

## Intramolecular Catalysis. Part III.<sup>1</sup> Hydrolysis of 3'- and 4'-Substituted Phthalanilic Acids [*o*-(*N*-Phenylcarbamoyl)benzoic Acids]

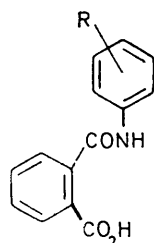
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Hydrolysis of 3'- and 4'-substituted phthalanilic [*o*-(*N*-phenylcarbamoyl)benzoic] acids between pH 0.63 and 5.08 proceeds *via* undissociated carboxy-group participation at a rate which shows a linear correlation with the  $pK_b$  of

$$k_{\text{obs}} = (k_1 + k_2[\text{H}^+]) / (1 + K_a/[\text{H}^+]) \quad (\text{i})$$

the aniline leaving group. The hydrolysis follows equation (i). In 1.0M-hydrochloric acid phthalanilic acid is hydrolysed nearly  $4 \times 10^3$  times faster than benzanilide. The rate controlling step is the breakdown of the tetrahedral intermediate, which can be generated independently from *N*-phenylisophthalimide. *N*-Phenylisophthalimide has a half-life of *ca.* 7 s at 24.6° in 0.1M-hydrochloric acid and is hydrolysed to phthalanilic acid *ca.* 500 times faster than phthalanilic acid itself and 12–13 times faster than phthalic anhydride. The effect of added dioxan and of increasing acidity on the experimental rate constant for the hydrolysis of phthalanilic acid is reported.

INTRAMOLECULAR catalysis of amide hydrolysis by the neighbouring carboxy-group has been reported for phthalamic acid<sup>2,3</sup> and the *N*-alkyl- or *N*-aryl-monamides of succinic,<sup>4</sup> maleic,<sup>5-9</sup> and phthalic acids.<sup>3,5,10,11</sup> Alkyl substitution of the dicarboxylic acid has been shown to have an enormous influence on these reaction rates owing to the easier formation of the cyclic intermediate.<sup>4,6,12</sup>



(I)–(XV)

In this study the hydrolysis of 3'- and 4'-phthalanilic [*o*-(*N*-phenylcarbamoyl)benzoic] acids (I)–(XV) was examined to find the effect of substituents in the aniline ring on the reaction rate. The rate constant for the hydrolysis of benzanilide was determined to give an indication of the rate enhancement obtained as a result of participation of the neighbouring carboxy-group.

### EXPERIMENTAL

**Materials.**—Analytical grade inorganic salts and B.D.H. spectroscopy grade 1,4-dioxan were used without further purification. Standard hydrochloric acid solutions were prepared by diluting ampoules of B.D.H. volumetric grade reagents. All water was either degassed and double distilled

<sup>1</sup> Part II, M. D. Hawkins, preceding paper.

<sup>2</sup> M. L. Bender, *J. Amer. Chem. Soc.*, 1957, **79**, 1258; M. L. Bender, Y.-L. Chow, and F. Chloupek, *ibid.*, 1958, **80**, 5380.

<sup>3</sup> J. Brown, S. C. K. Su, and J. A. Shafer, *J. Amer. Chem. Soc.*, 1966, **88**, 4468.

<sup>4</sup> T. Higuchi, L. Ebersson, and A. K. Herd, *J. Amer. Chem. Soc.*, 1966, **88**, 3805; T. Higuchi, T. Miki, A. C. Shah, and A. K. Herd, *ibid.*, 1963, **85**, 3655.

<sup>5</sup> G. Dalilgren and N. L. Simmerman, *J. Phys. Chem.*, 1965, **69**, 3626.

<sup>6</sup> A. J. Kirby and P. V. Lancaster, *J.C.S. Perkin II*, 1972, 1206.

<sup>7</sup> A. J. Kirby, R. S. McDonald, and C. R. Smith, *J.C.S. Perkin II*, 1974, 1495.

<sup>8</sup> M. F. Aldersley, A. J. Kirby, P. W. Lancaster, R. S. McDonald, and C. R. Smith, *J.C.S. Perkin II*, 1974, 1487.

from all-glass apparatus or was taken from an ion exchange column. Phthalic anhydride was of reagent grade and was recrystallised twice from chloroform and stored in a vacuum desiccator before use. Benzanilide, m.p. 161.5–162.5° (lit.,<sup>13</sup> 162°), was prepared from aniline and benzoyl chloride by the Schotten–Baumann reaction. The product was recrystallised three times from methylated spirits and air-dried. *N*-Phenylisophthalimide, m.p. 115–116° (lit., 116°,<sup>14</sup> 115–117°<sup>15</sup>) was prepared using a published method.<sup>14,15</sup>

**Substituted Phthalanilic Acids.**—These were prepared by adding the freshly distilled or recrystallised aniline (0.01 mol) to a solution of phthalic anhydride (0.01 mol) in chloroform contained in a 50 ml round-bottomed flask fitted with a reflux water condenser. Many of the reactions were strongly exothermic. The mixture was heated on a boiling water-bath for 20 min and then allowed to cool slowly to room temperature. The virtually pure product which separated in almost quantitative yield was filtered off using a Buchner funnel, washed well with chloroform, recrystallised twice from boiling chloroform, and air-dried.

There is considerable discrepancy, amounting to as much as 40° in the case of 4'-methoxyphthalanilic acid, between the various published values of the m.p.s of the phthalanilic acids. This is probably due to the fact that these compounds lose water on heating to form the imide, and the temperature of this decomposition also depends on such factors as the rate of heating, particle size, and the nature of the surface in contact with the compound. However in some cases it was reported that the acids had not been recrystallised<sup>16</sup> or had been washed with ethanol, which is known to react with phthalanilic acids to form the imide.<sup>17</sup> The m.p.s of the substituted phthalanilic acids prepared together with literature values are listed in Table 1.

***N*-Phenylphthalimide.**—This was prepared by a modifica-

<sup>9</sup> M. F. Aldersley, A. J. Kirby, and P. W. Lancaster, *J.C.S. Chem. Comm.*, 1972, 570.

<sup>10</sup> H. Morawetz and J. A. Shafer, *J. Amer. Chem. Soc.*, 1962, **84**, 3783.

<sup>11</sup> P. P. Nechaev, Yu. V. Moiseev, E. V. Kamzolchina, Z. V. Gerashchenko, Ya. S. Vygodskii, and G. E. Zaikov, *Izvest. Akad. Nauk. S.S.S.R., Ser. khim.*, 1972, **12**, 2723.

<sup>12</sup> M. D. Hawkins, unpublished results.

<sup>13</sup> A. I. Vogel, 'A Textbook of Practical Organic Chemistry,' Longmans, London, 1957, 3rd edn.

<sup>14</sup> M. L. Sherrill, F. L. Schaeffer, and E. P. Shoyer, *J. Amer. Chem. Soc.*, 1928, **50**, 474.

<sup>15</sup> A. van der Meulen, *Rec. Trav. chim.*, 1896, **15**, 282.

<sup>16</sup> N. V. Subba Rao and C. V. Ratnam, *J. Sci. Ind. Res., India*, 1962, **21B**, 47.

<sup>17</sup> J. Bishop, J. R. Tingle, and H. F. Roeker, *J. Amer. Chem. Soc.*, 1908, **30**, 1882.

TABLE I  
M.p.s of substituted phthalanilic acids (I)—(XV)

Substituent R	M.p. (°C)	Lit. m.p. (°C)
H (I)	169 (decomp.)	169 <sup>14,16</sup>
3'-Me (II)	156	157 <sup>16</sup>
4'-Me (III)	160—161 (decomp.)	155, <sup>16</sup> 160 <sup>17</sup> , 160—160.5 <sup>a</sup>
3'-MeO (IV)	171	151—153, <sup>b</sup> 171, <sup>c</sup> 159—161 <sup>17</sup>
4'-MeO (V)	156—157 (decomp.)	138, <sup>16</sup> 157—158, <sup>b</sup> 180—185 <sup>b,c</sup>
3'-Cl (VI)	184	184, <sup>16</sup> 183—184 <sup>14</sup> , 170—171.5 <sup>b</sup>
4'-Cl (VII)	184—185	183—184, <sup>b</sup> 190, <sup>16</sup> 187.5 <sup>14</sup>
3'-Br (VIII)	167 (sinters), 175 (melts)	
4'-Br (IX)	185.5—186.5	
4'-F * (X)	155 (sinters), 170 (melts)	
4'-I (XI)	179 (sinters), 185—186 (melts)	
3'-NO <sub>2</sub> (XII)	202 (decomp.), remelts at 250—251 (imide?)	202 (decomp.), <sup>14</sup> 240 <sup>16</sup>
4'-NO <sub>2</sub> (XIII)	192—193 (decomp.)	186, <sup>16</sup> 192 (decomp.) <sup>14</sup>
2'-Me (XIV)	166	166—167, <sup>17</sup> 173, <sup>16</sup> 168.5—169.5 <sup>a</sup>
2'-Cl (XV)	142	144 <sup>16</sup>

\* Recrystallised from benzene.

<sup>a</sup> R. D. Reynolds and G. L. Anderson, *J. Org. Chem.*, 1963, **28**, 3223. <sup>b</sup> R. D. Reynolds, M. J. Zeigler, D. J. Heuck, and C. Johnson, *J. Chem. and Eng. Data*, 1968, **13**, 558. <sup>c</sup> J. Rufener, G.P. 1,813,727/1969 (*Chem. Abs.*, 1969, **71**, 123,975).

ation of a published method.<sup>17</sup> Phthalanilic acid (1.2 g, 5 mmol) was gently heated at its m.p. for 3—4 min and then allowed to cool. The solidified product was dissolved in hot methylated spirit and heated under reflux for 1 h. The solution was then evaporated to small bulk and cooled. The crystals of *N*-phenylphthalimide which separated (0.7 g, 65%) were filtered off, recrystallised twice from ethanol, and air-dried, m.p. 207° (lit.,<sup>14,17</sup> 207°).

**Kinetic Methods**—The ionic strength of the sodium acetate–hydrochloric acid buffers was kept constant by the addition of sodium chloride. An E.I.L. pH-meter was used for pH measurements. The pH of sodium acetate–acetic acid buffers in aqueous dioxan was calculated using the published  $pK_a$  value of acetic acid in aqueous 20% v/v dioxan.<sup>18</sup>

Pseudo-first-order rate constants were evaluated using Guggenheim's method<sup>19</sup> or graphically from integrated first-order plots of  $\log(O.D._t - O.D._\infty)$  against time. The change in absorption at a convenient wavelength was followed using a Beckman model DU u.v. spectrophotometer. One drop of a solution of the phthalanilic acid in 1,4-dioxan was added to a 10 mm stoppered quartz spectroscopy cell containing the reaction medium which was heated to the required temperature in a specially constructed steel cell-holder through which water was circulated from a thermostatted bath controlled to  $\pm 0.02^\circ$ . The hydrolysis of benzanilide and of the less reactive substituted phthalanilic acids was followed by filling quartz spectroscopy cells with samples of the reaction mixture taken at suitable intervals from flasks heated in a thermostatted bath.

## RESULTS AND DISCUSSION

Hydrolysis of a series of 3'- and 4'-phthalanilic acids in aqueous sodium acetate–hydrochloric acid buffers over the pH range 0.63—5.08 gave sigmoid rate profiles characteristic of intramolecular catalysis by participation of the neighbouring undissociated carboxy-group. There is a linear relationship (gradient  $-0.344$ ; correlation coefficient  $r 0.987$ ) between the logarithm of the experimental first-order rate constant and the  $pK_b$  of the

aniline leaving group. However in spite of this high correlation coefficient the Hammett plot for the hydrolysis of phthalanilic acids (I)—(XII) is curved (Figure 1); and, although with most of the phthalanilic acids no evidence for anything but a purely hydrolytic reaction in aqueous solution could be found, examination of the reaction products of the 3'-nitro- and 4'-nitro-phthalanilic acids especially indicated that there was a change in

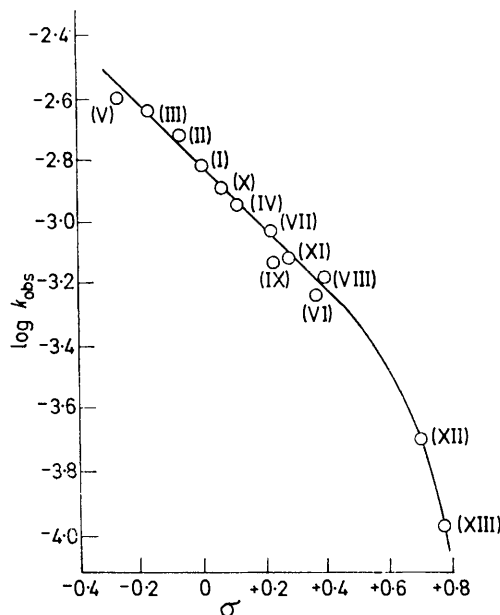


FIGURE 1 Hydrolysis of 3'- and 4'-phthalanilic acids in aqueous 20% v/v dioxan at 65.8° with sodium acetate–acetic acid buffer, pH 4.42

reaction mechanism to account for the non-linear plot. This alternative reaction, which is particularly apparent in aqueous dioxan (Figure 1), results in the formation of the imide and is discussed later in this section.

The hydrolysis follows the rate equation (1) from  $R = k_{\text{obs}}$  [total substrate]

$$= k_1 [\text{un-ionised substrate}] + k_2 [\text{un-ionised substrate}] [\text{H}^+] \quad (1)$$

<sup>18</sup> H. S. Harned and G. L. Kazanjian, *J. Amer. Chem. Soc.*, 1936, **58**, 1912; R. A. Robinson and R. H. Stokes, 'Electrolyte Solutions,' Butterworths, London, 1965, p. 538.

<sup>19</sup> E. A. Guggenheim, *Phil. Mag.*, 1926, **2**, 538.

which (2) is derived. Values of the constants  $k_1$  and  $k_2$  and of the kinetically apparent dissociation constant of

$$k_{\text{obs}} = (k_1 + k_2[\text{H}^+]) / (1 + K_a/[\text{H}^+]) \quad (2)$$

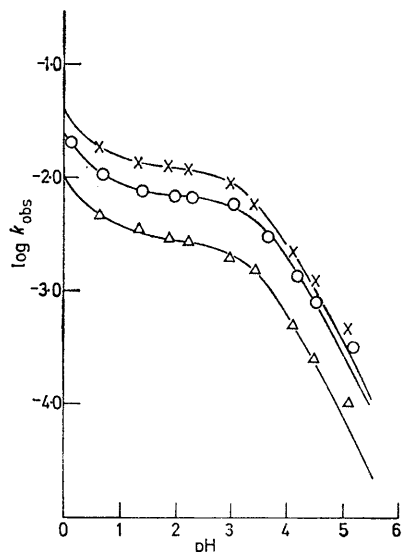


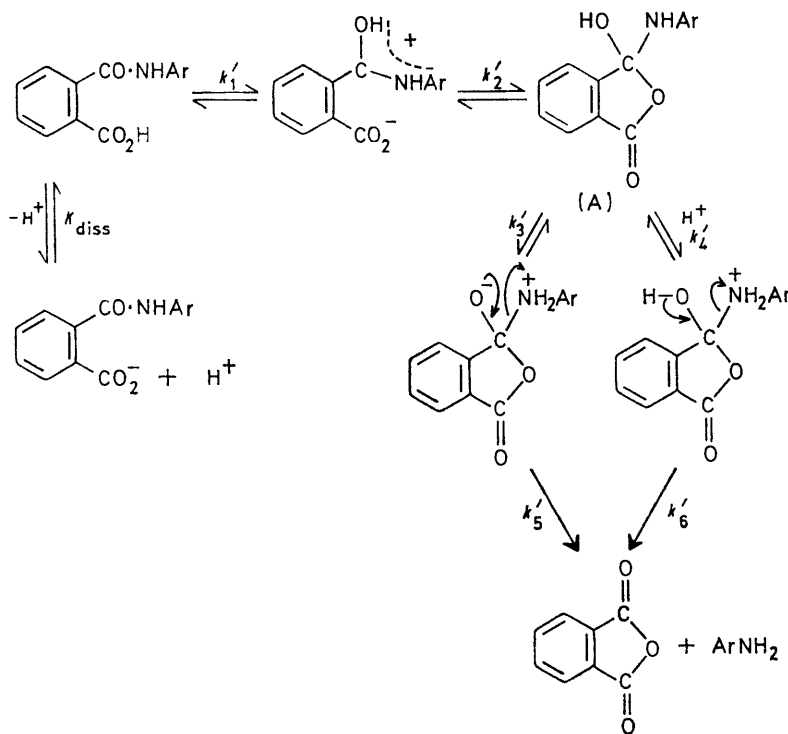
FIGURE 2 Rate profiles for hydrolysis of phthalanilic acids at 65.8° with sodium acetate-hydrochloric acid buffer: ×, R = 4'-MeO; ○, R = H; Δ, R = 3'-Cl

the phthalanilic acid were obtained by computer analysis of this equation. This gave theoretical rate profiles

$7.49 \times 10^{-3} \text{ s}^{-1}$ ] compounds (I)—(IX) and good agreement with published values of  $\text{p}K_a$  (e.g. kinetically apparent  $\text{p}K_a$  for phthalanilic acid 3.604, cf. lit.,<sup>10</sup> 3.62). However  $k_2$  showed very poor correlation with the Hammett equation ( $\rho -1.29$ ;  $r 0.215$ ). This was expected as this second-order term only becomes important at low pH values. Somewhat more reliable values of  $k_2$  were determined by finding the first-order rate constant in a series of moderately strong acid solutions ( $\text{pH} < 1$ ) and then calculating  $k_2$  from  $k_2 = (k_{\text{obs}} - k_1)/[\text{H}^+]$  using the values of  $k_1$  from the computer analysis. These values of  $k_2$  gave a better fit to the Hammett equation ( $\rho -0.67$ ;  $r -0.93$ ;  $10^3 k_2/\text{l mol}^{-1} \text{ s}^{-1} 24.5$  for phthalanilic acid).

The  $\rho$  value for the experimental first-order rate constant  $k_{\text{obs}}$  was analysed in terms of the corresponding values for  $k_1$  and  $K_a$  using equation (2). At pH values where  $[\text{H}^+] \ll K_a$ ,  $K_a/[\text{H}^+] \gg 1$  and  $k_1 \gg k_2[\text{H}^+]$ . Thus  $k_{\text{obs}} = k_1 [\text{H}^+]/K_a$  or,  $\log k_{\text{obs}} = \log k_1 - \log K_a + \log [\text{H}^+]$  and  $\rho_{\text{obs}} = \rho k_1 - \rho K_a$ . Although the  $\rho$  values are of the correct order of magnitude, the kinetically apparent dissociation constants were not sufficiently accurate to test the validity of this treatment.

Comparison of the pseudo-first-order rate constants obtained for the hydrolysis of benzanilide in 1.0 and 2.0M-hydrochloric acid at 65.8° ( $k_{\text{obs}} 4.95 \times 10^{-6}$  and  $1.04 \times 10^{-5} \text{ s}^{-1}$  respectively) with  $k_1$  and especially  $k_2$  for phthalanilic acid indicates that the neighbouring



SCHEME 1

which agreed well with the experimental results. Examples of such curves for hydrolysis at 65.8° are shown in Figure 2. The results gave satisfactory Hammett plots for  $k_1$  [ $\rho -1.05$ ;  $r -0.980$ ;  $k_1$  for phthalanilic acid

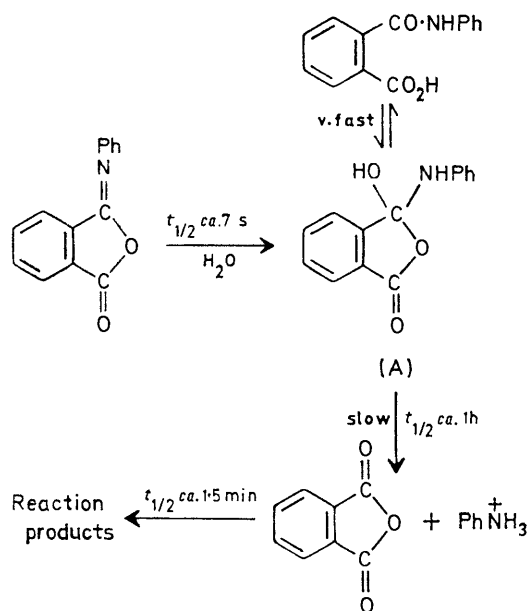
carboxy-group affects both the  $k_1$  and the  $k_2$  terms and results in a 3 600-fold rate increase. The activation parameters for the hydrolysis of phthalanilic acid ( $\Delta H^\ddagger 79 \text{ kJ mol}^{-1}$ ;  $\Delta S^\ddagger -50 \text{ J mol}^{-1} \text{ K}^{-1}$ ) and benzanilide

( $\Delta H^\ddagger$  85 kJ mol<sup>-1</sup>;  $\Delta S^\ddagger$  -120 J mol<sup>-1</sup> K<sup>-1</sup>) show the considerably more positive entropy of activation for the former compound expected for a reaction involving intramolecular catalysis. A possible reaction mechanism is shown in Scheme 1. This leads to the rate equation (3) which is of a similar form to (1) from which (2) was deduced.

$$\text{Rate} = \frac{k_5'k_3'k_2'k_1'}{k_6'k_4'k_2'k_1'}[\text{phthalanilic acid}] + k_6'k_4'k_2'k_1'[\text{phthalanilic acid}][\text{H}^+] \quad (3)$$

The negative values of  $\rho$  are consistent with Scheme 1 as the presence of electron-withdrawing substituents in the aniline ring would tend to inhibit substrate protonation and hence reduce the hydrolysis rate.

Attempts were made using the marked difference in behaviour between phthalic anhydride<sup>20</sup> and phthalanilic acid towards pH and added dioxan to obtain kinetic evidence for intermediate anhydride formation in this reaction, but were unsuccessful owing to its relatively



SCHEME 2 Half-lives are for hydrolysis in 0.1M-hydrochloric acid at 24.6°

rapid hydrolysis. However conclusive proof for the initial formation of the anhydride was obtained with the 3,6-dimethylphthalanilic acids<sup>12</sup> and has been reported for the hydrolysis of some of the corresponding aliphatic compounds, e.g. the *N*-alkyldimethylmaleamic acids.<sup>6</sup> Bender has obtained indirect evidence from tracer experiments using [*carbamoyl*-<sup>13</sup>C]phthalamic acid in H<sub>2</sub><sup>18</sup>O for the intermediate formation of phthalic anhydride during the hydrolysis of phthalamic acid.<sup>2</sup>

Further support for this reaction scheme and evidence that the breakdown of the tetrahedral intermediate to form the anhydride is the rate-determining step in the hydrolysis of phthalanilic acid is provided by generating the tetrahedral intermediate (A) independently from *N*-phenylisophthalimide (Scheme 2). A similar technique has been used by Cunningham and Schmir<sup>21</sup> and

by Kirby and Lancaster.<sup>6</sup> In 0.1M-hydrochloric acid at 24.6° *N*-phenylisophthalimide is hydrolysed to form phthalanilic acid >500 times faster than the hydrolysis of phthalanilic acid itself and 12–13 times faster than phthalic anhydride<sup>20</sup> (Table 2). The u.v. spectrum of

TABLE 2

Experimental first-order rate constants in 0.1M-hydrochloric acid at 24.6°

Compound	$k_{\text{obs}}/\text{s}^{-1}$
<i>N</i> -Phenylisophthalimide	$1.0 (\pm 0.1) \times 10^{-1}$
Phthalic anhydride <sup>20</sup>	$7.8 \times 10^{-3}$
Phthalanilic acid †	$1.88 \times 10^{-4}$

† Calculated from results at 39.5 and 65.8°.

the products of the isoimide after seven half-times at pH 1 is identical to that of phthalanilic acid. At 65.8° this initial reaction is too fast to be detected and the observed rate constant for the hydrolysis of *N*-phenylisophthalimide in 0.1M-hydrochloric acid is the same as that for phthalanilic acid.

This indicates that the rate-determining step must occur at some point in the reaction chain *after* the formation of the tetrahedral intermediate but before the hydrolysis of the anhydride. Bender<sup>2</sup> has suggested two mechanisms for carboxy-group participation in the hydrolysis of compounds of this type. Cyclisation after a pre-equilibrium involving transfer of the carboxy-proton to the carbamoyl group is the simpler mechanism and is preferred to the alternative concerted electrophilic-nucleophilic catalysis scheme in which the *o*-carboxy-group acts as a bifunctional catalyst.

Increasing hydrogen ion concentration increases the reaction rate by increasing the proportion of the unionised substrate (Scheme 1). This accounts for the characteristic sigmoid shape of the rate profiles (Figure 2) and for the dependance on the acid dissociation constant of the substrate.

Kirby<sup>6</sup> has shown that the rate-determining step in the hydrolysis of the maleamic acids is the cleavage of the carbon-nitrogen bond in the tetrahedral intermediate. He also demonstrated a change in mechanism in the case of di-isopropylmaleamic acid where a particular proton shift in a series of transfer intermediates becomes rate controlling at high buffer concentrations.<sup>8,9</sup> His mechanism implicates the *O*-protonated amide as the reactive species in dilute acid.<sup>9</sup>

In aqueous hydrochloric acid solutions of progressively higher concentration the rate constant for the hydrolysis of phthalanilic acid increases to a maximum at ca. 6M-HCl ( $H_0$  -2.12<sup>22</sup>) and then slowly decreases. Although in the case of the 2'-chloro- and 2'-methyl-phthalanilic acids, for example, the relative acid concentrations for maximum rate were in the order predicted from the expected basicities, it was not possible to determine the position of this rate maximum with any precision for the

<sup>20</sup> M. D. Hawkins, *J.C.S. Perkin II*, 1975, 282.

<sup>21</sup> B. A. Cunningham and G. A. Schmir, *J. Amer. Chem. Soc.*, 1966, **88**, 555.

<sup>22</sup> M. A. Paul and F. A. Long, *Chem. Rev.*, 1957, **57**, 1.

substituted phthalanilic acids owing to the small difference in the u.v. spectra of the strongly protonated reactants and the hydrolysis products in concentrated acid solution. Such maxima in the acid hydrolysis of other carboxylic acid derivatives have been attributed to hydrogen ion catalysis with increasing acid concentration up to the maximum. The decrease in rate is then ascribed to the reduction in water activity with increasing acid concentration making the second step, the attack of water on the protonated intermediate, rate determining.<sup>23</sup>

A similar explanation will account for the behaviour of phthalanilic acid. The  $pK$  value of the protonated substrate ( $-2.7$ ) calculated from the position of the rate maximum is of a similar order of magnitude to that published recently for hydrolysis in sulphuric acid.<sup>11</sup> It is also consistent with the value calculated from the position of the rate maximum for phthalamic acid ( $-2.5$ ),<sup>2</sup> as phenyl substitution of the  $NH_2$  group would be expected to decrease the basicity of the substrate.

The effect of dioxan on the hydrolysis of phthalanilic acid is interesting in that the rate decreases with the addition of the non-aqueous solvent up to ca. 80% v/v dioxan ( $x_{H_2O}$  0.543), after which it begins to increase again. Such minima have been observed in the hydrolysis of a number of carboxylic acid derivatives in solutions containing non-aqueous solvents and have been attributed to a variety of factors, such as the change in the dielectric constant of the reaction medium,<sup>24</sup> the change-over from an ionic to a polar activated state,<sup>25</sup> or the replacement of the water molecules solvating the reactants and activated complex by molecules of the non-aqueous solvent.<sup>26</sup> These different solvent effects have been extensively reviewed recently.<sup>27</sup>

The acidity function of hydrochloric acid itself in dioxan, acetone, or ethanol is known to show a minimum, owing first to the decrease in the stability of the hydroxonium ion as intermolecular hydrogen bonding with the surrounding solvent is reduced by the progressive replacement of the water molecules in the tetrahedral lattice by molecules of the organic solvent.<sup>28</sup> This is then followed by a rapid increase in acidity with decreasing water content once the proportion of the non-aqueous solvent is sufficiently large to replace the hydroxonium ions with organic oxonium ions, such as  $EtOH_2^+$  and  $Me_2COH^+$ . If however allowance is made for this variation in the acidity of 0.1M-hydrochloric acid in dioxan by checking the constancy of  $(\log k_{obs} + H_0)$  (Figure 3a) or, alternatively, by plotting  $\log k_{obs}$  against the acidity function of the solution (Figure 3b) the curves obtained indicate

that the effect is more complex in the case of phthalanilic acid.

Comparison of the u.v. spectra of the reaction products with spectra of synthetic mixtures of aniline and phthalic acid in aqueous hydrochloric acid containing varying amounts of dioxan indicates that the addition of non-aqueous solvent results in a change in the reaction mechanism. The phthalanilic acids are known to undergo dehydration on heating in the presence of alcohol to form the corresponding *N*-phenylphthalimide.<sup>17</sup> But, although the 3,6-dimethylphthalanilic acids react extremely quickly and dehydration to form the imide is complete in  $<30$  s at room temperature,<sup>12</sup> this reaction is slow in the case of the phthalanilic acids, where heating for 35 min at 65° in 95% alcohol results in only 9% conversion to the imide.<sup>17</sup> The alternative reaction, involving elimination of water from the tetrahedral

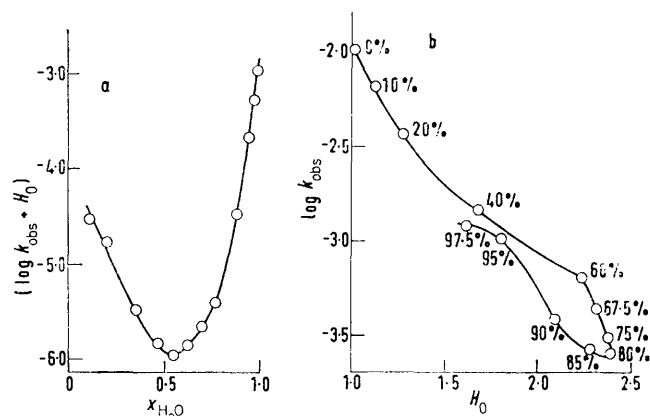


FIGURE 3 Effect of added dioxan on hydrolysis of phthalanilic acid in 0.1M-hydrochloric acid at 65.8°: a,  $(\log k_{obs} + H_0)$  versus  $x_{H_2O}$ ; b,  $\log k_{obs}$  versus  $H_0$

intermediate to form the *N*-phenylisoimide, can be discounted owing to the high reactivity of this compound (see Scheme 2) and to spectroscopic evidence (*cf.* *N*-phenylphthalimide,  $\lambda_{max}$  ca. 290 nm; *N*-phenylisophthalimide,  $\lambda_{max}$  ca. 330 nm). Comparison of the spectrum of the reaction products from phthalanilic acid in 0.1M-hydrochloric acid containing 80% v/v of 1,4-dioxan after 7 half-lives at 65.8° with the spectra of phthalic acid and *N*-phenylphthalimide indicates the presence of up to 20% imide. Shafer has reported the formation of similar amounts of *N*-methylphthalimide as a by-product in the hydrolysis of *N*-methylphthalamic acid in aqueous solution, but the almost identical rate constants for the hydrolysis of *N*-methyl- and *NN*-dimethyl-maleamic acid<sup>6</sup> (or of the corresponding *N*-ethyl and *NN*-diethyl derivatives<sup>5</sup>) indicate that this reaction is not significant in the hydrolysis of *N*-alkylmaleamic acids. Similarly an almost negligible amount of imide ( $<0.2\%$ ) is formed

<sup>23</sup> J. T. Edward and S. C. R. Meacock, *J. Chem. Soc.*, 1957, 2600.

<sup>24</sup> K. J. Laidler and C. A. Landskroener, *Trans. Faraday Soc.*, 1956, 52, 200.

<sup>25</sup> J. B. Hynes, *J. Amer. Chem. Soc.*, 1960, 82, 5129.

<sup>26</sup> E. Tommila, A. Koivisto, J. P. Lyyra, K. Antell, and S. Heimo, *Ann. Acad. Sci. Fennicae*, 1952, AII No. 47, 3; E. Tommila, *Suomen Kem.*, 1964, 37B, 117; E. Tommila and A. Hella, *Ann. Acad. Sci. Fennicae*, 1954, AII No. 53, 3; H. Sadek, M. S. Abu Elamayem, and M. Abu Elgehit, *Suomen Kem.*, 1964, B37, 33.

<sup>27</sup> R. F. Hudson, *J. Chem. Soc. (B)*, 1966, 761; E. S. Amis, 'Solvent Effects on Reaction Rates and Mechanisms,' Academic Press, New York and London, 1966, chs. 2 and 3; J. Leffler and E. Grunwald, 'Rates and Equilibria of Organic Reactions,' Wiley, New York, 1963, pp. 389 *et seq.*; F. Franks, 'Physicochemical Processes in Mixed Aqueous Solvents,' Heinemann, London, 1967.

<sup>28</sup> E. A. Braude and E. S. Stern, *J. Chem. Soc.*, 1948, 1976.

during the decomposition of phthalamic acid in aqueous solution.<sup>3</sup> The u.v. spectrum of the hydrolysis products of phthalanilic acid in aqueous 0.1M-hydrochloric acid is identical to that of a synthetic mixture of phthalic acid and aniline. There was no evidence for imide formation as a by-product in the hydrolysis of phthalanilic acid in aqueous solution, but the increasing contribution of this elimination reaction, in which the carbamoyl group acts as a nucleophile to displace water or a hydroxy-group from the molecule, would account for the complexity of the effect of added dioxan on the observed first-order rate constant. This reaction becomes increasingly important

at higher pH values where the concentration of the substrate anion is high and, as 3'- and 4'-nitrophthalanilic acids, which are the most highly ionised of the substituted phthalanilic acids, yield appreciable amounts of the corresponding *N*-phenylphthalimide even in aqueous solution, it also accounts for the curved Hammett equation plots obtained for the hydrolysis of 3'- and 4'-substituted phthalanilic acids (Figure 1). The effect of substrate structure, pH, and of added non-aqueous solvent on the contribution of this side-reaction is being examined.

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