608. *The Reactivities of Substituted Benzophenones in Oxime Formation.*

By J. D. DICKINSON and C. EABORN.

We have measured the rates of acid-catalysed formation of oximes from some monosubstituted benzophenones in aqueous methanol. The effects of substituents are not in accord with their Hammett σ-constants, but can be interpreted if account is taken of loss of conjugation between aryl and carbonyl groups on passing from the ground state to the transition state.

WE have measured spectrophotometrically the rates of acid-catalysed formation of oximes by some monosubstituted benzophenones in presence of excess of hydroxylamine hydrochloride in 70% methanol containing sodium acetate and acetic acid. First-order rate constants, *k*, are shown in Table 1, along with the apparent activation energies, *E*, and log *A* values.

TABLE 1. *Reaction of benzophenones,* $X{\cdot}C_6H_4{\cdot}CO{\cdot}C_6H_5$, *with hydroxylamine in acidic 70% methanol at 50°.*[a]

X	10^3k (min.$^{-1}$)	*E* (kcal./mole)	$\log_{10} A$ [b]	X	10^3k (min.$^{-1}$)	*E* (kcal./mole)	$\log_{10} A$ [b]
H	9·2	13·15	6·85	*m*-HO	8·7	13·0	6·7
p-Ph	8·3	13·55	7·05	*p*-HO	3·35	14·05	7·05
m-Me	9·05	13·3	6·95	*p*-Br	8·5	12·75	6·55
p-Me	7·3	13·6	7·05	*m*-NO_2 ...	9·65	11·75	5·9
m-MeO ...	9·0	13·15	6·85	*p*-NO_2	11·8	11·55	5·9
p-MeO	4·05	14·0	7·05				

[a] For exact medium see Experimental section. [b] $\log k = \log A - (2{\cdot}303\ E/\boldsymbol{R}T)$.

The reaction is hindered by strongly electron-releasing groups such as *p*-MeO and *p*-OH, and facilitated, less effectively, by strongly electron-withdrawing substituents such as *p*-NO_2, while *meta*-substituents have no significant effect. A plot of log *k*°/*k* (where *k*° is the rate of reaction of benzophenone) against the Hammett substituent constants, σ[1] (values of which are taken from ref. 2) shows a marked curvature (Fig. 1). A plot of σ against activation energy, *E*, is a straight line, but we cannot be certain that this is significant in view of the experimental uncertainty in *E*.

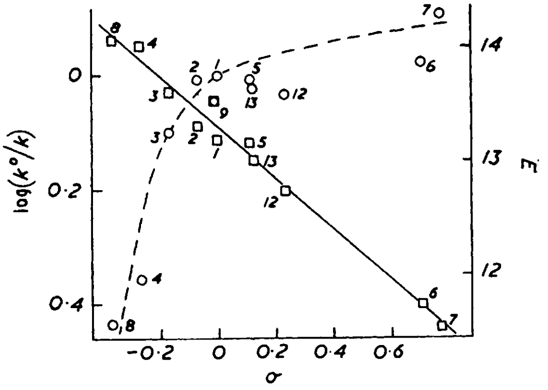


FIG. 1. *Plot of* log (*k*°/*k*) (*circles*) *and of activation energy, E* (*squares*) *against* σ.

Substituents: 1, H; 2, *m*-Me; 3, *p*-Me; 4, *p*-MeO; 5, *m*-MeO; 6, *m*-NO_2; 7, *p*-NO_2; 8, *p*-HO; 9, *p*-Ph; 10, *p*-Cl; 11, *m*-Cl; 12, *p*-Br; 13, *m*-HO.

Curvature of log *k*–σ plots seems to be general for reactions involving addition to carbonyl groups in aryl carbonyl compounds. The curve goes through a maximum in

---

[1] Jaffé, *Chem. Rev.*, 1953, **53**, 191.
[2] Brown and Okamoto, *J. Amer. Chem. Soc.*, 1958, **80**, 4979.

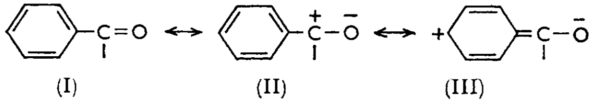
reaction of benzaldehydes with *n*-butylamine,[3] semicarbazide,[4] and hydrogen cyanide[5] (the logarithm of the equilibrium constant being plotted in the last case), but the existence of a maximum has no special significance since the curvatures are temperature-dependent, the entropies of activation not being constant for a series of substituents in a given reaction.[3] In formation of oximes from benzophenones, for example, if the values of E and $\log A$ in Table 1 are accurate, a maximum would be observed at 100°, while in reaction of benzaldehydes with butylamine there would be no maximum at 100° although one is observed at 25°.[3] The $\log k$–σ plot is said to be a straight line in semicarbazone formation by *para*-substituted acetophenones,[6] but the correlation is rather unsatisfactory at the experimental temperature of 50° even for the small number of substituents examined, and on the basis of the reported $\log A$ and E values the plot, which has a negative slope at 50°, would have a positive slope at 25° and show a rate minimum at 0°. (A plot of E against σ approximates to a straight line, as with benzophenones.)

The curvature of the $\log k$–σ plots in the benzaldehyde–*n*-butylamine and benzaldehyde–semicarbazide reactions, and particularly the occurrence of rate-maxima, have been attributed to the formation of intermediates.[3,4] It was not shown for the first reaction exactly why a maximum would result.[3] For the second, Noyce, Bottini, and Smith[4] postulated that the rate of return of the intermediate to the reactants was similar to the rate of its decomposition to products; in the general case $\mathrm{A} \underset{(2)}{\overset{(1)}{\rightleftharpoons}} \mathrm{B} \xrightarrow{(3)} \mathrm{C}$, the rate of formation of C is given by $k = k_1k_3/(k_2 + k_3)$, where k_1, k_2, and k_3 are the specific rates of reactions (1), (2), and (3), respectively, and for a change from the unsubstituted compound to one having a substituent of substituent-constant σ, the rate change from $k°$ to k is given by

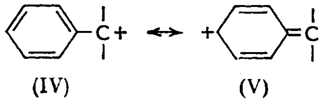
$$\log (k/k°) = (\rho_1 + \rho_3 - \rho_2)\sigma - \log\left[\left(1 + \frac{k_3°}{k_2°}\,10^{(\rho_3-\rho_2)\sigma}\right)\Big/\left(1 + \frac{k_3°}{k_2°}\right)\right]$$

[where $\log (k_1/k_1°) = \rho_1\sigma$, and so on]. This function is not linear in σ, and passes through a maximum. However, we believe that in practice the value of $(\rho_3 - \rho_2)$ will normally be too small for the log term to reverse the trend established by the $(\rho_1 + \rho_3 - \rho_2)$ term. Since, for this treatment, B must be an intermediate of high energy, and k_1 must be approximately equal to k_2, the transition states for reactions A ⟶ B and B ⟶ C are not far removed from the intermediate B, and are placed fairly symmetrically with respect to B, so that the effect of a change of structure will be rather similar on these transition states and on B.[7] The values of ρ_2 and ρ_3 will thus be small and rather similar, so the difference $(\rho_3 - \rho_2)$ will be very small and a linear $\log k$–σ plot will result.

Another objection to the explanation advanced by Noyce *et al.* is that the return of the intermediate to reactants is unlikely to be comparable with the rate of its decomposition to products when ketones are involved,[3,4] and yet the $\log k$–σ plots can be seriously curved as we have now shown. An explanation is required which is generally applicable to all of these carbonyl reactions, and we suggest that the common feature is that the conjugation between the aryl and the carbonyl groups [canonical forms (I), (II), and (III) are shown] has largely disappeared in the transition state of the rate-determining step. In oxime



(I) (II) (III)



(IV) (V)

---

[3] Santerre, Hansrote, and Crowell, *J. Amer. Chem. Soc.*, 1958, **80**, 1254.

[4] Noyce, Bottini, and Smith, *J. Org. Chem.*, 1958, **23**, 752.

[5] Branch and Calvin, "The Theory of Organic Chemistry," Prentice-Hall Inc., New York, 1941, pp. 347—351.

[6] Cross and Fugassi, *J. Amer. Chem. Soc.*, 1949, **71**, 223.

[7] Hammond, *ibid.*, 1955, **77**, 334.

formation this transition state probably lies between the benzophenone and the intermediate $Ph_2C(OH)\cdot NH\cdot OH$, subsequent dehydration being fast, but in general it is only necessary that the transition state is not greatly removed on the reaction co-ordinate from the intermediate of type $RR'C(OH)\cdot NHX$. The ordinary σ-constants do not serve to indicate the effects of substituents on the conjugation represented by resonance involving structures (II) and (III), but we suggest that the σ^+-constants, applicable to electrophilic reactions,[2] will so serve as an approximation, since by their derivation they reveal the effects of substituents on the analogous resonance involving (for example) structures (IV) and (V).* If the effect of the substituent were exerted only through this loss of conjugation then the relation $\log (k/k^\circ) = \rho_1\sigma^+$ would hold, the reaction being hindered by electron-releasing substituents. On the other hand, if there were no serious change in this conjugation on going from ground state to transition state the usual relation $\log (k/k^\circ) = \rho\sigma$ would hold. Overall the relation $\log (k/k^\circ) = \rho'\sigma^+ + \rho\sigma$ holds, or $\log (k^\circ/k) = \rho(x\sigma^+ - \sigma)$,

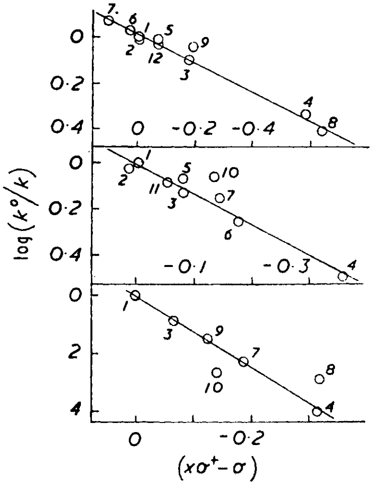


FIG. 2. *Plots of* log (k°/k) *against* $(x\sigma^+ - \sigma)$ *for*: (*top*) *oxime formation by benzophenones* (x = 1·1); (*centre*) *semicarbazone formation by benzaldehydes* (x = 0·8); (*bottom*) *decomposition of benzenediazonium salts* (x = 0·75).

1—13, As for Fig. 1.

where x is a constant and $\rho' = -x\rho$. Thus $\log (k^\circ/k)$ is proportional to $(x\sigma^+ - \sigma)$, and from values of $(x\sigma^+ - \sigma)$ listed in Table 2 it will be seen that plots of $\log (k^\circ/k)$ against σ may be seriously curved, or may go through a maximum, depending on the value of x.†

TABLE 2.[a]

Substituent	*p*-HO	*p*-MeO	*p*-Me	*m*-Me	*p*-Ph	*m*-MeO	*p*-Br	*m*-Cl	*m*-NO_2	*p*-NO_2
σ	−0·37	−0·268	−0·170	−0·069	−0·01	+0·115	+0·232	+0·373	+0·710	+0·778
σ^+	−0·92	+0·778	−0·311	−0·066	−0·179	+0·047	+0·150	+0·399	+0·674	+0·790
$(1{\cdot}1\sigma^+ - \sigma)$	−0·64	−0·580	−0·172	−0·004	−0·19	−0·063	−0·067	+0·066	+0·031	+0·091
$(0{\cdot}9\sigma^+ - \sigma)$	−0·46	−0·432	−0·110	+0·010	−0·17	−0·073	−0·097	−0·014	−0·103	−0·067
$(0{\cdot}7\sigma^+ - \sigma)$	−0·27	−0·277	−0·048	+0·023	−0·115	−0·082	−0·127	−0·093	−0·269	−0·225

[a] Values of σ^+ and σ are from ref. 2.

As required by our treatment, when $\log (k^\circ/k)$ is plotted against $(x\sigma^+ - \sigma)$ the points lie acceptably about a straight line for the benzophenone–hydroxylamine reaction (x = 1·1) (Fig. 2). Comparable results are obtained for the benzaldehyde–semicarbazide reaction (Fig. 2) and the benzaldehyde–*n*-butylamine reaction (x = 0·6).‡ In these three cases,

---

* It would probably be more correct to assume that the effect of a substituent on conjugation with the carbonyl group is indicated by $(\sigma^+ - \sigma)$, but in the present case the final conclusion would be the same.

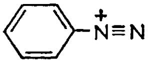
† We list figures only for a few relevant positive values of x. A positive x means that ρ and ρ' have opposite signs, and thus that the carbonyl-additions immediately under consideration would be facilitated by electron-releasing substituents in absence of the special effects of conjugation.

‡ Deviations for *p*-halogeno- and *p*-phenyl substituents are not surprising since the σ^+-constants do not adequately represent the effects of these groups even in electrophilic reactions.[8]

[8] Eaborn, *J.*, 1956, 4858; Deans, Eaborn, and Webster, *J.*, 1959, 3031.

points for *meta*-substituents lie reasonably close to the line. This is not always to be expected, since *para*-substituents influence conjugation with side-chains directly, while *meta*-substituents operate only through a secondary relay of effects, and the stabilisation energy of the ground state may be related to σ^+ by a different proportionality constant in the two cases. For dissociation of benzaldehyde cyanohydrins[5] a plot of log K against $(0{\cdot}775\sigma^+ - \sigma)$ is satisfactory for *para*-substituents, but a separate plot is required for *meta*-substituents.

The treatment suggested above is applicable to some analogous cases. Thus the Curtius rearrangement of substituted benzoyl azides in toluene shows a rate maximum (both *p*-MeO and *p*-NO_2 groups, for example, deactivate) which has been qualitatively attributed to stabilisation of the ground state by electron-supplying substituents,[9] and we find that the points for *para*-substituents lie satisfactorily about a log (k°/k)–$(0{\cdot}75\sigma^+ - \sigma)$ plot. Perhaps the best known example of unusual effects of *para*-substituents is the decomposition of substituted benzenediazonium salts in aqueous acid,[10] and again these effects have been qualitatively attributed to ground-state stabilisation by groups having $+T$ effects.[11] In this case ground state stabilisation might be expected to follow σ^+ rather closely, since a positive charge in the conjugated side-chain is to be distributed [see structure (VI)]. On the other hand, in the ion (VII), which is formed in the rate-determining step, there cannot be direct resonance between the π-electron system and the positively charged carbon since the π-orbitals are antisymmetric and the sp^2 carbon orbital is symmetric with respect to the plane of the ring, so that stabilisation of the ion (VII) (or of a transition state close to it) would be expected to follow σ and not σ^+. Thus a straight-line log (k°/k)–$(x\sigma^+ - \sigma)$ plot results (Fig. 2).

(VI)


(VII)

The type of treatment above is also applicable to some side-chain reactions of benzyl compounds which do not show satisfactory log k–σ correlation[12] [the reaction of benzyl chlorides with trimethylamine,[12] for example, for which a log (k°/k)–$(\sigma^+ - \sigma)$ plot is satisfactory for *para*-substituents]. In such reactions it is the transition state and not the ground state which has the extra resonance stabilisation.[13] We do not, however, propose to extend or refine out treatment,* because we believe it to be a simplified equivalent of a more fundamental division of substituent constants into inductive and resonance components now being developed by Taft and his co-workers.[14]

EXPERIMENTAL

The same stock solution of hydroxylamine hydrochloride in water (4·20M, as determined by titration[15]) was used throughout. Immediately before a run, 30 ml. of this solution were diluted to 100 ml. with methanol, and 10 ml. of this mixture were added to 10 ml. of a solution of the benzophenone (of concentration shown in Table 3) in " 70% methanol " (30 volumes of water diluted to 100 volumes with methanol) containing sodium acetate (0·20M) and acetic acid (0·20M). Some of the mixture thus obtained was transferred to a 1 cm. stoppered cell held in an Adkins thermostat in a Unicam S.P. 500 Spectrophotometer. After 15 min., to allow the

---

* We understand that Professor Yukawa is testing a similar treatment more extensively.

[9] Yukawa and Tsuno, *J. Amer. Chem. Soc.*, 1957, **79**, 5530.

[10] Crossley, Kienle, and Benbrook, *ibid.*, 1940, **62**, 1400.

[11] Ingold, " Structure and Mechanism in Organic Chemistry," G. Bell and Sons, Ltd., London, 1953, pp. 800—802: Bunnett and Zahler, *Chem. Rev.*, 1951, **49**, 273.

[12] Swain and Langsdorf, *J. Amer. Chem. Soc.*, 1951, **73**, 2813.

[13] Bartlett, in Gilman's " Organic Chemistry," Wiley and Sons, New York, Vol. III, 1953, pp. 33—35.

[14] Taft, " Steric Effects in Organic Chemistry " (Ed., M. S. Newman), Wiley and Sons, New York, 1956, Chapter 13; cf. Taft and Lewis, *J. Amer. Chem. Soc.*, 1958, **80**, 2436 and refs. therein.

[15] Vogel, " Quantitative Inorganic Analysis," Longmans, Green and Co., London, 2nd Edn., 1951, p. 375.

solution to reach the thermostat temperature (50·0° or 40·0°, maintained within ±0·03°), readings of the optical density were taken at the wavelengths, λ, shown in Table 3, and continued for 10 times the half-life period. The pH of the reaction mixture (5·02, measured directly with a glass electrode) was unchanged at the end of the reaction. Constancy of the first-order rate constants was excellent during more than 90% of reaction, and overall rate constants were reproducible within ±1%. Activation energies are believed to be accurate to within 0·4 kcal. mole^{-1}.

TABLE 3.

X (in $X{\cdot}C_6H_4{\cdot}CO{\cdot}C_6H_5$)	H	*m*-Me	*p*-Me	*p*-Ph	*m*-MeO	*p*-MeO
Concn. (g./l.)	1·6—1·9	1·7	1·0	0·20	0·78	1·1
λ (mμ)	335	335	325	335	345	350

X (in $X{\cdot}C_6H_4{\cdot}CO{\cdot}C_6H_5$)	*m*-OH	*p*-OH	*p*-Br	*m*-NO_2	*p*-NO_2
Concn. (g./l.)	0·82	0·046	1·6	0·46	0·094
λ (mμ)	350	345	325	324	330

THE UNIVERSITY, LEICESTER.

[*Received, March* 13*th*, 1959.]