Kinetics and Mechanism of Formation and Hydrolysis of 3-Iminoisoindolin-1-one and Related Studies

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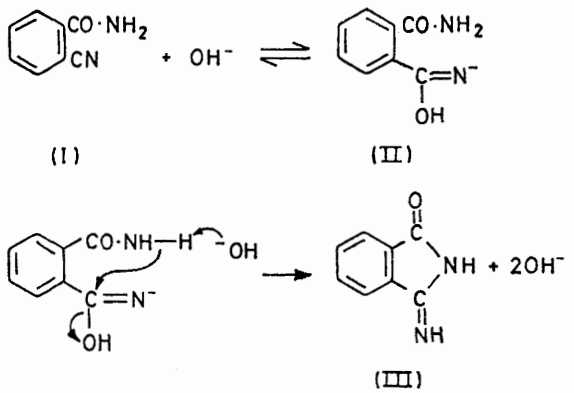
The kinetics of the cyclisation of *o*-cyanobenzamide to give 3-iminoisoindolin-1-one in aqueous solution have been studied, and the mechanism of alkaline hydrolysis of this compound has been compared with that of phthalimide and *N*-methylphthalimide.

BOTH heat [1] and alkali [2] will effect the cyclisation of *o*-cyanobenzamide (I) to 3-iminoisoindolin-1-one (III). The occurrence of the former reaction has now been confirmed by thermogravimetric analysis. In a previous study [3] of the latter reaction, it was proposed that reaction in aqueous ethanol proceeds by attack of hydroxide ion on an intermediate (II) formed by addition of hydroxide ion to the cyano-group (Scheme 1). This is a surprising mechanism as it involves attack by an incipient anion on a group which is already negatively charged. The work reported here shows that this is not the mechanism for the reaction in water and that, after cyclisation, further hydrolytic reactions ensue.



SCHEME 1

RESULTS AND DISCUSSION

The dependence of the rate of cyclisation on the hydroxide ion concentration at 10° (Table 1) demonstrates that the reaction is first-order in hydroxide ion in this solvent, and not second-order as found by

[1] T. Posner, *Ber.*, 1897, **30**, 1693.
[2] A. Braun and J. Tcherniac, *Ber.*, 1907, **40**, 2709.
[3] J. Zabicky, *Chem. and Ind.*, 1964, 236.

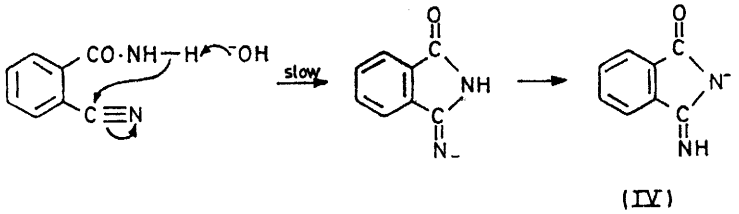
Zabicky.[3] The same dependence, over a more limited concentration range, applies at 25°. From an Arrhenius plot of the data in Table 1 the values of $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ were calculated to be 13·7 kcal mol^{-1} and −18·7 cal deg^{-1} mol^{-1} at 25°. The observed rate constant for reaction in

TABLE 1

Observed first-order rate constants for the cyclisation of *o*-cyanobenzamide

Temp. (°C)	[KOH]/M	10^2k_{obs}/s^{-1}
10	0·002	0·67
10	0·004	1·41
10	0·006	2·62
10	0·008	3·64
10	0·010	4·12
25	0·002	2·45
25	0·004	4·48
25	0·006	7·60
35	0·004	10·80

0·005M-KOD in D_2O at 25° is 10·1 × 10^{-2} s^{-1}, and this gives a $k(H_2O)/k(D_2O)$ value of 0·60. All these results are consistent with the mechanism shown in Scheme 2.



SCHEME 2

The anion OD$^-$ in D_2O is known to be a stronger nucleophile than OH$^-$ in H_2O [4] and, as the reaction depends upon removal of a proton from the amide group, the reaction should be faster in D_2O than H_2O. The observed change is in agreement with this. Amides are very weak acids (the pK_a value of benzamide [5] is greater than 19) and it is surprising, therefore, that a reaction depending upon the acidity of the amide group should occur as readily as this cyclisation. It indicates that the amide and the cyano-group must be in a particularly favourable position for intramolecular nucleophilic attack to occur. Such cyclisations are common with *ortho*-substituted nitro-compounds [6] but fewer examples involving the cyano-group have been reported. However, from this study it is clear that cyclisation involving the cyano-group occurs readily. In Scheme 2 the final step is a prototropic shift to give the anion (IV) for, although the exocyclic imino-group is known to undergo reactions,[7] resonance considerations indicate that (IV) would be the more stable anion.

Spectral studies show that 3-iminoisoindolin-1-one undergoes slow ring opening in alkaline solution; the absorption peak at 300 nm, which appears during cyclisation, slowly disappears. The second reaction is *ca.* 100 times slower than the first and, therefore, does not interfere with the kinetics of cyclisation. The products of ring opening were difficult to identify. Ficken and Linstead [8] report that the imidine (V) of tetrahydrophthalic acid reacts with hot water to give, first the imino-imide, and finally tetrahydrophthalimide (VI). This cannot be the course of the present reaction, as ring opening should then occur at the same rate as that of phthalimide, which is not the case (see later). The slow step cannot be conversion of the exocyclic imino-group into a carbonyl group as this would not be accompanied by the observed spectral change. Therefore, the most probable course of ring opening is attack of OH$^-$ on the C=NH and C=O groups to give a mixture of phthalamide (VII) and phthalamic acid (VIII). In the latter reaction the first product would be an amidine, but these compounds undergo ready hydrolysis to amides. Acidification of the reaction mixture gave crystals, analysis of which gave results consistent with the presence of the above mixture (the two products have essentially identical carbon and hydrogen contents and the figure for nitrogen was intermediate between those for phthalamide and phthalamic acid).

The rate of ring opening was examined as a function of hydroxide ion concentration, and, as the figures in

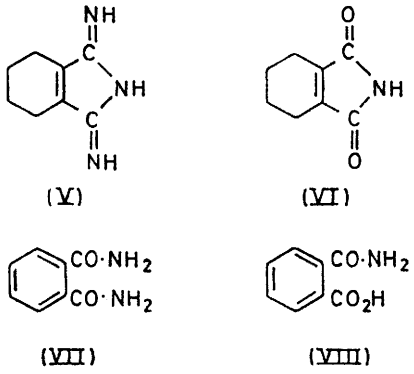


Table 2 indicate, shown to be independent of pH. This may be understood if we consider that, by analogy

TABLE 2

Observed first-order rate constants for the hydrolysis of 3-imino-1-oxo*iso*indoline at 25°

[KOH]/M	0·02	0·10	0·40	0·60	0·80	1·00
10^4k_{obs}/s^{-1}	2·41	2·56	2·36	2·62	2·76	2·56

with phthalimide, compound (III) is a weak acid. If reaction occurs between the un-ionised form of (III)

[4] W. F. K. Wynne-Jones, *Trans. Faraday Soc.*, 1936, **32**, 1392; J. G. Pritchard and F. A. Long, *J. Amer. Chem. Soc.*, 1956, **78**, 6008.
[5] J. Hine and M. Hine, *J. Amer. Chem. Soc.*, 1952, **74**, 5266.
[6] P. N. Preston and G. Tennant, *Chem. Rev.*, 1972, **72**, 627.
[7] R. P. Linstead and G. A. Rowe, *J. Chem. Soc.*, 1940, 1070; J. A. Elvidge and R. P. Linstead, *ibid.*, 1952, 5000.
[8] G. E. Ficken and R. P. Linstead, *J. Chem. Soc.*, 1955, 3525.

and hydroxide ion then, as the hydroxide ion concentration is increased, the anticipated increase in k_{obs} will be balanced by a decrease in the concentration of the reactive form of (III) owing to increased ionisation. Therefore, k_{obs} is independent of pH. The pK_a value of phthalimide is 8·3. Half neutralisation of (III) indicates a pK_a value of *ca.* 10·5, and it is not surprising that (III) is a weaker acid than phthalimide as the negative charge will be less readily delocalised over the C=NH group. If the proposed mechanism is correct then succinimide and phthalimide should show the same behaviour. This is known to be the case for the former [9] but, although the hydrolysis of phthalimide has been examined by a number of workers,[10] none has used the exact conditions of this study. We have therefore measured the rate of alkaline hydrolysis (Figure 1). At low pH values the rate, as with (III), is pH-independent, but at higher pH values there is an increase in rate, possibly due to attack of hydroxide on the phthalimide anion. This is not

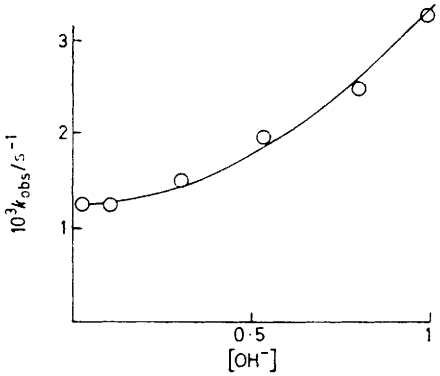
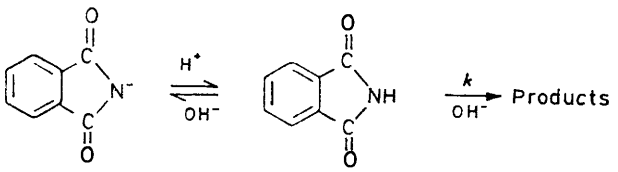


FIGURE 1 Effect of [OH⁻] on the hydrolysis of phthalimide

observed with (III) as it is a much weaker acid. The mechanism of alkaline hydrolysis of phthalimide at low pH is, therefore, that shown in Scheme 3.



SCHEME 3

The correctness of this mechanism is confirmed by the fact that the rate of hydrolysis of *N*-methylphthalimide, which is not capable of ionisation, to give *N*-methylphthalamic acid [11] is directly proportional to the hydroxide ion concentration (Figure 2). A similar result has been reported for the hydrolysis of *N*-methylsuccinimide.[12]

From these results the effect of *N*-substitution on the rate of reaction may be determined. From the pK_a value it is possible to calculate the fraction of the phthalimide present in the un-ionised form and, taking

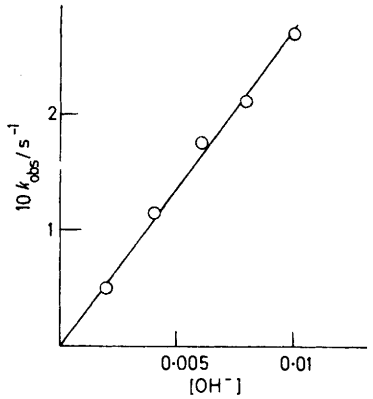


FIGURE 2 Effect of [OH⁻] on the hydrolysis of *N*-methylphthalimide

k_{obs} as $1{\cdot}22 \times 10^{-3}$ s^{-1}, this gives k as $6{\cdot}1 \times 10^2$ l mol^{-1} s^{-1}. The corresponding value for *N*-methylphthalimide is $0{\cdot}27 \times 10^2$ l mol^{-1} s^{-1}, in good agreement with that previously reported.[13] Thus *N*-methylation reduces the rate by a factor 23 but *N*-methylation of benzamide [14] reduces the rate of hydrolysis by a factor of only 2 and it seems probable that, in the cyclic system, the methyl group exerts a greater steric effect.

EXPERIMENTAL

Materials.—*o*-Cyanobenzamide was recrystallised from water [m.p. 171° (lit.,[2] 172°)] and phthalimide from ethanol [m.p. 232° (lit.,[15] 235°)]. 3-Iminoisoindolin-1-one was prepared by heating *o*-cyanobenzamide at 200° for 10 min and was crystallised from acetic acid [m.p. 199° (lit.,[2] 203°)]. *N*-Methylphthalimide was prepared by the method of Graebe and Pictet [16] and recrystallised from aqueous ethanol [m.p. 129° (lit.,[16] 132°)].

Kinetic Method.—All reactions were followed spectrophotometrically by use of a Unicam SP 500 spectrophotometer. One drop of a solution of the substrate in dioxan was added to the potassium hydroxide solution contained in a cell in the thermostatted cell holder of the spectrophotometer. The variation of optical density with time was then measured. Cyclisation is accompanied by the appearance of an absorption peak at 300 nm; all the other reactions are associated with the disappearance of absorption at this wavelength. All reactions were first-order over three half lives. The ionic strength was not kept constant.

Thermogravimetric Analysis.—This was carried out on a Stanton Thermobalance (model TR1). No significant weight loss was indicated but the temperature trace gave evidence of an exothermic transition at 170°.

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[16] C. Graebe and A. Pictet, *Ber.*, 1884, **17**, 1174.