The Darzens Condensation. Part III.[1] Effects of Substituents on the Rate of Condensation of Substituted Phenacyl Chlorides with Benzaldehyde

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The rates of condensation of phenacyl chloride and its *p*-methoxy-, *p*-methyl, and *p*-chloro-derivatives with benzaldehyde were measured polarographically in methanol with sodium methoxide as catalyst, and in ethanol with hydrogen chloride gas as catalyst. A proposal is made for the mechanism and the rate-determining step in the acid-catalysed condensation. In both the base- and acid-catalysed reactions the rates were increased by electron-donating substituents. The Hammett relation is valid for the reaction.

THE mechanism of the base-catalysed Darzens condensation of phenacyl halides with benzaldehyde is generally regarded as established by the results of Ballester.[2,3] There is no kinetic work, however, on the mechanism of the acid-catalysed condensation [4] and on the effect of substituents on the rate.[1] To investigate these questions, a kinetic study has been made of the base- and acid-catalysed condensations of phenacyl chloride and its *p*-methoxy-, *p*-methyl, and *p*-chloro-derivatives with benzaldehyde. The measurements were carried out polarographically as the reactants and the epoxy-ketones produced in the condensation proved suitable for polarographic analysis.[5]

The base-catalysed condensations were performed in methanol with sodium methoxide as catalyst, and the acid-catalysed ones in ethanol with hydrogen chloride gas as catalyst.

EXPERIMENTAL

LP 55 A and PO4 polarographs were employed.

Materials.—Benzaldehyde,[6] phenacyl chloride, m.p. 56—57°,[7] *p*-methoxyphenacyl chloride, m.p. 98—99°,[8] *p*-methylphenacyl chloride, m.p. 56—57°,[9] and *p*-chlorophenacyl chloride, m.p. 101—102°,[10] of suitable purity were prepared.

Solutions for Calibration and for Kinetic Experiments.—For the base-catalysed reactions 10^{-1}M-solutions of benzaldehyde, of the phenacyl chlorides, and of benzoyl(phenyl)oxiran were prepared in absolute methanol. The catalyst was 2×10^{-1}M-sodium methoxide in absolute methanol and the supporting electrolyte was 10^{-1}M-calcium chloride in 75% methanol–water. Acid-catalysed reactions were carried out in ethanol with 3·3M-HCl gas as catalyst and 5×10^{-1}M-ammonium hydroxide as supporting electrolyte.

Calibration.—Solutions were prepared in which the concentrations of the components [benzaldehyde, phenacyl chloride, benzoyl(phenyl) oxiran] corresponded to conversions of 0—100%. The concentrations of catalyst and supporting electrolyte were the same in all experiments.

From the polarograms of the base-catalysed reactions the corresponding i_d values were obtained as a function of the concentration of epoxy-ketones. For calibration purposes the increases in concentration of 1-*p*-methoxybenzoyl- and 1-*p*-methylbenzoyl-2-phenyloxiran were measured at −500 mV (Figures 1 and 2). Figures 1 and 2 show that the change of i_d with concentration of epoxy-ketones is linear. The differences between the decrease in concentration of phenacyl chloride and *p*-chlorophenacyl chloride and the increase in concentration of benzoyl(phenyl)oxiran and 1-*p*-chlorobenzoyl-2-phenyloxiran were followed at −1050 mV. As a

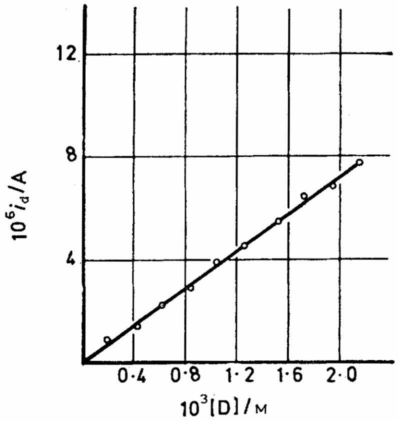

FIGURE 1 Calibration curve for base-catalysed condensations at 30°: [D] = concentration of 1-*p*-methoxybenzoyl- and 1-*p*-methylbenzoyl-2-phenyloxiran at −500 mV

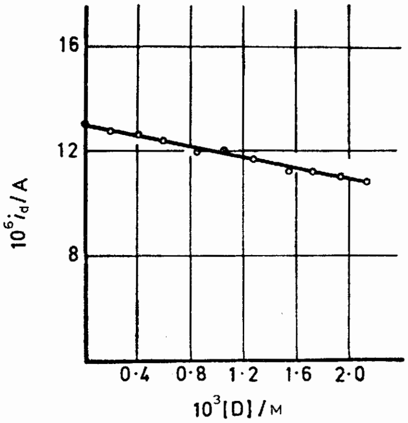

FIGURE 2 Calibration curve for base-catalysed condensation at 30°: [D] = difference between the decrease in concentrations of phenacyl chloride and *p*-chlorophenacyl chloride and the increase in concentration of 1-benzoyl- and 1-*p*-chlorobenzoyl-2-phenyloxiran at −1050 mV

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[1] Gy. Sipos and Gy. Schöbel, *J. Chem. Soc.* (*C*), 1970, 1154.

[2] M. Ballester and P. D. Bartlett, *J. Amer. Chem. Soc.*, 1953, **75**, 2042.

[3] M. Ballester, *Chem. Rev.*, 1955, **55**, 284.

[4] Gy. Sipos and F. Sirokmán, *Nature*, 1964, **202**, 898.

[5] Gy. Schöbel and Gy. Sipos, *Acta Phys. Chem. Szeged*, 1969, **15**, 151.

[6] D. S. Noyce and W. A. Pryor, *J. Amer. Chem. Soc.*, 1955, **77**, 1897.

[7] D. A. Shirley, 'Preparation of Organic Intermediates,' Wiley, New York, 1951, p. 71.

[8] A. L. Wilds and T. L. Johnson, *J. Amer. Chem. Soc.*, 1945, **67**, 287.

[9] F. Kunckell, *Ber.*, 1897, **30**, 578.

[10] A. Collet, *Compt. rend.*, 1897, **125**, 718.

result the corresponding calibration curve does not pass through the origin (Figure 2). For the acid-catalysed reaction (supporting electrolyte NH_4OH-NH_4Cl; pH 9·1), the i_d values were obtained at -1480 mV (Figure 3).

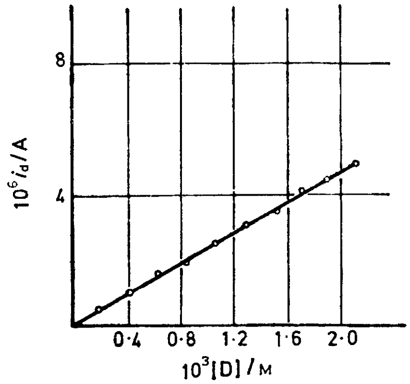


FIGURE 3 Calibration curve for acid-catalysed condensation at 30° and -1480 mV

It should be noted that during the relatively short time of calibration, the reactions of the phenacyl chlorides with benzaldehyde could be neglected.

TABLE 1

Initial concentrations and rate constants for base-catalysed kinetic runs at 30°

					Average		
Run	p-Substituent	$10^2[p\text{-}XC_6H_4COCH_2Cl]$/M	10^2[PhCHO]/M	10^2[NaOMe]/M	10^2k_1/l mol min^{-1}	10^3k_2/l mol min^{-1}	n *
1	OMe	0·10	1·08	1·00	1·96	4·42	4
2	Me	0·10	1·10	1·00	2·08	4·17	8
3	H	0·10	1·12	1·00	1·20	3·92	5
4	Cl	0·10	1·08	1·02	0·82	3·29	5
5	NO_2				0·26 †	2·55 †	

* Number of runs. † Calculated (see text).

TABLE 2

Initial concentrations and rate constants for acid-catalysed kinetic runs at 30°

					Average		
Run	p-Substituent	$10^2[p\text{-}XC_6H_4COCH_2Cl]$/M	10^2[PhCHO]/M	10^2[HCl]/M	$10k$/l mol^{-1} min^{-1}	$10k$/l mol^{-1} min^{-1}	n *
1	OMe	1·00	1·10	330·0	3·54		3
2		5·03	5·54	330·0	3·26		3
3		9·35	10·30	330·0	3·38	3·39	3
4	Me	1·30	1·43	330·0	2·66		3
5		3·00	3·30	330·0	2·91		3
6		7·52	8·27	330·0	2·72	2·76	3
7	H	1·12	1·23	330·0	2·19		3
8		5·21	5·73	330·0	2·23		3
9		10·41	11·45	330·0	2·16	2·19	3
10	Cl	1·00	1·10	330·0	1·34		3
11		5·00	5·50	330·0	1·29		3
12		10·00	11·00	330·0	1·32	1·32	3
	NO_2					0·51 †	

* Number of runs. † Calculated (see text).

Experimental Procedure.—Appropriate volumes of catalyst, benzaldehyde, and phenacyl chloride solutions were mixed at 30° to give the concentrations shown in Tables 1 and 2. For the base-catalysed reaction curves $i_d = f(t)$ for the reaction mixture were recorded at constant values of potential (-500 and -1050 mV). From these curves and from the function $i_d = f([D])$ (D = product), the curves $[D] = f(t)$ were obtained (Figure 4). Because of the large excess of catalyst, the pH change during the reactions did not exceed the error in the polarographic method (3—5%). The method requires low concentrations. Hence, the reactions were relatively slow, and measurements were not continued after 320 min (46—60% conversion).

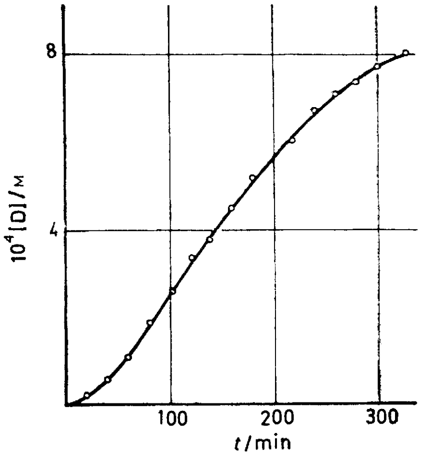


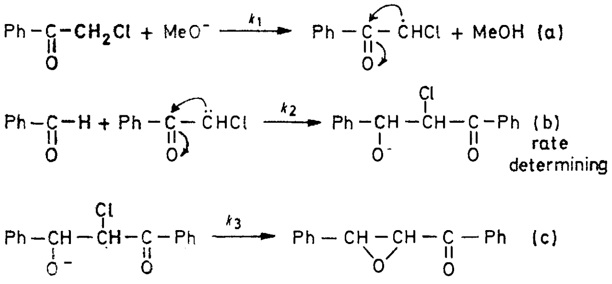
FIGURE 4 Plot of [D] against f(t) for base-catalysed condensation of p-methylphenacyl chloride with benzaldehyde at 30°

For the acid-catalysed reaction, with 10^{-1}M-benzaldehyde and -phenacyl chloride, conversion after 2 h was 66—83%.

RESULTS AND DISCUSSION

Base-catalysed Reaction.—On the basis of the kinetic results, the mechanism of the base-catalysed condensation is shown in Scheme 1.

Calculation of rate constants. According to the experiments of Ballester,[2,3] step (b) is rate determining and step (c) is much faster than (b). For this reason and also because of the large catalyst and benzaldehyde excesses used in our experiments, the condensation may be considered kinetically to consist of two consecutive pseudo-first-order processes with rate constants k_1 and k_2.



Scheme 1

In the kinetic runs the change of the concentration of product was measured during the reaction and its rate of formation can be calculated from equation (1) where A = phenacyl chloride. Solution of equation (1)

$$d[D]/dt = k_2\{[A]_0[1 - \exp(k_1t)] - [D]\} \quad (1)$$

results in (2) which gives the concentration of product in terms of the consecutive first-order rate constants.[11]

$$[D] = [A]_0\left\{1 + \frac{1}{k_1 - k_2}[k_2 \exp(-k_1t) - k_1 \exp(-k_2t)]\right\} \quad (2)$$

The rate constants k_1 and k_2 were calculated from equation (1) in the following way. Arbitrary times (t_1,t_2) were selected with the condition that $t_2 = 2t_1$. The values of rates and concentrations associated with t_1,t_2 are denoted by w_1,w_2 and $[D]_1,[D]_2$, and with this notation equation (1) yields equations (3a and b.)

$$w_1 = k_2\{[A]_0[1 - \exp(-k_1t_1)] - [D]_1\} \quad (3a)$$

$$w_2 = k_2\{[A]_0[1 - \exp(-2k_1t_1)] - [D]_2\} \quad (3b)$$

Eliminating k_2 and using the notation $\exp(-k_1t_1) = u$ gives equation (4). The graphical or numerical differentiation of the function $[D] = f(t)$ (see Figure 4) results in the function $w = g(t)$ which yields the values of w that are necessary for the calculation of k_1 and k_2. In solving equation (4) the negative square root has to be taken for u and thus k_1 is obtained directly from $\ln u = -k_1t_1$. If the average of the values of k_1 is substituted into equation (3a) the value of k_2 can be calculated.

$$u^2 - \frac{w_2}{w_1}\cdot u + \frac{w_2}{w_1}\frac{[A]_0 - [D]_1}{[A]_0} + \frac{[D]_2 - [A]_0}{[A]_0} = 0 \quad (4)$$

The rate constants k_1 and k_2 in Table 1 are in fact second-order constants according to the relationships $k_1 = k_1'[MeO^-]$ and $k_2 = k_2'[PhCO]$, where k_1' and k_2' are pseudo-first-order rate constants.

The averages of k_1 and k_2 associated with some time-pairs t_1,t_2 were substituted into equation (2) and the resulting values of [D] showed $\pm 2{\cdot}5\%$ deviation from the measured ones.

Effect of Substituents.—We checked the validity of the Hammett equation for the condensation. It can be seen from Figure 5 that there is indeed a linear σ–log k relation. The substituents can be arranged in the following series in regard to their effect in accelerating the condensation: $NO_2 < Cl < H < Me < OMe$. This agrees with the results of our earlier, preparative experiments.[12]

It should be noted that benzoyl(phenyl)oxiran and phenacyl chlorides containing a nitro-group cannot be distinguished one from another polarographically, and therefore the rate constants k_1 and k_2 were calculated from the Hammett equation for the reaction of *p*-nitrophenacyl chloride with benzaldehyde (Table 1).

It can be concluded that the rate of the base-catalysed condensation of a substituted phenacyl chloride with benzaldehyde is increased by electron-donating substituents. The rate differences arising as a result of the presence of the various substituents are fairly small (Table 1).

Using the least squares method, we also calculated the values of the reaction constant ρ: for ionization, $\rho = -0{\cdot}85$, and for aldolization, $\rho = -0{\cdot}24$. The negative values point to an electrophilic reaction, while the low value for aldolization shows that the reaction centre is fairly insensitive to changes in the electron density.

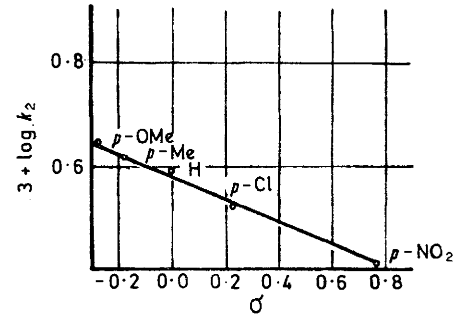
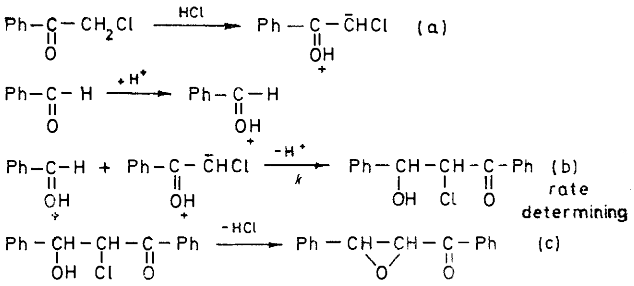


Figure 5 Hammett plot for base-catalysed condensations

Acid-catalysed Reaction.—Calculation of rate constant. The reaction mechanism assumed for the condensation is shown in Scheme 2.[1,4] Confirmation that the condensation is kinetically of second-order was provided by the plots of $1/[A]$ against $f(t)$ which were straight lines (Figure 6).



Scheme 2

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[11] A. A. Frost and R. C. Pearson, 'Kinetics and Mechanism,' Wiley, London, 1961, 2nd edn., p. 166.

[12] Gy. Sipos, Gy. Schöbel, and L. Baláspiri, *Acta Chim. Acad. Sci. Hung.*, 1971, **68**, 149.

The rate constant k of the condensation (Table 2) was calculated from the kinetic data by means of the second-order kinetic equation[13] $1/[A] - 1/[A]_0 = kt$. This equation can be used despite the concentrations of the two reagents being only approximately equal because with $[A]_0 = [B]_0$ ($[B]_0$ = initial concentration of aldehyde) or with the concentration data of Table 2, the deviation is minimal. For instance in the case of 1-*p*-methylbenzoyl-2-phenyloxiran, the two calculated rate constants proved to be 2·87 and 2·76 l mol^{-1} min^{-1}. Similar deviations have been obtained with the rate constants of the other reactions.

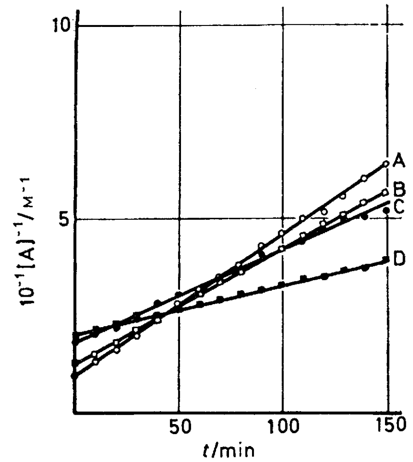
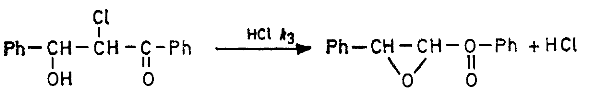


FIGURE 6 Second-order rate plots for acid-catalysed condensations at 30°: A, *p*-methoxyphenacyl chloride; B, *p*-methylphenacyl chloride; C, phenacyl chloride; D, *p*-chlorophenacyl chloride

The second-order kinetics indicate that the rate determining step is second order and in view of the large excess of catalyst, the only second order step in Scheme 2 with equal concentrations of reagents is (b).

Cyclisation of chlorohydrin.[14] In the kinetic experiments the increase of the quantity of epoxy-ketone was measured by continuous polarographic recording at −0·7 V. A 2·74 × 10^{-1}M ethanolic solution of hydrogen chloride gas was used as catalyst leading to reaction (5).


(5)

$$\mathrm{Ph{-}CH(OH){-}CHCl{-}C(=O){-}Ph} \xrightarrow{\mathrm{HCl}\ k_3} \mathrm{Ph{-}CH{-}CH{-}C(=O){-}Ph} + \mathrm{HCl} \quad (5)$$

The rate constant can be calculated by means of the first-order kinetic equation[11] (Figure 7). The rate constant $k_3 = 4{\cdot}71 \times 10^{-2}$ min^{-1}.

Effect of substituents. The Hammett equation holds for the acid-catalysed condensation (Figure 8). The rate-increasing series for the substituents is $NO_2 <$ Cl < H < Me < OMe.[1] For the reason mentioned for base catalysis, the rate constant for the *p*-nitrophenacyl chloride reaction was calculated from the Hammett equation. ρ Was found to be −0·81. Hence, the rate-increasing series for the substituents is the same as that for base catalysis, and electron-donating substituents on phenacyl chlorides slightly increase the rate of the acid-catalysed condensation. The relatively small effects can be explained as for the base-catalysed condensation.

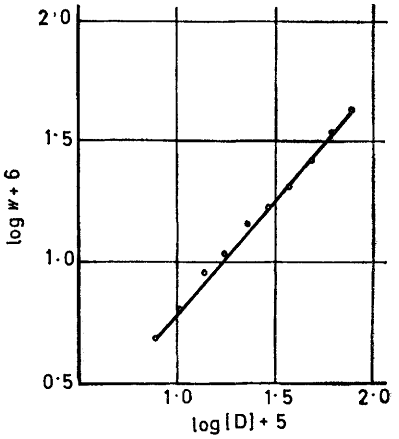


FIGURE 7 First-order rate plot for acid-catalysed cyclisations of 2-benzoyl-2-chloro-1-phenylethanol

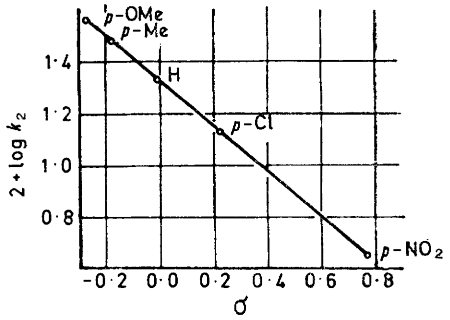


FIGURE 8 Hammett plot for acid-catalysed condensations

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[13] Ref. 11, p. 13.

[14] O. Widman, *Ber.*, 1915, **48**, 477.