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# STUDIES IN HETEROCYCLIC CHEMISTRY—III*

## THE MECHANISM OF FORMATION OF BENZIMIDAZOLES FROM *o*-AMINO ANILIDES

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**Abstract**—The cyclization of *o*-aminoacetanilide provides a route to 2-methylbenzimidazole under a wide range of conditions. The kinetics of the reaction have been studied over the pH range −2·12·5: for comparison purposes the cyclizations of the two isomeric N-Me derivatives, *o*-aminobenzanilide, and *o*-aminotrifluoroacetanilide have been examined. The experimentally determined *pseudo* first-order rate constants show the influence of catalysis by acids and bases according to the expression:

$$k = k_0 + k_{H^+}[H^+]/(1 + k_C[H^+]) + k_{OH^-}[OH^-] + k_{HA}[HA] + k_A[HA] + k_{A^-}[A^-]$$

The results indicate that under both acidic and basic conditions the slow step in the cyclization reaction is formation of hydroxybenzimidazoline. Base catalysis is ascribed to proton abstraction from the amino group being concerted with the nucleophilic attack. The greater efficiency of acid catalysis ($k_{H^+}/k_{OH^-} = 5000$) is attributed to the ability of the amino group to act both as a proton trap and subsequently as an intramolecular general acid. Under strongly acidic conditions when both the amino and amido groups are protonated hydrolysis to *o*-phenylenediamine becomes important.

A GENERAL method of synthesis of the benzimidazole ring system lies through treatment of an *o*-phenylenediamine with an acylating agent.[1–3] Frequently the benzimidazole can be isolated directly from the reaction mixture; alternatively the N-acyl derivatives may be obtained and readily converted to the benzimiazole.[3–5] The most commonly employed synthesis of this type is that introduced by Phillips[6] in which the *o*-phenylenediamine is treated with a carboxylic acid in the presence of hot dilute hydrochloric acid.

A number of mechanisms has been considered for this reaction[1–7] (Chart 1). Addition of amine to the carboxylic acid gives an adduct (**1**) which can eliminate water in the usual way leaving the monoacyl derivative (**2**). Subsequent intramolecular nucleophilic attack by the second amino group can then lead to the cyclic carbinolamine (**3**) which, by elimination of water, gives benzimidazole (**4**). It is also possible that the initial adduct could cyclize directly to the carbinolamine. Alternatively, further acylation of the monoacyl compound (**2**) leads to the diacyl compound (**5**) which might, by cyclization and a facile hydrolysis give the benzimidazole.

Of these routes the third can be immediately discounted. Under the reaction conditions, diacyl derivatives of *o*-phenylenediamine (**5**) decompose too slowly to provide significant quantities of benzimidazole and studies of their decomposition have shown[8] that they hydrolyse initially to the monoacyl compounds.

* Part II, K. J. Morgan and A. M. Turner, *Tetrahedron*, **22**, 1175 (1966).

CHART 1

CHART 2

Since the collapse of adducts such as **1** to amides is known to be a relatively fast reaction,[9] the more probable of the remaining two routes is that leading to the formation and decomposition of the monoacyl compound. Direct evidence for the formation of *o*-aminoacetanilide during the course of the reaction of *o*-phenylenediamine with acetic acid is provided by TLC; by working on a larger scale it was possible to isolate the monoamide from the reaction mixture. It may be noted that 2-methylbenzimidazole is entirely stable under the conditions of this reaction and consequently there is no possibility of the monoamide being formed by a ring cleavage reaction.

Cyclization under acidic conditions of monoacyl derivatives of *o*-phenylenediamines has frequently[1–4] been suggested as a route to benzimidazoles and a related reaction has been reported[8] for alkaline conditions. These processes are at least formally analogous to those encountered in many cases for the biosynthesis of naturally occurring compounds containing imidazole rings.[10] To examine this cyclization in more detail a study has been made of the reaction with *o*-aminoacetanilide and some related compounds.

## RESULTS

The decomposition of *o*-aminoacetanilide was studied under *pseudo*-first order conditions for aqueous solutions at 50°. For solutions of pH in the range 2–12·25 the only detectable product was 2-methylbenzimidazole; for strongly alkaline solutions, pH > 12·25, a small amount of *o*-phenylenediamine is formed; and with highly acidic solutions formation of *o*-phenylenediamine becomes increasingly important (Table 1). The rate of formation of 2-methylbenzimidazole was followed kinetically using UV spectroscopy.

TABLE 1. RATE CONSTANTS FOR REACTION OF *o*-AMINOACETANILIDE UNDER AQUEOUS ACIDIC CONDITIONS AT 50°

| Medium | pH | $10^6 K_B$[a] ($sec^{-1}$) | $10^6 K_D$[b] ($sec^{-1}$) |
|---|---|---|---|
| $CH_2ClCO_2H/CH_2ClCO_2^-$[c] | 3·3 | 21 | — |
| $CCl_3CO_2H/CCl_3CO_2^-$[c] | 2·5 | 38 | — |
| $CCl_3CO_2H/CCl_3CO_2^-$[c] | 2·0 | 41 | — |
| $CCl_3CO_2H/CCl_3CO_2^-$[c] | 1·2 | 42 | — |
| $H_2SO_4$[d] | −0·07[e] | 29 | 35 |
| $H_2SO_4$[f] | −2·05[e] | 30 | 240 |

[a] *Pseudo*-first order rate constant for formation of 2-methylbenzimazole
[b] *Pseudo*-first order rate constant for formation of *o*-phenylenediamine
[c] Total ionic strength 0·5 molar.
[d] 1·89 Molar.
[e] $H_0$ value.
[f] 9·45 Molar.

For solutions of constant ionic strength the reaction showed good *pseudo*-first order kinetics according to the expression

$$\text{rate} = k\,(\text{Aminoacetanilide})$$

where $k$, the experimentally determined first order rate constant, is dependent on

both pH and buffer concentration. The variation of $k$ within the pH range 3·5–12·5 conforms to the simple expression

$$k = k_0 + k_{H+}(H^+) + k_{OH^-}(OH^-) + k_{HA}(HA) + k_B(B)$$

where $k_0$ refers to the solvent catalysed reaction, $k_{H+}$ and $k_{OH-}$ to specific hydroxonium and hydroxyl ion catalysis, and $k_{HA}$ and $k_B$ to catalysis by general acids and general bases. By determining the rates of reaction at constant pH for varying concentrations of buffer and extrapolation to zero buffer concentration the specific rates, $k_{H+}$ and $k_{OH-}$, were established (Table 2). They define a classical plot for log $k$ against pH (Fig. 1) which allows[11] the evaluation of $k_0$ and adequately accounts for the experimental results over the range pH 3·5–12·5 (Fig. 1). For more acidic solutions the dependence of $k$ on acidity requires a more complex expression:

$$k = k_{H+}(H^+)/[1 + k_C(H^+)]$$

where $k_C$ = 1,900 l.mole$^{-1}$ sec$^{-1}$.

TABLE 2. SECOND-ORDER RATE CONSTANTS (l.mole$^{-1}$sec$^{-1}$) FOR THE FORMATION OF 2-METHYLBENZIMIDAZOLE FROM *o*-AMINOACTANILIDE

| | |
|---|---|
| $k_{H_3O^+}$ | $8{\cdot}12 \times 10^{-2}$ |
| $k_{OH^-}$ | $1{\cdot}6 \times 10^{-5}$ |
| $k_{HPO_4^{2-}}$ | $3{\cdot}7 \times 10^{-6}$ |
| $k_{H_2PO_4^-}$ | $2{\cdot}0 \times 10^{-5}$ |
| $k_{CH_3COH_2H}$ | $2{\cdot}2 \times 10^{-5}$ |
| ($k_0$ | $9 \times 10^{-9}$ sec$^{-1}$) |

The observation that at constant pH and constant total ionic strength the value of $k$ shows significant variation with changes in the concentration of buffer solutions is characteristic of reactions showing general acid/base catalysis: the greater slope of plots of log $k$ against buffer molarity at lower pH suggests that the catalysis is predominantly general acid in character. For phosphate buffer, used in the pH range 5·6–11·0 the value of $k$ at constant pH is given by

$$k = \text{constant} + (HPO_4^{2-})\{k_{HPO_4^{2-}} + k_{HPO_4^-}\ (H_2PO_4^-)/(HPO_4^{2-})\}$$

Plots of $k$ against $(HPO_4^{2-})$ are sensibly linear and from the gradients of these plots $k_{HPO_4^{2-}}$ and $k_{H_2PO_4^-}$ were obtained (Table 2). In acetate buffer solutions (pH 3–5) similar plots show that the catalytic activity is largely due to acetic acid molecules.

For comparison purposes the rates of reaction of *o*-aminoacetanilide, its two N-Me derivatives (**6**, **7**), and *o*-aminobenzanilide were observed under similar conditions. Under these conditions the sole aromatic products were the appropriate benzimidazoles. Formation of 2-phenylbenzimidazole is slower than formation of 2-methylbenzimidazole under both acidic and basic conditions; formation of 1,2-dimethylbenzimidazole (**9**) is notably the faster from *o*-acetamido-N-methylaniline (**7**) but both N-Me derivatives appear to be more reactive than the parent compound (Table 3).

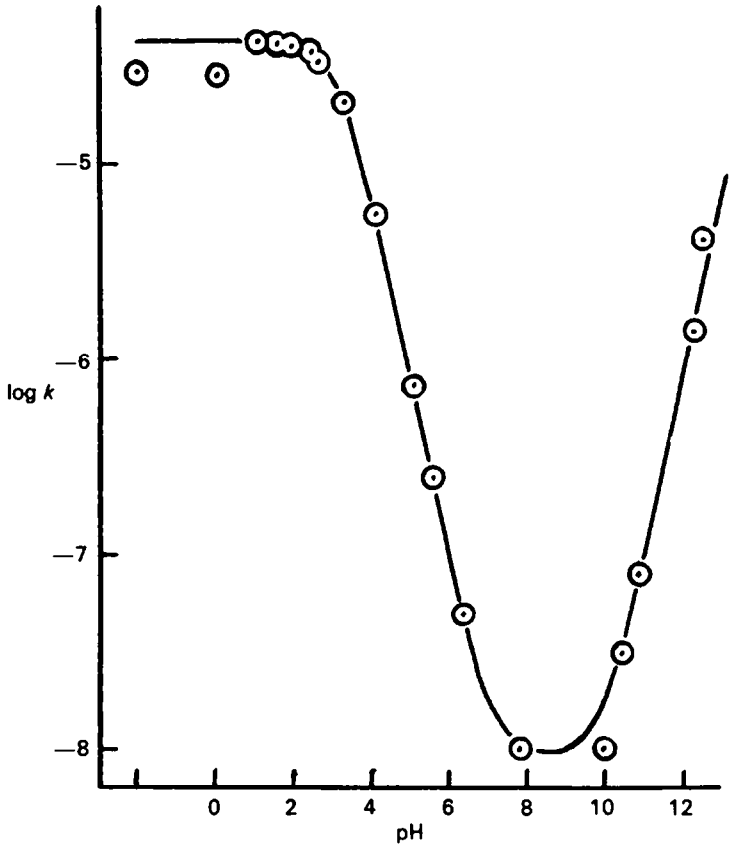



FIG. 1 Effect of pH on *pseudo*-first order rate constant for the formation of 2-methylbenzimidazole from *o*-aminoacetanilide. Experimental values are marked as points; the solid line is the curve calculated from the second order rate constants.

TABLE 3. RATE CONSTANTS FOR CYCLIZATION OF SOME *o*-AMINO ANILIDES AT 50°

| Anilide | *pseudo*-First-order rate constants ($sec^{-1}$) | |
|---|---|---|
| | 0·1N KOH pH 12·25 | $CH_3CO_2H/CH_3CO_2^-$ pH 4·7 |
| *o*-Aminoacetanilide | $1·5 \times 10^{-6}$ | $2·1 \times 10^{-6}$ |
| *o*-Aminobenzanilide | $6·2 \times 10^{-7}$ | $5·5 \times 10^{-7}$ |
| *o*-Amino-N-methylacetanilide | $2·8 \times 10^{-5}$ | $7·7 \times 10^{-6}$ |
| *o*-Acetamido-N-methylaniline | $1·65 \times 10^{-4}$ | $3·4 \times 10^{-4}$ |

## DISCUSSION

Condensations of amino and carbonyl groups have been widely investigated, notably by Jencks *et al.*,[12] and the general pattern of the reaction has been clearly defined. The initial adduct is a carbinolamine which subsequently loses water giving

the product:

$$RNH_2 + \rangle C{=}O \underset{k_2}{\overset{k_1}{\rightleftharpoons}} RNH{-}\underset{|}{\overset{|}{C}}{-}OH \xrightarrow{k_3} R{-}N{=}C\langle .$$

If the stationary state approximation can be applied, the kinetic expression corresponding to this sequence of reactions has the form:

$$k = k_1/(1 + k_2/k_3)$$

where $k$ is the experimentally observable rate constant. In the extreme case where $k_2 \ll k_3$, $k$ can be put equal to $k_1$ and the addition reaction forms a true rate determining step. Conversely when $k_2 \gg k_3$, $k$ is given by $(k_1/k_2)k_3$ and the sequence of reactions corresponds to a pre-equilibrium between addends and adduct followed by a rate determining elimination reaction.

For the formation of oximes, Schiff's bases, and semicarbazones from ketones and aldehydes both extreme forms of the kinetic expression are encountered.[12] For these reactions plots of the logarithm of the experimental rate constants against pH have a characteristic bell-shape. On the alkaline side of the maximum in these curves the elimination step forms a rate determining stage; on the acidic side acid catalysed elimination is facile and the addition step is the slower reaction.

A similar sequence of steps and a similar kinetic expression is encountered with nucleophilic reactions at a carbonyl group incorporated in a carboxyl system:

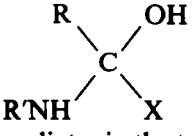
$$RCOX + Y^- \underset{k_2}{\overset{k_1}{\rightleftharpoons}} R{-}\underset{\displaystyle X}{\overset{\displaystyle O^-}{\overset{|}{C}}}{-}Y \xrightarrow{k_3} RCOY + X$$

$$k = k_1/(1 + k_2/k_3)$$

The simplified, extreme forms of the kinetic expression are rarely encountered with carboxylic compounds, the specific rates of decomposition of the tetrahedral adduct being of similar magnitude.[13,14] Thus the experimentally determined rate constant is dependent on $k_2/k_3$ although its magnitude is largely determined by $k_1$. This contrast to the behaviour observed for ketonic compounds is to be expected by virtue of the delocalization energy of the carboxyl system which gives rise both to its lower susceptibility to nucleophilic attack and to the greater driving force of the elimination reaction. In consequence, although carboxyl systems are subject to extensive acid/base catalysis, in most cases no fundamental change in mechanism is observed over a wide range of conditions. A typical plot against pH of the logarithm of the experimentally determined *pseudo*-first-order rate constant for a carboxyl reaction shows a minimum near neutrality; the operation of catalysis by hydroxonium and hydroxyl ions is indicated by linear gradients of $-1$ and $+1$ for this rate profile under acidic and alkaline conditions respectively.

The characteristics of the reaction leading to the formation of 2-methylbenzimidazole from *o*-aminoacetanilide appear to be closely similar to those of nucleophilic attack on simple carboxylic amides. The rate profile (Fig. 1) has a form similar to

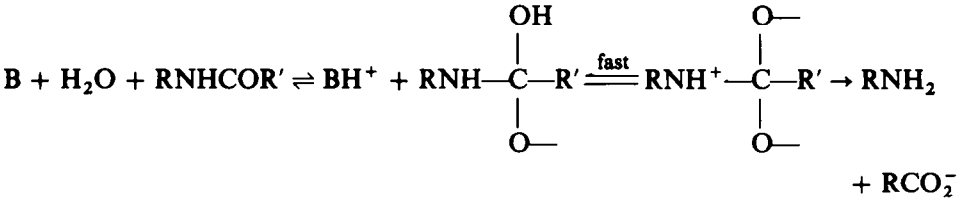
that for amide hydrolysis and gives no indication of any discontinuity corresponding to a change in rate determining step. Indeed the substantial delocalization energy of the benzimidazole ring[15] system suggests that elimination of water from the carbinolamine intermediate should not be a slow reaction. However, it is of interest that different behaviour has been reported[16] for the alkaline hydrolysis of acetanilide where a value of 9 has been found for the ratio $k_2/k_3$. It has further been suggested[13] that reactions involving attack by nitrogen nucleophilies on carboxyl systems may be characterized by a pre-equilibrium ($k_2 \gg k_3$). Particularly relevant in this respect are the reactions of imidate esters (**10**) with amines[17] which proceed through carbinolamine intermediates (**11**) to products (**12**) which are structurally analogous to the intermediate **3** and product **4** of the ring closure reaction. The rate profile for aminolysis of imidates is bell-shaped, having the addition reaction as rate determining step under alkaline conditions ($k_2 \ll k_3$) and elimination as a slow step under acidic conditions ($k_3 \ll k_2$). Similarly, intramolecular attack by the imidazole ring of phenyl γ-(4-imidazolyl)-butyrate giving the lactam (**13**) is marked[18] by a pre-equilibrium stage followed by a slow elimination reaction ($k_3 \ll k_2$).

Although the reaction intermediates formed in amide hydrolysis and in the cyclization reaction can be represented generally as  there is an inverse relation between the decomposition of the intermediates in the two reactions to products and starting materials. Thus regeneration of starting material in amide hydrolysis involves loss of OH; in the cyclization reaction a similar step yields product. Consequently the structural features leading to a ratio $k_2/k_3 \simeq 9$ for acetanilide hydrolysis should tend to produce an inverse ratio, $k_2/k_3 \simeq 0{\cdot}1$ for the cyclization reaction. Moreover it is to be expected that base catalysed addition of imidazole to esters and acid catalysed addition of amines to imidates should be faster than attack by a weakly nucleophilic amine on an amide; and that elimination to a lactam or amidine should be slower than elimination to a benzimidazole. Nevertheless it seemed desirable to examine further the possibility that elimination might become a rate determining step in the formation of benzimidazoles. To this end the rates of cyclization of *o*-aminobenzanilide and *o*-aminotrifluoroacetanilide were studied. Mesomeric stabilisation of the ground state renders benzoyl derivatives less susceptible to nucleophilic attack than acetyl compounds and the kinetic dominance of the addition step is generally reflected in slower rates of reaction for benzoyl compounds. By contrast, were elimination to be the rate determining step in the formation of benzimidazoles the greater delocalization energy of 2-phenylbenzimidazole should tend to make its rate of formation greater than that of 2-methylbenzimidazole. Comparison of the *pseudo*-first-order rate constants (Table 3) shows that 2-methylbenzimidazole is formed the faster by factors of 2·5 for alkaline conditions and 4 for acidic conditions.

For trifluoroacetyl compounds the rate of nucleophilic attack is normally increased by the polar properties of the fluoroalkyl group while elimination from the carbinolamine adduct should be similarly retarded. The rate of formation of 2-trifluoromethylbenzimidazole from *o*-aminotrifluoroacetanilide is faster at pH 7 by a factor of ca. $10^5$ than formation of 2-methylbenzimidazole from the acetyl derivative.

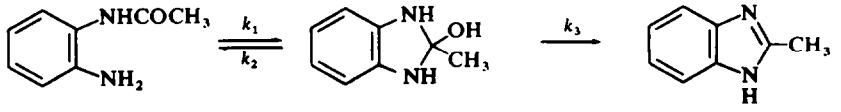
More direct evidence for the relative slowness of the addition reaction is provided by the properties of the isomeric N-methyl *o*-aminoacetanilides, (6, 7). Were the formation of the carbinolamine other than the rate determining step in the cyclization, equilibration of the amides would occur. The two N-Me derivatives exist as separate entities and can be distinguished by their characteristic IR and UV spectra and by their behaviour on chromatography. Attempts to achieve their interconversion under the reaction conditions gave only a mixture of starting material and 1,2-dimethylbenzimidazole. Clear indication that the step of greatest kinetic significance occurs before formation of the common intermediate is provided by the substantial difference between the specific rates of reaction of the two isomers (Table 3).

The formal relationship of the cyclization reaction to other reactions involving nucleophilic attack on carboxyl systems suggests that the mechanisms of acid and base catalysis may also be related. General base catalysis of amide hydrolysis has been widely investigated[13,14] and shown to be consistent with the scheme:[16]



Base catalysis of the cyclization reaction can be represented either as catalysis of addition of the amino group or as catalysis of elimination from the carbinolamine intermediate. Possible mechanisms having identical kinetic form for the catalysis are listed in Table 4. Those in which loss of water in the elimination stage is facilitated can probably be discounted by virtue of the separate identities of the two N-Me isomers and of the effects of structural change on reactivity. The remaining two mechanisms differ only in the timing of the loss of a hydrogen ion from the amino group. Although on the present evidence no distinction can be drawn between these two modes of catalysis, it seems unlikely in an intramolecular process that an amine anion could be generated in the vicinity of a carbonyl group; for this reaction as for

TABLE 4. POSSIBLE MECHANISMS FOR CATALYSIS BY BASE OF CYCLIZATION OF *o*-AMINOACETANILIDE



*Catalysis of addition reaction* ($k_1$)

(a) Pre-equilibrium removal of $H^+$ by base followed by general acid catalysis of addition.

(b) Loss of $H^+$ to base concerted with intramolecular nucleophilic attack.

*Catalysis of product formation* ($k_3$) *at the expense of regeneration of aminoanilide* ($k_2$)

(c) Base catalysis of elimination of $H^+$ concerted with loss of $OH^-$.

(d) Stepwise removal of $H^+$ by base and $OH^-$ by conjugate acid.

certain intermolecular aminolyses[19,20] the concerted process appears to be the more plausible.

Specific acid catalysis of carboxyl reactions can usually be ascribed to facilitation of nucleophilic attack by protonation of the carbonyl O atom.[13] While the ring closure of *o*-aminoacetanilide must be subject to a related catalytic process, the observed form of the kinetic expression is complex and indicates the occurrence of a competitive acid catalysed reaction. The competitive reaction can be identified with hydrolysis of the amide to *o*-phenylenediamine. Formation of *o*-phenylenediamine becomes significant only under conditions of acidity sufficiently high to ensure that protonation of the nucleophilic amino group ($pK_A$ 3·2 at 50°) is essentially complete (Table 4). A simplified reaction scheme incorporating these processes is given in the following equations.

$$A + H^+ \overset{K}{\rightleftharpoons} AH^+ \text{ (fast)}$$

$$AH^+ \underset{k_2}{\overset{k_1}{\rightleftharpoons}} I^+ \xrightarrow{k_3} B$$

$$I^+ + H^+ \underset{k_5}{\overset{k_4}{\rightleftharpoons}} IH^{2+} \xrightarrow{k_6} D$$

$$AH^+ + H^+ \underset{k_8}{\overset{k_7}{\rightleftharpoons}} IH^{2+}$$

(A, B and D represent aminoacetanilide, benzimidazole, and phenylenediamine respectively.)

With the usual stationary state assumptions this reaction scheme leads to an expression for the rate of formation of benzimidazole:

$$\text{rate} = \frac{(k_1k_3/K)(A)(H^+)}{k_2 + k_3 + k_4(1 - k_\alpha)(H^+)} + \frac{(k_3k_7k_\alpha/K)(A)(H^+)^2}{k_2 + k_3 + k_4(1 - k_\alpha)(H^+)}$$

where $k_\alpha = k_5/(k_5 + k_6 + k_8)$. Under conditions such that $k_7k_\alpha(H^+)$ is small by comparison with $k_1$ this expression has the same form as that found empirically where $k_{H^+} = k_1k_3/K(k_2 + k_3)$ and $k_C = k_4(1 - k_\alpha)/(k_2 + k_3)$.*

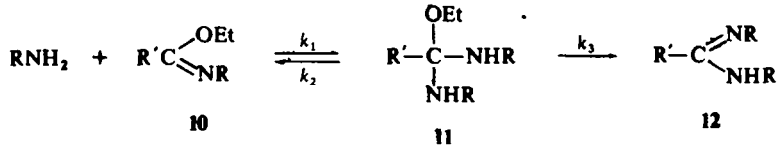
From the kinetic expression alone it is not possible to identify the details mechanism of specific acid catalysis of ring closure: pre-equilibrium protonation of the carbonyl group, protonation concerted with nucleophilic attack, and internal general acid catalysis by $-NH_3^+$ all lead to kinetic equations of the same form. However, by comparison with the characteristics of the reactions of other carboxyl systems some distinctions can be drawn between the possible catalytic processes. Acid catalysed nucleophilic attack on a carboxyl system is usually less efficient than the related base catalysed reaction. Thus for the hydrolysis of acetanilide[21] at 50°, $k_{H^+}/k_{OH^-}$ = 0·78; acetamide,[21] 0·25; benzamide,[22] 0·28; for ester hydrolysis[23] the ratio tends to be smaller lying in the range 0·1–0·0001. The empirical values for the

* The expressions resulting from a more general and explicit statement of the possible reaction sequence are more complex but the extended analysis does not significantly change the form of the resultant kinetic equations.

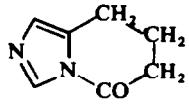
catalytic constants of the ring closure reaction give a ratio of 5000, an unusually high value. Direct comparison of the catalytic constants in this way is appropriate only if, as with most carboxyl reactions, the concentration of reactants is not substantially modified by pre-equilibrium protonation;[24] under these conditions the important kinetic step becomes effectively $A + H^+ \rightarrow I^+$ and the corresponding kinetic equation gives $k_{H+} = k_1k_3/(k_2 + k_3)$. In contrast if kinetically significant pre-equilibrium protonation does occur the ratio of catalytic constants should give $k_{H+}/k_{OH-} \sim 1/K$, where $K$ is the dissociation constant of the conjugate acid, $HA^+$. The observed value gives $K \sim 2 \times 10^{-4}$, a value which is consistent with protonation occurring at the amino groups of *o*-aminoacetanilide, $K_A$, $6{\cdot}3 \times 10^{-4}$.

Although it is obvious that the amino group can act as a proton trap, the establishment of a catalytic process requires further that the $-NH_3^+$ group should function as an intramolecular general acid and that the nitrogen atom should be able to act as a nucleophile. The possibility of general acid catalysis by intramolecular hydrogen bonding[25] is indicated in IR spectra. The spectra of *o*-aminoacetanilide show the presence of strong hydrogen bonds by the low frequencies of both amino and carbonyl bands[8] and low carbonyl frequencies persist even for solutions in isopropanol. The strength of the hydrogen bond and the possibility of proton transfer to oxygen should be increased for the ammonium salt.[26] The extension of hydrogen bonding to general acid catalysis of carboxyl reactions is well known. Of particular interest are the intramolecular catalyses shown by phthalamic acid,[27] γ-(4-imidazolyl)-butyramide,[28] 2-methoxymethoxybenzoic acid[29] and acrylic acid-acrylanilide copolymers[30] where proton transfer appears to be concerted with nucleophilic attack on an amide group. The ring closure reaction can be represented similarly in terms of a four centre transition state involving proton transfer to oxygen and nucleophilic attack at the carbonyl group.[27] The geometries of the imidazoline ring and the transition state leading to it—including the requirement that nucleophilic attack must occur perpendicularly to the plane containing the trigonal bonds of the carbonyl group—are all satisfied by rotation of the acyl group about the N—CO bond during reaction. On the available evidence no clear distinction can be drawn between this mechanism and one in which proton transfer forms a discrete step. The latter would, however, require a fast nucleophilic attack if equilibration of the protonated amide is to be prevented and in consequence there may remain no clear distinction between this sequential process and the concerted mechanism.

Intermolecular general acid catalysis of carboxyl reactions is less common than other modes of catalysis but it has been reported, e.g. for the esterification of acetic acid,[31] the hydrolysis of amides and formamidines,[20,32] and the aminolysis of phenyl acetate.[19,33] Of various reaction schemes which appear kinetically as general acid catalysis, proton catalysed nucleophilic attack and pre-equilibrium hydrogen bond formation provide possible mechanisms for the ring closure reaction. The former has been preferred for amide hydrolysis[32] but, as with specific acid catalysis, it seems unlikely that direct protonation of the amide group could compete with protonation of the amino group sufficiently to induce the necessary reactivity of the carboxyl system under mild conditions. Conversely, hydrogen bonding to the more basic amino group must be expected to occur and, by increasing the strength of the intramolecular N—H ... O=C bond, will provide a catalytic route for the ring closure reaction.



10 11 12



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## EXPERIMENTAL

*Preparation of* o-*amino*-N-*methylacetanilide*

(i) A soln of *o*-nitroacetanilide (10 g) in dry benzene (200 ml) was boiled under reflux for 1 hr with sodamide (4 g). MeI (12 g) in dry benzene (25 ml) was added and the mixture was boiled under reflux for 12 hr. After a further addition of MeI (6 g) in dry benzene (12 ml) the mixture was boiled for 1 hr and then filtered. Evaporation of the solvent left a residue which was purified chromatographically giving *o*-nitro-N-methylacetanilide, m.p. 68° (from ether).

(ii) A methanolic soln of nitroamide (1·2 g) was reduced catalytically by hydrogen in the presence of 10% Pd–C giving *o*-amino-N-methylacetanilide, m.p. 145–146° from light petroleum–benzene. (Found: C, 66·0; H, 7·4; N, 17·0. $C_9H_{12}N_2O$ requires: C, 65·9; H, 7·4; N, 17·1%).

*Preparation of* o-*acetamido*-N-*methylaniline*

A methanolic soln of *o*-nitroacetanilide (1·5 g) was reduced catalytically by hydrogen in the presence of 10% Pd–C. After the addition of 4% formalin (8 ml) the reduction was completed. The soln was filtered, the MeOH removed under reduced press, and the residue chromatographed over silica gel using benzene–EtOAc. The eluate gave *o*-acetamido-N-methylaniline, m.p. 90° from light petroleum–benzene. (Found: C, 66·0; H, 7·3; N, 17·3%).

The isomeric N-Me derivatives had characteristic and distinctive IR and UV spectra.

*Acetylation of* N-*methyl*-o-*phenylenediamine*[4]

An ethereal soln of N-methyl-*o*-phenylenediamine, obtained by the action of alkali on the dihydrochloride, was treated with $Ac_2O$ (0·7 ml) and $NaHCO_3$. After 1½ hr the mixture was filtered. Evaporation of the filtrate and extraction of the residue into light petroleum (2 × 50 ml) gave a colourless product, m.p. 71–76°. IR spectroscopy showed this to be a mixture of *o*-amino-N-methylacetanilide and *o*-acetamido-N-methylaniline (Roeder and Day[4] give m.p. 71·5–79·5° for their product).

*Attempted isomerization of* N-*methyl*-o-*aminoacetanilides*

Solns of *o*-amino-N-methylacetanilide (0·1 g) and *o*-acetamido-N-methylaniline (0·1 g) in 0·1 N methanolic KOH (10 ml) were allowed to stand separately at 50°. After periods of 1–5 half lives, samples were removed, neutralized, and extracted into $CCl_4$. The IR spectra of the solns contained only bands characteristic of 1,2-dimethylbenzimidazole and starting material.

o-*Nitrotrifluoroacetanilide*.[34] This was obtained by heating under reflux for 30 min a mixture of trifluoroacetic anhydride (2 g) in dry benzene (10 ml) with *o*-nitroaniline (1 g) in the presence of an excess of $K_2CO_3$. The soln was then filtered, evaporated under reduced press giving *o-nitrotrifluoroacetanilide*, m.p. 86–87° from aq. EtOH. (Found: C, 41·3; H, 2·0; N, 12·1. Calc. for $C_8H_5N_2O_3F_3$: C, 41·0; H, 2·1; N, 12·0%).

Reduction of an etheral soln of the nitroamide with 10% Pd–C gave colourless crystals of *o*-aminotrifluoroacetanilide, characterized by IR spectroscopy (NH 3495, 3405, 3250 $cm^{-1}$; C=O 1718 $cm^{-1}$; $NH_2$ 1627 $cm^{-1}$). On standing at room temp, on warming, or on dissolution in MeOH 2-trifluoromethylbenzimidazole, m.p. 209–210° was formed in good yield (half life in MeOH, 14 hr). In aqueous phosphate

*Preparation of benzimidazoles*

(i) *Phillips reaction.* AcOH (0·015 mole) and *o*-phenylenediamine (0·01 mole) were allowed to react for 30 min at 70° in the presence of 4N HCl (20 ml). The reaction mixture was then cooled, neutralized, and evaporated under reduced press. MeOH (10 ml) was added and the soln was filtered. Examination of the soln by TLC revealed the presence of *o*-phenylenediamine, *o*-aminoacetanilide, and 2-methylbenzimidazole. Chromatography of the residue left after removal of the MeOH over silica gel using EtOAc–acetone *o*-aminoacetanilide, m.p. 130–131°, characterized by UV and IR and by comparison with an authentic specimen.

An attempt to hydrolyse 2-methylbenzimidazole under similar conditions gave no *o*-aminoacetanilide.

(ii) 2-Methylbenzimidazole, m.p. 175° (from water) was prepared by boiling under reflux for 30 min *o*-phenylenediamine (0·1 mole), AcOH (0·15 mole) and 4N HCl (200 ml). 1,2-Dimethylbenzimidazole, m.p. 110° (from water) was prepared similarly using *o*-amino-N-methylaniline dihydrochloride. 2-Phenylbenzimidazole, m.p. 293–294° (from aq. methanol) was prepared by fusing a mixture of *o*-phenylenediamine (0·05 mole) and benzoic acid (0·05 mole) at 180° for 3 hr.

*Kinetic measurements*

Aqueous solns of *o*-aminoacetanilides and other amides were prepared and the appropriate amount of KCl added to bring the total ionic strength of the reaction soln to 0·5M. The solns (100 ml) were brought to equilibrium at 50° and reactions started by the rapid addition of buffer solution (10 ml). Aliquots (5 ml) were withdrawn at suitable intervals of time and the reaction brought to a halt by dilution. The resulting solns were examined by UV spectroscopy. Absorbance readings at the following wavelengths were used to calculate *pseudo*-first order rate constants: *o*-aminoacetanilide, 274 nm (2-methylbenzimidazole), 230 nm (*o*-phenylenediamine); *o*-aminobenzanilide, 295, 308 nm. For buffer solns the following systems were used: AcOH/KOH (pH 1·2–2·0); $CH_2ClCOOH$/KOH (pH 2·3–3·3); AcOH/KOH (4·1–5·0); $KH_2PO_4$/KOH (pH 5·6–11); $Na_2B_4O_7$ (pH 9·0).

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