily, ethyl cyanoacetate was added very rapidly from a drop pipette calibrated to produce an elevation of 64 ± 2 divisions. A curve was then produced on the chart corresponding to formation of the adduct (Fig. 2).

The reactants were purified by conventional methods. The products were isolated in 90—96% yield in each case.

Calculations.—For a second-order reaction between reactants at equal initial concentrations (a moles $l.^{-1}$), we have $kt = x/a(a - x)$, where x is the amount of product (moles $l.^{-1}$) formed at time t.

On the chart (Fig. 2) the initial elevation 64 divisions is proportional to a, the ebulliometer constant being 272 divisions per mole $l.^{-1}$; therefore, $a = 64/272$ mole $l.^{-1}$. The elevation at $t = 0$ was 128 divisions after the addition of the ethyl cyanoacetate; at a later time t, the observed elevation, D divisions, is proportional to $(2a - x)$; hence $x/(a - x) = (128 - D)/(D - 64)$, which is dimensionless, and $kt = (128 - D)/(D - 64) \times 272/64$ l. mole^{-1}.

The zero of time becomes uncertain for the faster reactions, and, to eliminate the error from this source, D_0 was measured at an arbitrary time t_0 as near to zero as possible. Then

$$k(t - t_0) = 272/64[(128 - D)/(D - 64) - (128 - D_0)/(D_0 - 64)].$$

---

[7] Heitler, *Analyst*, 1958, **83**, 223.

When the right-hand side of this equation is plotted against $(t - t_0)$, the slope gives the rate constant k.

The combined errors are estimated to be ±4% of the values of k.

Much of the experimental work described here was carried out by Mr. D. W. Francis at this College. I also thank Mr. P. A. Claret for many helpful discussions.

CHEMISTRY DEPARTMENT, NORTHAMPTON COLLEGE OF ADVANCED TECHNOLOGY,
ST. JOHN STREET, LONDON E.C.1.

[*Received, January 8th,* **1963**.]