REACTIONS OF ORTHO-SUBSTITUTED BENZANILIDES
AND RELATED HETEROCYCLIC COMPOUNDS IN
AQUEOUS SULFURIC ACID SOLUTION

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We have continued our earlier work on the o-substituted benzanilides [1] by studying the kinetics of
acid-catalyzed reactions of the following compounds:

\[
\begin{align*}
\text{XH} & \quad \text{X} = \text{NH}, \quad \text{O} = \text{C} - \text{O} \\
\end{align*}
\]

EXPERIMENTAL

Experiments were carried out according to the procedures of [1]. The physical constants of the com-
pounds used here, 2-phenylbenzimidazole, o-aminobenzanilide (ABA), 2-phenyl-4H-3,1-benzoxazinone (PhBA),
N-benzoylanthranilic acid (BAA), and anthranilic acid (AA), agreed with the values cited in the literature [2-5].

The reaction kinetics were studied through the change in optical density at 255 and 297 nm. Preliminary
experiments showed that 2-phenylbenzanilide did not hydrolyze under our working conditions. Applicability of
the spectrophotometric method to the hydrolyzing ABA system was checked by studying the addition of o-phenyl-
enediamine to 3,5-di-tert-butyl-1,2-benzoquinone. Effective rate constants for ABA hydrolysis and cycliza-
tion were calculated from the first-order equations for irreversible parallel reactions [6].

The reactions of BAA and PhBA were followed from measurements of the optical densities at 265 and
305 nm. Effective rate constants were calculated from the equations for first-order reactions, irreversible
and reversible, respectively [6]. Irreversibility was confirmed by the identity of the spectra of the reaction
products and the solution left at the end of the experiment.

The effective rate constants could be satisfactorily described by an Arrhenius type equation (Tables 1
and 2). The calculated effective activation energies: 19 ± 1 kcal/mole for PhBA hydrolysis; 20 ± 1 and 19 ± 1
kcal/mole for the hydrolysis and cyclization of ABA; 21 ± 1 and 22 ± 1 kcal/mole for the hydrolysis and cycli-
zation of BAA, were essentially independent of the acid concentration.

DISCUSSION OF RESULTS

The reactions of the various heterocyclic compounds generally followed a reversible sequential reaction
scheme, the heterocycles being hydrolyzed, and the amide hydrolyzed and cyclized.

\[
\begin{align*}
\text{N} & \quad \text{NHCO} - \quad \text{NH} \\
\text{X} & \quad \text{X} \\
\text{H}_2\text{O} & \quad \text{H}_2\text{O} \\
\text{NH}_2 & \quad \text{HOOC} \\
\end{align*}
\]

Amide Hydrolysis. The hydrolysis of ABA was appreciable only in H$_2$SO$_4$ solutions of moderate concen-
trations, cyclization tending to be the more significant process in dilute solution; BAA did not hydrolyze in con-
centrated H$_2$SO$_4$ solution, cyclization proceeding much more rapidly than amide hydrolysis.
TABLE 1. Values of the Effective Rate Constants for Cyclization ($k_1$), and Hydrolysis ($k_2$), of o-Aminobenzanilide, at Various Temperatures and $\text{H}_2\text{SO}_4$ Concentrations

<table>
<thead>
<tr>
<th>$\text{H}_2\text{SO}_4$</th>
<th>$T_1$, $\degree$C</th>
<th>$k_1$, $10^3$, min$^{-1}$</th>
<th>$\text{H}_2\text{SO}_4$</th>
<th>$T_2$, $\degree$C</th>
<th>$k_2$, $10^3$, min$^{-1}$</th>
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<td>0.01–0.20</td>
<td>25</td>
<td>7.95 $10^{-3}$ *</td>
<td>50</td>
<td>25</td>
<td>1.50 $10^{-2}$ *</td>
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<td></td>
<td>60</td>
<td>0.23</td>
<td>60</td>
<td>0.10</td>
<td>0.063</td>
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<td>0.55</td>
<td>70</td>
<td>0.25</td>
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<td>0.56</td>
<td>0.50</td>
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<tr>
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<td>90</td>
<td>2.50</td>
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<td>1.30</td>
<td>1.20</td>
</tr>
<tr>
<td>32</td>
<td>25</td>
<td>4.00 $10^{-2}$ *</td>
<td>54</td>
<td>25</td>
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</tr>
<tr>
<td></td>
<td>60</td>
<td>0.12</td>
<td>70</td>
<td>0.063</td>
<td>0.23</td>
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<tr>
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<td>0.30</td>
<td>80</td>
<td>0.15</td>
<td>0.50</td>
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<td>0.36</td>
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<td>100</td>
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<tr>
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</table>

* Extrapolated.

Measured relative to the acid concentration, the effective rate constant passed through a characteristic maximum (cf. Tables 1 and 2). It is presently believed that attack of the hydrated $\text{H}^+$ ion on the unprotonated amide bond is the limiting step in amide hydrolysis.* Protonation of the carboxyl oxygen led to the formation of an inactive form. The mechanism in question is described through the equation:

$$k_{\text{eff}} = \frac{k_{\text{tr}} \cdot C_{H^+aq}}{1 + h_A/K_{BH^+}} \cdot \frac{f_B \cdot f_{H^+aq}^*}{f^*}$$

$k_{\text{tr}}$ being the true hydrolysis rate constant, $C_{H^+aq}$ the concentration of the hydrated proton [8], $h_A$ the amide acidity [9], $K_{BH^+}$ the thermodynamic basicity constant for the carboxyl oxygen of the amide bond, and $f_B$, $f_{H^+aq}$, and $f^*$ the respective activity coefficients for the unprotonated forms of amide, hydrated proton, and activated complex.

Values of $k_{\text{tr}}$ and $K_{BH^+}$ were determined, as usual, from a graphical solution of Eq. (1), the latter rewritten in the form†

$$C_{H^+aq}^* = \frac{1}{k_{\text{tr}} \cdot \text{const}} + \frac{1}{k_{\text{tr}} \cdot K_{BH^+} \cdot \text{const}} \cdot h_A$$

Values of $K_{BH^+}$ were exact,‡ while values of $k_{\text{tr}}$ obtained from Eq. (2) were exact to within constancy of $f_B \cdot f_{H^+aq}^*/f^*$. Calculated values of $k_{\text{tr}}$ and $K_{BH^+}$ are shown in Table 3.

Amide Cyclization. It is seen from Table 1 that ABA differed from o-hydroxybenzanilide [1] insofar as the effective rate constant for its cyclization remained constant as the $\text{H}_2\text{SO}_4$ concentration was varied from 0.01 to 20%, and then fell off rapidly in more concentrated solutions. This difference in the effective rate constants for cyclization traces back to protonation of the N atom of the ABA amino group.

Estimated from the variation of $pK_{BH^+}$ of the o-substituted anilides with the o-position inductive constant ($\alpha_o$) [11, 12], the amino group basicity constant had the value 3.5 ± 0.2, in good agreement with the 3.2 (50°C) reported for o-aminocetanilide [13]. From this it followed that the nitrogen of the primary ABA amino group was actually protonated at the acid concentrations in question here.

* Recent data [7] has suggested that the stable particle in acid solution is not the $\text{H}_3\text{O}^+$ ion, but an $\text{H}_5\text{O}_2^+$ hydrate containing two water molecules.
† Analysis of data on the hydrolysis of amides in acid solution reported by various investigators shows that the ratio of activity coefficients does not alter under a change in the solution composition.
‡ For many amides, values of $K_{BH^+}$ obtained from kinetic data agree with the corresponding values obtained from spectral measurements [10].