Mechanism of the Baeyer–Villiger Reaction

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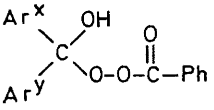
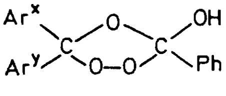
Summary Examination of the effects of substituents on the rate and the migratory aptitude in the oxidation of substituted *pp*′-dimethoxybenzophenones with peroxybenzoic acid in dichloroacetic acid to give aryl benzoates suggests that the rearrangement of peroxybenzoic acid–ketone adducts to esters is rate-determining.

IT has been suggested that the oxidation of ketones with peroxy-acids to give esters involves the Criegee intermediate (Ia)[1] or a possible alternative adduct (Ib)[2], and it appears to be a controversial problem whether the formation of the adduct is rate-determining or not.[3]

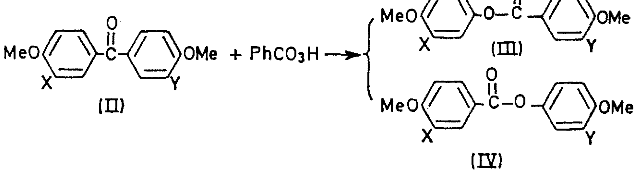


(Ia)

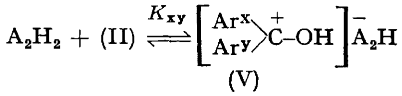


(Ib)

We studied the oxidation of substituted *pp*′-dimethoxybenzophenones (II) with peroxybenzoic acid in dichloroacetic acid at 25°, and now present convincing evidence in support of a mechanism in which the rate-determining step is the formation of esters from the adduct rather than the formation of the adduct.



It was found that in dichloroacetic acid all of the *pp*′-dimethoxybenzophenones studied are converted almost completely into the conjugate acids; the equilibrium constant K_{XY} for the following equilibrium



$$A_2H_2 + \text{(II)} \overset{K_{XY}}{\rightleftharpoons} \left[{}^{\text{Ar}^X}_{\text{Ar}^Y}\!\!>\overset{+}{\text{C}}\text{–OH}\right]\overset{-}{A_2H}$$

(V)

where A_2H_2 represents dichloroacetic acid dimer,[4] determined by u.v.-spectroscopic measurements in 1,2-dichloroethane [K_{XY} (l. mole^{-1}) at 15°: X, Y = H, 21·6; X = H,

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† Incidentally, the relation $K_{XY}/(K_{XX}{\cdot}K_{YY})^{1/2} = 1$, of the same form as equation (1), should hold, since protonation takes place at the carbonyl oxygen, *i.e.* at the site which is symmetrical with respect to both benzene rings. In fact, the experimental data (X = H, Y = NO_2) give a value (0·92) close to unity.

$Y = NO_2$, 9·0; X, $Y = NO_2$, 4·6]† indicates that, even in the case of (II; X, $Y = NO_2$) which shows the least basicity, 97% of the ketone exists in the form of a conjugate acid in dichloroacetic acid. Accordingly, the reaction under the present experimental conditions may be represented by the following sequence:

$$\text{(V)} + \text{PhCO}_3\text{H} \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} \text{(I)} \xrightarrow{k_2} \text{(III)} + \text{(IV)}$$

Second-order rate constants, k_{obs}, measured by iodometric titration of peroxybenzoic acid (Table 1) should be expressed as follows: if the formation of esters (III) and (IV) is rate-determining, $k_{\text{obs}} = k_1k_2/k_{-1}$, and if the formation of adducts (I) is rate-determining, $k_{\text{obs}} = k_1$.

TABLE 1

Rate constants

Substituents X	Substituents Y	10^2k (l. mole^{-1} min.$^{-1}$)
H	H	2·44
H	NO_2	2·02
NO_2	NO_2	0·163
H	Br	2·46
Br	Br	1·24
H	Cl	2·56
Cl	Cl	1·76

TABLE 2

Correlation between rates and isomer ratios

Substituents X	Substituents Y	Chemical shifts of methoxy protons in $CHCl_3$ (δ p.p.m.) (III)	Chemical shifts of methoxy protons in $CHCl_3$ (δ p.p.m.) (IV)	Isomer ratios r (III)/(IV)	$(r^{1/2} + r^{-1/2})/2$	$k_{xy}/(k_{xx} \cdot k_{yy})^{1/2}$
H	Br	3·83 3·97	3·87 3·89	7·4	1·5	1·4
H	Cl	3·82 3·98	3·87 3·90	8·1	1·6	1·2
H	NO_2	3·83 4·06	3·89 3·98	55—40[a]	3·8—3·2[a]	3·2

[a] Calculated values, see text.

These two mechanisms may be distinguished on the basis of the correlation between the rate and the product isomer ratio that has been put forward in previous communications.[5,6] The effect of substituents on the rate k_1 of the formation of the adduct (I) may be expressed, on the assumption of the additivity rule of the substituent effect, by

$$k_{1,xy}/(k_{1,xx} \cdot k_{1,yy})^{1/2} = 1 \qquad (1)$$

where subscripts xy, xx, and yy denote unsymmetrical and symmetrical di-substitution of *pp'*-dimethoxybenzophenone by group X and/or Y. As regards the rate constant k_2 for the conversion of the adduct into the esters, on the other hand, the correlation with the product isomer ratio r will be

$$k_{2,xy}/(k_{2,xx} \cdot k_{2,yy})^{1/2} = (r^{1/2} + r^{-1/2})/2 \qquad (2)$$

If the conversion step of the adduct is rate-determining, k_{obs} values for various substituted reactants satisfy equation (2), taking the place of k_2 values, since $k_{\text{obs}} = k_1k_2/k_{-1}$ and since for k_1 equation (1) holds and evidently it is also the case with k_{-1}.

Product isomer ratios were determined by n.m.r. measurements, the intensities of methoxy proton signals from the isomeric esters formed being compared, and the results are summarized in Table 2. The *p*-methoxyphenyl group migrates much more readily than *p*-methoxy-*m*-Y-phenyl group (Y = Cl, Br, and NO_2), in keeping with the results reported by Doering and Speers.[7] As shown in Table 2, the experimental data for the *m*-bromo-derivative fit equation (2) rather than (1), while those for the *m*-chloro-derivative offer no conclusive evidence in view of the present experimental accuracy. The rate term $k_{xy}/(k_{xx} \cdot k_{yy})^{1/2}$ for the compound carrying a *m*-nitro-group is 3·2, clearly incompatible with equation (1). Although the extremely large difference in migratory aptitude made it impossible to determine the precise isomer ratio in this case, it might be estimated from the isomer ratios found for the bromo- or chloro-derivative by virtue of the correlation of the isomer ratio with Hammett's σ values, *i.e.* $\log r_1 = (\sigma_1/\sigma_2) \log r_2$.[5] The isomer ratio calculated in this way (r = 40—55) is in accord with the kinetically predicted one (r = 40) calculated from equation (2). These observations strongly suggest that the formation of the isomeric esters from the adduct is the rate-determining step in the Baeyer–Villiger reaction, at least under the present experimental conditions, in agreement with Hawthorne and Emmons's conclusion.[8]

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