

Reaction of Aromatic Amides with Phenyl Iodosylacetate: an Oxidative Rearrangement

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The oxidative rearrangement of primary amides with phenyl iodosylacetate (PIA) yields the corresponding acylamines in acetic acid. The kinetics of the reaction of PIA with a number of substituted benzamides have been studied in solvent acetic acid and also in acetic acid-water mixtures. Electron-releasing substituents in the benzene ring accelerate the rate of the reaction while electron-withdrawing substituents retard the rate. The Hammett ρ value is -0.81 , indicative of an electron deficient transition state. The results have also been analysed using the Yukawa-Tsuno equation. A mechanism involving the formation of an iodine(III)-amide complex which rearranges in a concerted fashion to the isocyanate is proposed.

THE oxidation of primary amides with lead tetra-acetate (LTA) is known to parallel the Hofmann reaction. The preparative aspects of this reaction have been studied extensively,¹⁻⁴ but no kinetic work has been reported. However, attempts to follow the kinetics of these reactions in these laboratories failed because fairly high temperatures were required to follow the conversions and also because lead tetra-acetate oxidised almost every solvent that was used. Further the reactions were too slow to be followed in any of the standard solvent systems which did not react with the oxidant. However, the amides entered into smooth reactions with phenyl iodosylacetate (PIA). In view of the similarities between LTA and PIA, we have now thoroughly investigated the kinetics of the oxidation of

benzamides and substituted benzamides by PIA in pure acetic acid and acetic acid-water solvent mixtures.

RESULTS AND DISCUSSION

Effect of [PIA] and [Benzamide].—The oxidation of benzamide and substituted benzamides has been studied in detail from the kinetic point of view. The dependence of the rate of the reaction on [PIA] and [benzamide] is brought out in Table 1 while Table 2 gives the dependence of the rate on a few of the substituted benzamides.

It is observed that there is a clean first-order dependence on PIA and the reaction is also of the first order in benzamide, a plot of $\log k_1$ versus $\log[\text{benzamide}]$ giving

³ B. Acott, A. L. J. Beckwith, A. Hassanali, and J. Redmond, *Tetrahedron Letters*, 1965, 4039.

⁴ J. Zabacki, 'The Chemistry of Amides,' Wiley-Interscience, London, 1970, p. 793; B. Acott, A. L. J. Beckwith, and A. Hassanali, *Austral. J. Chem.*, 1968, **21**, 185, 197.

¹ H. E. Baumgarten and A. Staklis, *J. Amer. Chem. Soc.*, 1965, **87**, 1141.

² B. Acott and A. L. J. Beckwith, *Chem. Comm.*, 1965, 161.

TABLE 1

Dependence of rate on benzamide and PIA concentration
Solvent 90% HOAc-10% H₂O; temperature 50°

[Benzamide]/M	[PIA]/M	10 ⁴ k ₁ /s ⁻¹	10 ³ k ₂ /mol ⁻¹ s ⁻¹
0.05144	0.005230	1.16	2.27
0.05144	0.007693	1.26	2.35
0.05133	0.01081	1.17	2.27
0.05246	0.01509		2.32
0.07553	0.005249	1.63	2.15
0.1005	0.005249	2.09	2.08
0.1260	0.005249	2.66	2.11
0.1522	0.005249	2.98	1.96

TABLE 2

Dependence of rate on substituted benzamides
Solvent 90% HOAc-10% H₂O; [PIA] 0.003M; temperature 50°

Substituent	[Substrate]/M	10 ⁴ k ₁ /s ⁻¹	10 ³ k ₂ /mol ⁻¹ s ⁻¹
<i>p</i> -Me	0.02967	1.43	4.80
	0.04131	2.00	4.84
<i>p</i> -MeO	0.06645	3.09	4.65
	0.01697	1.30	7.64
	0.02497	2.00	8.02
<i>o</i> -Cl	0.04966	3.81	7.67
	0.03084	5.70	18.5
	0.04536	8.13	17.9
<i>o</i> -NO ₂	0.05773	10.1	17.5
	0.03042	0.576	1.89
	0.05162	0.982	1.90
	0.07199	1.39	1.93

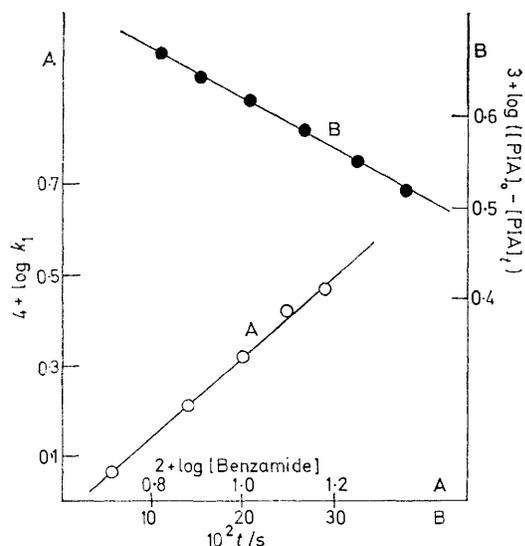


FIGURE 1 A Dependence on benzamide, $\log k_1$ versus \log [benzamide]; B first order dependence on PIA, $\log([PIA]_0 - [PIA]_t)$ versus t . Both at 30° in 90% HOAc-10% H₂O

a straight line with slope 1 (Figure 1). It may, therefore, be stated that the PIA oxidation of benzamides follows the rate law (1).

$$-d[PIA]/dt = k_2[PIA][amide] \quad (1)$$

A number of substituted benzamides with suitably positioned substituents were subjected to reaction with PIA and the rates have been followed in binary mixtures of acetic acid and water and also in 100% acetic acid over the range 40–55°. Table 3 gives the temperature dependence of the reaction rate in 70% HOAc-30% H₂O.

The Arrhenius activation parameters derived from plots of $\log k_2$ against $1/T$ are collected in Table 4. The reaction exhibited the following additional features. (i) Studies on stoichiometry indicated an amide : PIA ratio of *ca.* 1. (ii) Polymerisation tests with acrylonitrile revealed the absence of free radical formation.

TABLE 3

Variation of rate with temperature
Solvent 70% HOAc-30% H₂O; [PIA] 0.003M; [Substrate] 0.03M

Substrate	10 ⁴ k ₂ /mol ⁻¹ s ⁻¹			
	40°	45°	50°	55°
Benzamide	17.8	35.8	51.9	115
<i>o</i> -Chlorobenzamide	227	348	532	823
<i>o</i> -Methylbenzamide	645	1000	1430	2190
<i>o</i> -Nitrobenzamide	13.4	26.2	49.8	89.4
2,5-Dimethylbenzamide	742	1110	1670	2340
2,4-Dinitrobenzamide	1.93	3.99	8.48	14.4
3,5-Dinitrobenzamide	4.89	8.98	17.6	26.2
<i>m</i> -Nitrobenzamide	4.73	9.36	20.0	33.6
<i>p</i> -Chlorobenzamide	8.5	16.4	29.7	56.5
<i>p</i> -Methylbenzamide	28	56.5	110	192
<i>p</i> -Methoxybenzamide	56.5	91.5	159	276
<i>p</i> -Nitrobenzamide			8.03	

TABLE 4

Arrhenius parameters for the PIA oxidation of benzamides

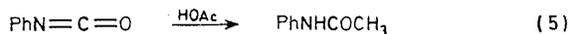
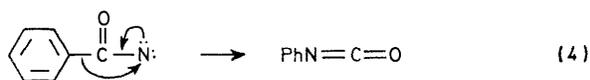
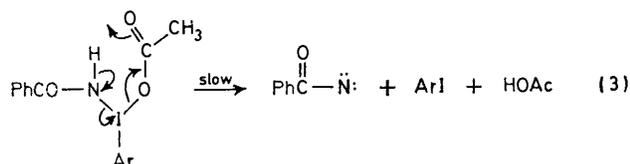
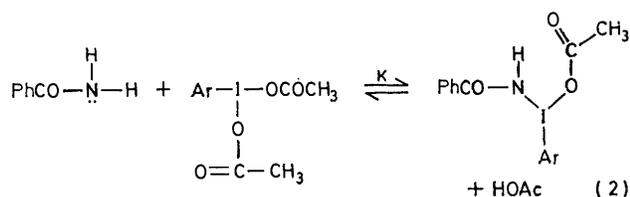
Compound	Solvent 70% HOAc-30% H ₂ O			ΔS^\ddagger / cal mol ⁻¹ K ⁻¹
	E_a / kcal mol ⁻¹	ΔH^\ddagger / kcal mol ⁻¹	$\log A$ at 50°	
Benzamide	25.7	25.1	15.1	+11
<i>o</i> -Chlorobenzamide	17.7	17.0	10.7	-9.9
<i>o</i> -Methylbenzamide	16.6	16.0	10.4	-11
<i>o</i> -Nitrobenzamide	25.9	25.3	15.2	+11
2,5-Dimethylbenzamide	15.9	15.3	9.98	-13
2,4-Dinitrobenzamide	27.1	26.4	15.2	+11
3,5-Dinitrobenzamide	24.3	23.7	13.7	+3.9
<i>m</i> -Nitrobenzamide	27.2	26.5	15.7	+13
<i>p</i> -Chlorobenzamide	25.9	25.2	15.0	+9.8
<i>p</i> -Methylbenzamide	25.2	24.5	15.1	+10
<i>p</i> -Methoxybenzamide	22.1	21.5	13.2	+1.5

(iii) The effect of added mineral acids showed the reaction to be strongly retarded by perchloric acid and totally inhibited by 1M-acid. (iv) The product of oxidation of benzamide by PIA is acetanilide.

Mechanism.—The foregoing kinetic picture shows that (i) the reaction exhibits a first-order dependence on each reactant and (ii) the reaction exhibits a pronounced polar effect with electron-releasing groups facilitating the reaction and electron-withdrawing groups decelerating the rate significantly. A mechanism which can be put forth for this oxidation (which has a formal resemblance to the Hofmann reaction) will be analogous to the proposal of Baumgarten¹ for the LTA-amide reaction. It is well documented that LTA and PIA behave similarly in many of their reactions.

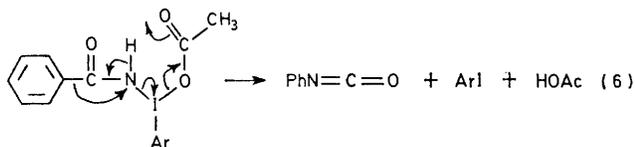
This mechanism (Scheme 1) envisages the formation of an iodine(III)-amide complex which rearranges in a slow step in a stepwise or concerted fashion to the

isocyanate. In acetic acid solvent, this is converted to the acylamine presumably *via* the amine formed by hydrolysis.⁴



SCHEME 1

The formation of the iododiacetate-amide complex is probably similar to other complexes that iododiacetate is capable of forming with 1,2-diols or α -hydroxyacids.^{5,6} The fact that the reaction exhibits a total second-order dependence does not, of course, preclude such an intermediate complex being formed if the equilibrium constant K is small. Also the reaction being considerably inhibited by added mineral acids is good evidence that the lone pair on the amide nitrogen is involved in co-ordination with I^{III}. The decomposition of this complex presumably takes place in a slow step, but this could be either a step-wise reaction as depicted in Scheme 1 or a concerted intramolecular rearrangement (Scheme 2).



SCHEME 2

A choice between the two alternatives can be made from an analysis of the substituent effects. Hence it was of interest to see if the substituent effects had any correlation with the Hammett constants of the substituents (Table 5). Figure 2 gives a Hammett plot for this reaction. It is observed that while the *meta*- and *para*-substituted compounds generally fall on a line giving a ρ -0.81 , all the *ortho*-compounds including the 2,5-dimethyl- and 2,4-dinitro-benzamides fall on a line which is nearly parallel to the former. It is also

⁵ K. H. Pausacker and J. P. Cordner, *J. Chem. Soc.*, 1953, 102.

⁶ N. Venkatasubramanian and K. Vaidynathan, *Current Sci.*, 1970, **39**, 233.

TABLE 5
Correlation of the reaction rate with Hammett substituent constants

Solvent 100% HOAc; temperature 50°		
R	$\sigma, \sigma^+, \text{ or } \sigma^0$	$10^4 k_2 / \text{l mol}^{-1} \text{s}^{-1}$
1	H	16
2	<i>o</i> -Cl	66.7
3	<i>o</i> -Me	136
4	<i>o</i> -NO ₂	15.8
5	2,5-Me ₂	177
6	2,4-(NO ₂) ₂	6.21
7	<i>m</i> -NO ₂	4.24
8	<i>p</i> -NO ₂	3.75
9	<i>p</i> -Cl	12.8
10	<i>p</i> -Me	28.8
11	<i>p</i> -MeO	68.4

The σ , σ^+ , and σ^0 values were taken from J. Hine, 'Physical Organic Chemistry,' McGraw-Hill, New York, 1962.

* σ^0 . † σ . ‡ σ^+ .

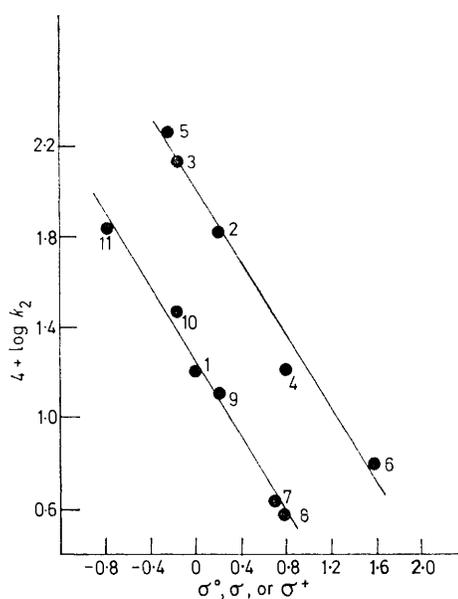


FIGURE 2 Hammett plot for substituted benzamides at 50° in 100% HOAc. For key see Table 5

observed that all the *para*-substituents give a better plot with σ^+ than with σ .

An application of the linear aromatic substituent-reactivity relationship (7)⁷ can be made to the present

$$\log k/k_0 = \rho(\sigma + \gamma\Delta\sigma^+R) \quad (7)$$

data where σ is the normal substituent constant, γ is a constant depending on the resonance requirements in the reaction, and $\Delta\sigma^+R$ measures the capacities of the substituents to donate electrons by resonance (equivalent to $\sigma^+ - \sigma$). By rearranging (7) to form (8) one can

$$[1/\rho \log k/k_0] - \sigma = \gamma\Delta\sigma^+R \quad (8)$$

evaluate the resonance parameter γ . In the present investigation γ turns out to be equal to +1 (Figure 3).

⁷ Y. Yukawa and Y. Tsuno, *Bull. Chem. Soc. Japan*, 1959, **32**, 971.

For the interpretation of the reaction mechanism, both the ρ value of -0.81 and the resonance parameter are useful, particularly to consider the effect of conjugation in the initial and transition states.

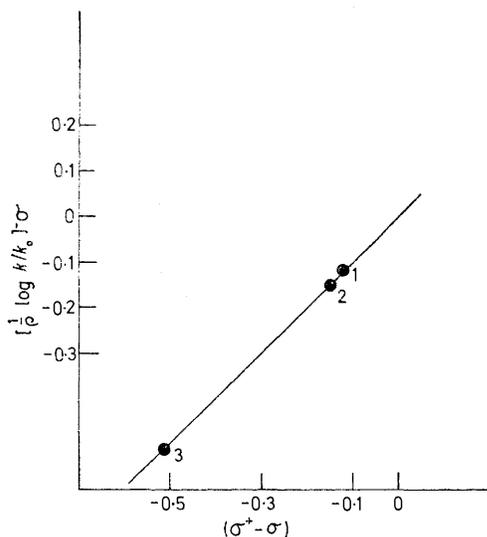
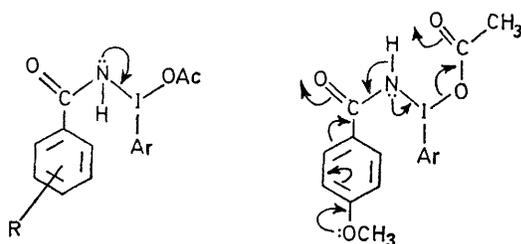


FIGURE 3 $[1/\rho \log k/k_0] - \sigma$ versus $\sigma^+ - \sigma$ at 50° in 100% HOAc: 1, *p*-chlorobenzamide; 2, *p*-methylbenzamide; 3, *p*-methoxybenzamide

If the decomposition of the amide-PIA complex is rate determining, then the $d\pi-p\pi$ conjugation of the N-I bond in the initial state may be considered to be an important factor influencing reactivity; this conjugation will increase the bond order of the N-I bond and make it more difficult to release the ArI system from the rest of the molecule. The extent of this conjugation will be affected especially by an electron-releasing ($+M$) substituent at the *para*-position. A *p*-methoxy-group, for example, would strengthen the conjugation of the carbonyl with the phenyl group and would weaken the conjugation of the carbonyl group with the nitrogen



p-orbital, resulting in a relative increase in the $d\pi-p\pi$ conjugation of the N-I bond. Therefore if the present reaction is controlled solely by $d\pi-p\pi$ conjugation effects, in the initial state, the resonance parameter γ would be expected to be negative, as has been observed in the Curtius rearrangement in toluene ($\gamma = -1.04$)⁸

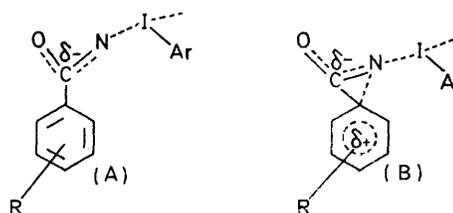
⁸ Y. Yukawa and Y. Tsuno, *J. Amer. Chem. Soc.*, 1959, **81**, 2007.

⁹ Y. Yukawa, Y. Tsuno, and Y. Ibata, *Bull. Chem. Soc. Japan*, 1967, **40**, 2613.

¹⁰ D. E. Pearson, J. F. Baxter, and J. C. Martin, *J. Org. Chem.*, 1952, **17**, 1511.

and in the Wolf rearrangement ($\gamma = -1.7$).⁹ The present result (γ ca. $+1$) indicates that the bond energy effect mentioned above is not necessarily a predominant factor in influencing the reactivity in the present reactions.

The transition state of the amide-PIA reaction may be represented by either of the two models (A) and (B). Model (A) is for a two-step mechanism where the release of iodobenzene takes place in the first step and the univalent nitrogenous intermediate (a nitrene) rearranges immediately to an isocyanate. In this model, the substituent effect on the stabilisation of this state can be expected to have a low γ value of ca. 0.27 as in the benzoate anion. Model (B) envisages, however, a one step mechanism, where the release of iodobenzene and the migration of the phenyl group are simultaneous processes. This mechanism would demand a large positive value, as in the Beckmann rearrangement of acetophenone oximes ($\gamma = 0.60-0.65$). We can, therefore, conclude that the observed γ value in our case is strongly indicative of model (B).



In the analogous LTA-amide reactions, no free nitrenes were detected^{2,3} and the reaction was thought to proceed in a concerted fashion. Because of the similarity of the reactions of LTA and PIA, one can justifiably conclude that a nitrene is not an intermediate in the present reaction and the one-step mechanism (Scheme 2) is the more likely route for this reaction.

The ρ value of -0.81 , while being indicative of an electron deficient transition state, is on the low side. This low value is further evidence for the concerted (or one-step mechanism). The Curtius reaction of substituted azides is known to have a low ρ value (-1.1)⁸ although other reactions proceeding *via* an electron deficient nitrogen intermediate have higher values (Beckmann rearrangement, $\rho -2.0$;¹⁰ Hofmann rearrangement, -2.36 ;¹¹ Lossen rearrangement, -2.6)¹².

It is also of interest to discuss the effect of *ortho*-substituents on the reaction mechanism. Although the polar effects of *ortho*-substituents are generally recognised to be nearly equal to those of *para*-substituents,¹³ the *ortho*-substituents produce a large rate enhancement not only over the unsubstituted compound (except for the *o*-nitro-compound) but also over the corresponding *para*-compound. The *ortho* : *para* ratios and the relative

¹¹ Y. Yukawa, Y. Tsuno, and T. Imamoto, *Bull. Chem. Soc. Japan*, 1971, **44**, 1632.

¹² W. B. Renfrow, jun., and C. R. Hanser, *J. Amer. Chem. Soc.*, 1937, **59**, 2308.

¹³ R. W. Taft, jun., 'Steric Effects in Organic Chemistry,' Wiley, New York, 1956, p. 556.

value of activation parameters are collected in Table 6. Except for the nitro-substituent, these large ratios seem to depend more on the differences in the entropy of activation than on ΔH^\ddagger . The introduction of an *ortho*-substituent restricts the rotation of the phenyl ring

TABLE 6
ortho : *para* Ratios and relative values of activation parameters

Solvent 70% HOAc-30% H₂O; temperature 50°

Substituent	Relative ratio	k_o/k_p	$\Delta\Delta H^\ddagger/\text{kcal mol}^{-1}$	$\Delta\Delta S^\ddagger/\text{cal mol}^{-1}\text{K}^{-1}$
H	1	1	0	0
<i>o</i> -Cl	10.25	17.9	8.1	20.9
<i>o</i> -Me	27.55	13.0	9.1	22
<i>o</i> -NO ₂	0.96	6.2	0.2	0

and lessens the entropy in the initial state more than that of the corresponding *para*-substituent. If the reaction proceeds by a two-step mechanism, the difference in the entropy of the *ortho*- and *para*-derivatives in the initial state will not have any effect on the relative value of the entropy of activation. In the case of a concerted mechanism, however, the entropy of activation of the *para*-derivative is lowered below that of the corresponding *ortho*-compound by the restriction of the motion of the phenyl ring on proceeding from the reactant to the transition state. Therefore, the relative value of the entropy of activation $\Delta\Delta S^\ddagger$ depends considerably on the difference in entropy in the initial state. The observed values of $\Delta\Delta S^\ddagger$ in the case of *o*-CH₃ and *o*-Cl are in line with the above arguments. The data for the *o*-nitro-compound appear anomalous. However, an *o*-nitro-substituent may exert, in addition to polar and steric influences, an electrostatic field effect on the reaction centre, leading to an additional lowering of rate.

Another qualitative explanation for the observed *ortho*-rate effects is as follows. The introduction of a bulky *ortho*-group will reduce the co-planarity of the molecule thereby reducing the extended conjugation between the phenyl and the carbonyl groups. This effect will increase the conjugation of the carbonyl group with the nitrogen lone pair, but will correspondingly decrease the $d\pi-p\pi$ conjugation of the N-I bond. This lowered $d\pi-p\pi$ conjugation may play a role in bringing about rate acceleration.

The Hammett correlation appears to apply to reaction series in which either the entropies of activation for the series are constant or in which the variation in the entropy of activation is linearly related to changes in the enthalpy of activation.^{14,15} The ΔH^\ddagger and ΔS^\ddagger values collected in Table 4 show that the reactions are not isoentropic. There are also large variations in the enthalpy values. Therefore one can expect that the observed correlation between $\log k_2$ and σ^+ , σ , or σ^0 should be reflected in a linear relationship between ΔS^\ddagger and ΔH^\ddagger . A plot of ΔH^\ddagger versus $-\Delta S^\ddagger$ is given in Figure 4. There is indeed a fair linearity among the

¹⁴ J. Leffler, *J. Org. Chem.*, 1955, **20**, 1202.

¹⁵ P. R. Wells, *Chem. Rev.*, 1963, **63**, 171.

parameters and the line has a least square slope of 425.1 K ($r\ 0.9893$).

The fact that β , the isokinetic temperature, is 98.5° away from the experimental temperature shows that the

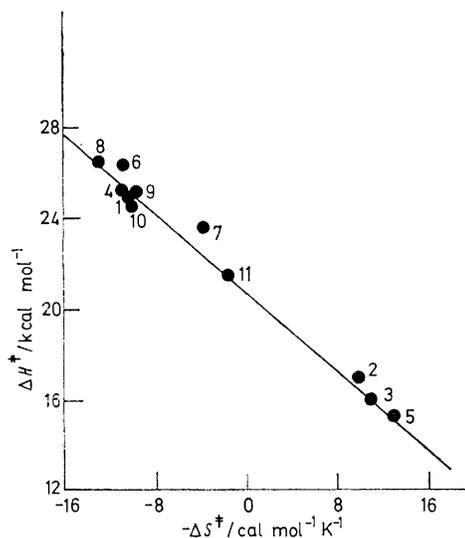
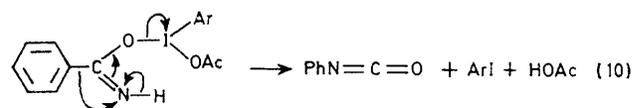
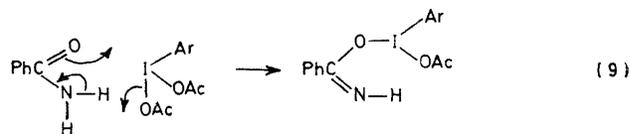


FIGURE 4 ΔH^\ddagger versus ΔS^\ddagger for substituted benzamides. For key see Table 5

isokinetic relationship is a true and valid one for this reaction. One might therefore conclude that the above detailed correlation between rate and amide structure is also probably valid.

Although the PIA-amide complex was conceived as being formed by an initial substitution on the amide



SCHEME 3

nitrogen atom, it is quite likely that the amide might suffer initial *O*-substitution as outlined in Scheme 3. In the absence of definitive evidence, choice between Schemes 2 and 3 can at best be only speculative.

EXPERIMENTAL

Phenyl iododiacetate (PIA) was prepared by the modified method of Böeseken and Schneider.¹⁶ Hydrogen peroxide (30%; 70 ml) and acetic anhydride (305 ml) were stirred together for 4 h at 40°. Iodobenzene (50 g) was added to the solution which was then kept overnight. Some phenyl iododiacetate crystallised and was filtered off. The filtrate was concentrated to a small volume under

¹⁶ J. Böeseken and G. C. C. Schneider, *J. prakt. Chem.*, 1931, **131**, 285.

reduced pressure (70 mmHg) and a second crop of crystals obtained. The combined crystals (52 g) were washed with ether and dried, m.p. 158°. Acetic acid was purified by the method of Orton and Bradfield.¹⁷ Conductivity water was used in all experiments.

Kinetic Measurements.—The substrate and oxidant solutions were thermostatted for at least 3 h before performing the experiment. The oxidant was estimated by iodometry. Portions were withdrawn from the reaction mixture and pipetted into a solution of iodate-free potassium iodide (0.3 g) and sodium hydrogen carbonate (0.3 g) in water (20 ml). 6M-H₂SO₄ (2 ml) was added and the flask was stoppered and set aside for a few minutes. The solution was then diluted with distilled water (50 ml) and the iodine liberated was titrated with standard thiosulphate to a starch end point. Most of the experiments were carried out with a large excess of substrate and the pseudo-first-order rate constants (k_1) were calculated by the method of least squares using the integrated equations for a first-order reaction. The second-order rate constants (k_2) were calculated by dividing k_1 by the initial reductant concentration. All the velocity constants were reproducible to within $\pm 3\%$. Activation energies were obtained by plotting $\log k_2$ against $1/T$ from which other thermodynamic parameters were calculated.

Stoichiometry. PIA [0.06M in acetic acid (50 ml)] and benzamide [0.02M in acetic acid (50 ml)] were taken in two different standard flasks and were thermostatted. Benz-

amide solution (25 ml) was introduced into a previously thermostatted reaction bottle followed by PIA solution (25 ml). The excess of oxidant was estimated after the reaction was complete. The ratio of benzamide to PIA was *ca.* 1 : 1.

Polymerisation Tests with Acrylonitrile.—The following mixtures were prepared: (i) a solution of 0.1M-PIA (5 ml)–benzamide (0.5 g) in glacial acetic acid (20 ml)–acrylonitrile (5 ml); (ii) glacial acetic acid (20 ml)–acrylonitrile (5 ml); (iii) benzamide (0.5 g) in glacial acetic acid (20 ml)–acrylonitrile (5 ml); and (iv) 0.1M-PIA in glacial acetic acid (5 ml)–acrylonitrile (5 ml). The four solutions were kept in a thermostat at 50° for 3 h. Dry, peroxide-free ether was added to all the solutions to precipitate any polymerised acrylonitrile. There was no formation of any polymerised material in any of the systems. This established clearly the absence of free radical formation during PIA oxidation of benzamide.

Product Analysis.—The product of the reaction between benzamide and PIA in acetic acid was shown to be acetanilide.

K. S. thanks the University Grants Commission, Government of India, for the award of a Research Fellowship.

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¹⁷ K. J. P. Orton and A. Bradfield, *J. Chem. Soc.*, 1924, 960.