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Observation of a Tetrahedral Intermediate and Its Anion in a Hydrolysis Reaction. Ring Opening of a Quinazolinium Ion

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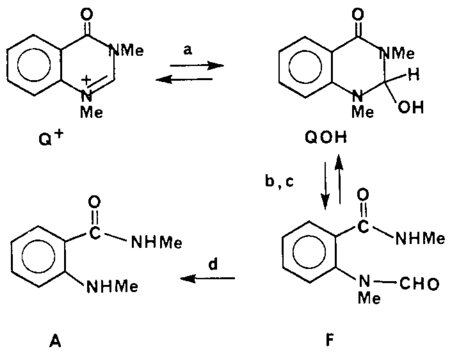
Abstract: The behavior of the 3,4-dihydro-1,3-dimethyl-4-oxoquinazolinium ion (Q^+) in basic aqueous solution (pH 7-14) has been studied. Kinetic studies afforded information about four distinct processes: (a) the relatively fast equilibration of Q^+ with its pseudobase QOH; (b) the slower equilibration of the manifold comprised of Q^+, QOH, the pseudobase anion QO^-, and the ring-opened form, a formanilide derivative, F (equilibrium is approachable starting from Q^+ or from F, which exists in solution as a 3:1 mixture of two atropisomers); (c) slower equilibration of the less stable atropisomer of F into the same manifold as above; and (d) hydroxide ion catalyzed hydrolysis of the formanilide moiety to give the benzamide A. The species QOH and QO^-, which are observable by UV and NMR spectroscopy, are tetrahedral intermediates at the carboxylic acid level of oxidation. The present work is a rare instance where such intermediates have been observed and where analysis of the kinetic data has provided rate constants for their formation and decomposition starting from different precursors. In strongly basic solutions the equilibrium $F \rightleftarrows QO^- + H^+$ is displaced toward QO^-; that is, the tetrahedral intermediate anion is thermodynamically stable relative to its acyl precursor.

The addition of hydroxide ion to heterocyclic cations to produce pseudobases is well documented.[3] In those cases where the carbon attached to the hydroxyl group is also bonded to two heteroatoms, as in QOH (see eq 1), the pseudobase can be regarded as a tetrahedral intermediate of an acyl transfer reaction. Such species are not generally observed, although their presence as transient intermediates has been established for some time.[4]



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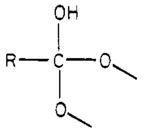
Recently a number of studies have indicated that tetrahedral intermediates of the hemiorthoester type (**1**) can be observed in reactions of various reactive precursors.[5] These species are, of course, pseudobases of an appropriate dialkoxycarbocation, and in those cases where the two oxygens form part of a ring these are also heterocyclic pseudobases.



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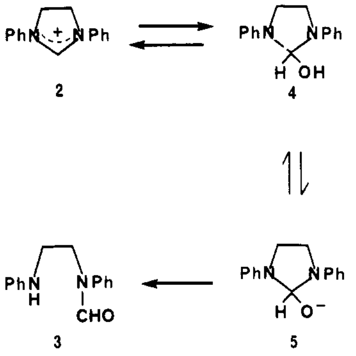
Examination of the literature also reveals a number of reports of heterocyclic pseudobases with two nitrogen atoms at the carbon of hydroxyl addition.[3,6-8] In most of these cases a detailed study of the formation and decomposition of the intermediate is lacking, and the actual observation of it may be open to question because of ring-chain tautomerism[3] (for example, QOH $\rightleftarrows$ F in eq 1). One notable exception is the study by Robinson[7] of the hydrolysis of the 1,3-diphenyl-2-imidazolinium ion **2** to form the formanilide **3**. The reaction does clearly involve an intermediate which, on the basis of UV spectral and kinetic analysis, was suggested to be the tetrahedral intermediate **4** or its anion **5**, depending on the pH (see eq 2). However, Capon and Cuthbert were unable to observe either **4** or **5** by NMR spectroscopy, using a mixed aqueous solvent system.[9]



(2)

We have initiated a detailed study of this type of system and report here the results obtained with the 4-oxoquinazolinium ion Q^+. A previous investigation[8] showed that the pseudobase QOH is an intermediate in the aqueous bromination of this cation. Some spectral evidence for its existence was obtained, although the irreversible formation of the aminobenzamide A in alkaline solution was also noted.[8] In the present work clear NMR and UV

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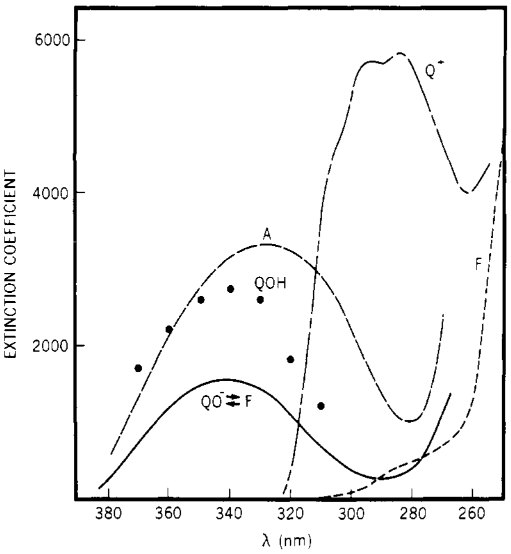


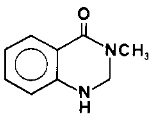
Figure 1. UV spectra: Q^+, in 0.002 M HCl; QOH, obtained after 10 ms in pH 10.5 buffer; F, obtained after 1 min in pH 10 buffer; $QO^- \rightleftharpoons$ F, obtained after 1 min in 0.5 M NaOH; A, obtained after 16 h in 0.5 M NaOH.

spectral evidence has been obtained of the intermediate QOH, and its anion. Furthermore, a kinetic analysis has furnished rate and equilibrium constants for the various steps in the overall ring opening of eq 1.

Results and Analysis

Our detailed study reveals that a series of distinct transformations can be observed upon the addition of the quinazolinium ion Q^+ to basic solutions. Some of these are very rapid and require stopped-flow spectroscopy to be seen, while others are quite slow. The basic reaction scheme which we propose is that shown in eq 1, with ring opening of the pseudobase QOH leading to the formanilide F, which undergoes irreversible hydrolysis to give the anthranilamide A. Some UV spectra obtained under various conditions are shown in Figure 1, while first-order rate constants associated with the transformations are presented in Figure 2. For the purposes of discussion, the rate–pH profiles are labeled (a)–(d). In the following analysis the chemical transformations associated with each of these profiles will be discussed, and a mechanism and rate expression will be derived to account for their general form. The lines drawn in Figure 2 are based on these equations and the constants derived from the best fit to the experimental data. The general consistency of our analysis can be noted in the excellence of the fit, particularly in light of the fact that the same constants appear in several rate expressions.

Transformation a. The initial change (a) is characterized by a decrease in absorbance of the quinazolinium ion Q^+ at 290–310 nm,[10] with a peak centered at 340 nm[10] appearing at the same rate. This change can be attributed to the equilibration reaction of the cation with its pseudobase QOH. The assignment of the 340-nm peak to QOH is supported by comparison with the closely analogous heterocycle **6**, which has λ_{max} at 338 nm, ε 2570, in methanol.[11] Further confirmation comes from our observation that addition of Q^+ to anhydrous methanol containing a 2-fold excess of sodium methoxide results in the formation of a species with λ_{max} of 337 nm, ε 2620. This reaction should produce[3] the pseudobase methyl ether QOMe.



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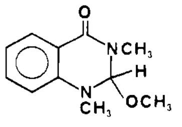

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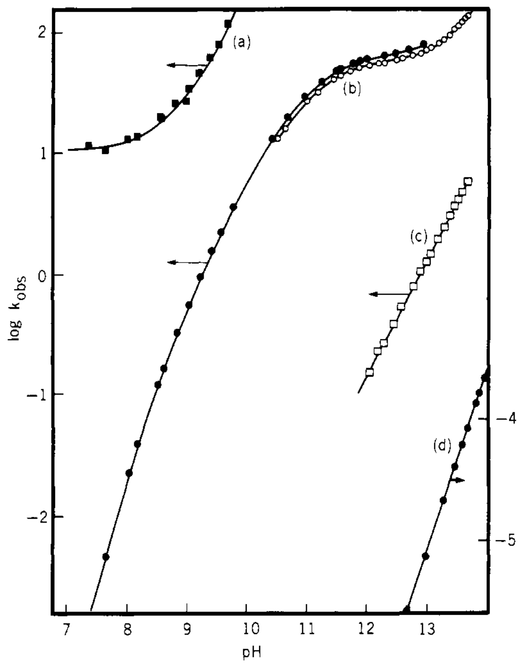


Figure 2. First-order rate constants (see text for explanation): ionic strength = 0.1, closed symbols (a and b); ionic strength = 1.0, open circles for b, and for c and d.

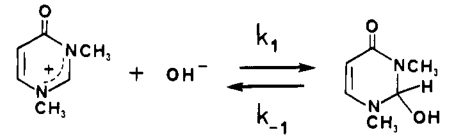
The kinetics associated with change a were investigated following the first-order disappearance of Q^+ at 295 nm (curve a, Figure 2). They can be analyzed in terms of the scheme:[3,12]

$$Q^+ + OH^- \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} QOH \qquad (3)$$

with the rate referring to the approach to equilibrium, so that

$$k_{obsd}(a) = k_1[OH^-] + k_{-1} \qquad (4)$$

Values of $k_1 = 2.12 \times 10^6$ M^{-1} s^{-1} and $k_{-1} = 10.6$ s^{-1} are obtained from the experimental data. Their ratio[13] provides the equilibrium constant $pK_{R^+} = 8.7$. Unfortunately, the subsequent reaction of the system is sufficiently rapid (compare curves a and b of Figure 2) that an accurate spectroscopic determination of this constant is not possible. We can note, incidentally, that the above rate constants are similar to those obtained with the analogous pyrimidinium cation **7**, for which $k_1 = 1.7 \times 10^7$ M^{-1} s^{-1} and $k_{-1} = 8$ s^{-1}.[6d]



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Transformations b and c. The subsequent change results in the disappearance of the UV peaks due to both pseudobase and cation, and at pH <12, in the production of a spectrum characterized by having little absorbance above 280 nm (curve F, Figure 1). The product from this reaction has been isolated from a pH 10.2 buffer and is assigned the ring-opened formanilide structure F. An interesting feature of this compound whose importance will become apparent latter is the presence of two atropisomers in a ratio of 3:1. This is indicated in its proton NMR spectrum by the presence of two signals for the formyl hydrogens, and four *N*-methyl signals (Figure 3). This transformation represents therefore the ring opening of the pseudobase QOH, following its equilibration with Q^+.

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[10] The λ_{max} values given for Q^+ and QOH in ref 8 are too low by 10 nm.

[11] "The Sadtler Standard Spectra"; Sadtler Research Laboratories: Philadelphia, PA, Spectrum No. 16495.

[12] No improvement of the fit to the experimental data is found by including a reaction involving water addition to Q^+ and its microscopic reverse, H^+-catalyzed loss of OH from QOH.[3]

[13] K_{R^+} is defined[3] as $[QOH][H^+]/[Q^+]$ and is equal to k_1K_w/k_{-1}.

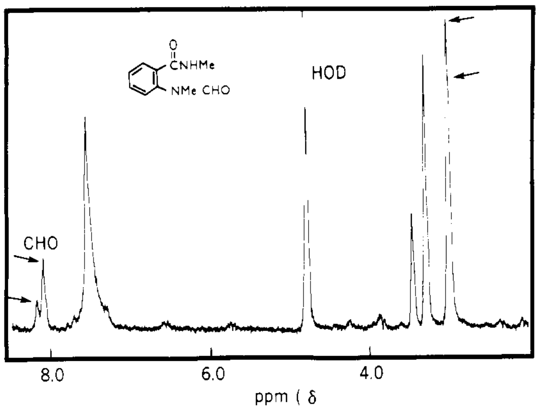


Figure 3. Proton NMR spectrum of formanilide F and D_2O. Due to atropisomerism there are two formyl signals and four *N*-methyl signals, although the two at high field are not well resolved. In $CDCl_3$ the upfield methyl signals are better separated and show coupling with the adjacent NH proton, but the two formyl signals are coincident.

First-order rate constants were obtained by following the disappearance of Q^+ at 295 nm (pH <8.7) or the disappearance of QOH at 340 nm (pH >8.7). Up to pH 12 the kinetic behavior (curve b, Figure 2) can be accounted for in terms of the ring-opening reaction occurring by way of the anion of the pseudobase, with this anion being in equilibrium with both neutral pseudobase and quinazolinium ion. A near second-order dependency on hydroxide ion is observed near pH 7 when the cation is the predominant species in this preequilibrium. This shifts toward a first-order dependency between pH 8 and 9 as the equilibrium shifts toward neutral pseudobase, and then when the pseudobase becomes ionized, a near-zero-order dependency is found, this occurring near pH 11. A comparable change in hydroxide ion dependence was observed in the decomposition of the imidazolinium ion **2**.[7]

Above pH 12, however, QOH shows a different behavior. The first indication of something unusual is the observation that after the rate constants of curve b appear to have almost leveled near pH 12, they begin to increase again with increasing hydroxide ion concentration. Up to this point, the absorbance at 340 nm after complete reaction has been essentially zero, but concomitant with this unexpected rate increase a significant endpoint absorbance is found (see the curve labeled $QO^- \rightleftarrows F$ of Figure 1). Moreover the absorbance decrease at 340 nm that is observed now occurs in two stages (Figure 4). There is a large initial decrease whose rate extrapolates into the rate–pH profile (curve b, Figure 2) obtained below pH 12. This is followed by a second smaller change occurring at about a 100-fold slower rate whose rate constants are represented by curve c in Figure 2. We define the quantities A_a, A_b, and A_c from Figure 4 and plot the variation of these with pH in Figure 5. The term A_c is the absorbance value obtained upon completion of both reactions while A_b is the absorbance value after completion of the faster reaction only, the values for the latter being less accurately determined since the two kinetic phases are not completely separate. The quantity A_a represents the initial absorbance corrected for reaction occurring during the dead time of the stopped-flow instrument. (Note the difference in apparent initial absorbance in Figure 4 and the position of A_a). It should be noted that in strongly basic solutions the quinazolinium ion is converted to pseudobase within the dead time, so that A_a refers to pseudobase in equilibrium with its anion. We in fact feel that the small absorbance change seen in A_a between pH 11.0 and 12.0 in Figure 5 represents pseudobase ionization, since our kinetic analysis places a pK_a value of 11 on this process. We are, however, unable to obtain data for A_a in more dilute base to complete the titration curve since the rate of formation of pseudobase from quinazolinium ion becomes sufficiently slow that an accurate absorbance value referring to neutral pseudobase cannot be obtained.

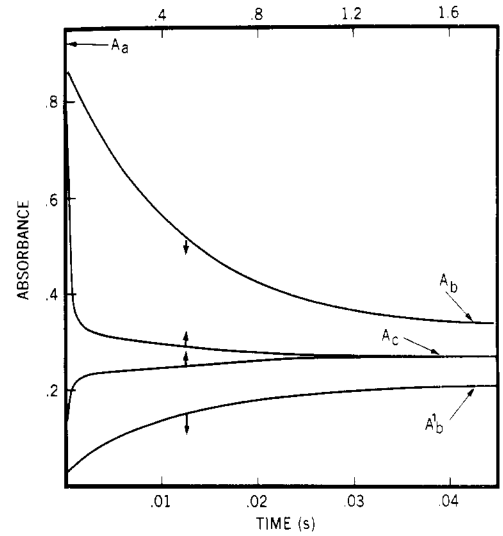


Figure 4. Absorbance (340 nm) vs. time traces in 0.15 M NaOH. Curves with decreasing absorbance were obtained starting with Q^+, those with increasing absorbance with F. Substrate concentration = 1.5×10^{-4} M. Top and bottom curves refer to the faster time scale; middle curves to the slower scale. A_a is the initial absorbance starting with Q^+ (process a, complete), A_b is the absorbance obtained after the rapid initial decrease (process b) is complete and A_c is that obtained upon completion of the slower decrease (process c). $A_b{}^1$ was obtained starting with F and refers to the absorbance upon completion of the rapid increase (process b). The slower increase (process c) leads to a final value A_c identical with that obtained starting with Q^+.

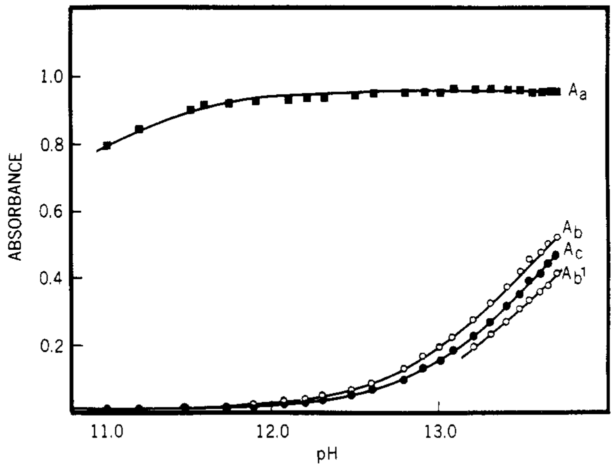


Figure 5. UV absorbance values at 340 nm as a function of pH. Concentration = 1.5×10^{-4} M.

To explain this behavior, we propose that a pH-dependent equilibrium is being established between the formanilide F and the ionized pseudobase QO^-. Although the equilibrium between the neutral pseudobase QOH and F favors the latter to such an extent that none of the former can be observed, this equilibrium can be displaced toward pseudobase anion in concentrated base, the driving force being the formation of a relatively stable anion. The following further observations are consistent with this proposal. Adjustment to pH 10 of a concentrated base solution, where a significant endpoint 340-nm absorbance is present, results in the rapid disappearance of this signal and the appearance of the spectrum of the formanilide F. More importantly, addition of formanilide F to a concentrated base solution results in the appearance of the 340-nm signal. This increase in absorbance also occurs in two phases (Figure 4), the rates for which exactly match those obtained following the absorbance decrease at 340 nm starting with quinazolinium ion. Moreover, the final absorbance is identical with that obtained starting with the same concentration of quinazolinium ion, the intermediate absorbance being slightly smaller ($A_b{}^1$ of Figures 4 and 5).

These UV observations led us to the experiment that unequivocally proves our interpretation, namely, the observation of

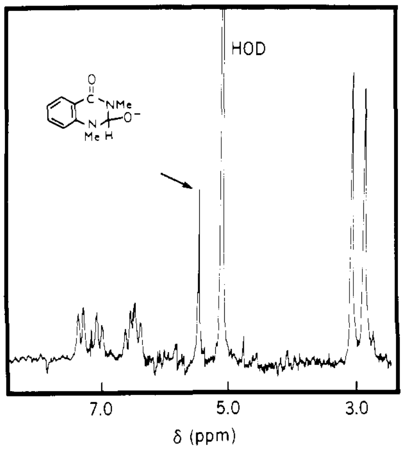


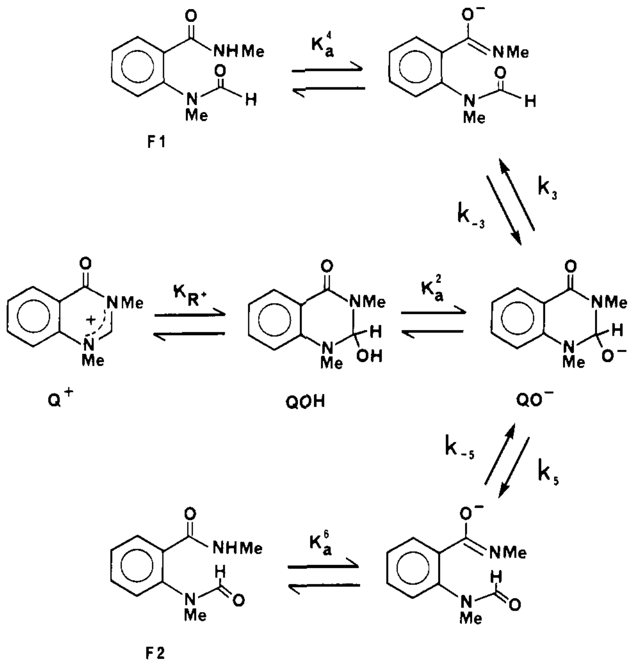
Figure 6. NMR spectrum obtained from formanilide F in 3 M NaOD/D_2O (spectrum recorded at 5 °C 5 min after addition).

the proton NMR spectrum of the pseudobase anion QO^- (Figure 6). This spectrum was obtained by adding isolated formanilide F to 3 M NaOD/D_2O. The presence of a pseudobase structure rather than a formanilide one (cf. Figure 3) is best seen by the upfield shift of the formyl hydrogen to about δ 5.5, a position appropriate for the 2-hydrogen of the pseudobase anion. Moreover, the peaks due to the aromatic protons show a considerable difference. In F (Figure 3) they appear as a compact group at δ 7.5, whereas for QO^- they are more spread out (Figure 6), being comprised of two groups at δ 6.5 and 7.2. By way of confirmation we note that proton NMR spectrum of the anthranilamide A in CCl_4 likewise shows two distinct regions for the aromatic protons at δ 6.2–6.7 and 7.0–7.5, and with similar fine structure.

The mechanism and constants to be used in our kinetic analysis of changes b and c are presented in Scheme I. The analysis is relatively straightforward, the complicating feature being the occurrence of the two kinetic stages. To account for these, we note the presence of the two atropisomers of the formanilide, designated F1 and F2 in Scheme I (see Discussion), and propose that one of these, F1, undergoes equilibration with the pseudobase anion QO^- at a greater rate ($k_3 > k_5$; $k_{-3}K_a{}^4 > k_{-5}K_a{}^6$). We also note that on the time scale of reactions b and c the equilibration of Q^+ and QOH is rapid, as is obviously the proton transfer equilibration of the latter with QO^-. In the experiments starting with quinazolinium ion therefore, a rapid equilibration of these three species occurs, followed by the further reaction b representing equilibration with the kinetically favored formanilide isomer F1. Below pH 12 the equilibrium lies entirely to the F1 side so that complete disappearance of Q^+ and QOH is observed. Above pH 12 however significant amounts of QO^- remain upon attainment of equilibrium. In these cases the second slower change c is observed, due to the further equilibrium of QO^- with the other formanilide isomer F2. This is seen as a further decrease in absorbance at 340 nm, as the overall pseudobase anion: formanilide equilibrium is shifted more to the formanilide side.

Starting in the formanilide direction, we note first that under the conditions in which this species is prepared an equilibrium mixture of the two atropisomers is obtained.[14] The initial increase in absorbance corresponds therefore to the approach to equilibrium of QO^- and the F1 isomer only, with the second slower increase representing the further equilibration involving F2. The same equilibrium position is eventually attained starting from both the cation side and the formanilide side, so that the final absorbance values A_c in Figure 4 are the same. The intermediate absorbance value $A_b{}^1$ starting with formanilide is slightly smaller, since the species present when this is measured are an equilibrium mixture of QO^- and F1, and unequilibrated F2.

Scheme I



On the basis of this interpretation, the following rate expression is derived for profile b, noting that the rate proceeding in either direction refers to a sum of forward and reverse rates:

$$k_{\mathrm{obsd}}(\mathrm{b}) = \left(\frac{k_3 K_a{}^2 K_{R^+}}{[H^+]^2 + K_{R^+}[H^+] + K_a{}^2 K_{R^+}} \right) + \frac{k_{-3} K_a{}^4}{[H^+]} \quad (5)$$

In qualitative terms the first term on the right-hand side accounts for the previously noted transition from second- to first- to zero-order dependency in hydroxide ion due to the shifting equilibrium involving Q^+, QOH, and QO^-. The second term accounts for the increase in rate observed in more concentrated base which is associated with the onset of importance of the reverse cyclization reaction and the presence at equilibrium of some pseudobase anion.

Equation 5 can be fit to curve b to provide the following values of the constants: $pK_{R^+} = 8.4$, $pK_a{}^2 = 11.06$ (11.08), $k_3 = 64\ s^{-1}$ (59 s^{-1}), and $k_{-3}K_a{}^4 = 2.34 \times 10^{-12}\ M\ s^{-1}$ ($1.60 \times 10^{-12}\ M\ s^{-1}$), with the first value referring to ionic strength = 0.1 and the value in parentheses to ionic strength = 1.0. The tautomeric equilibrium constant $K_T{}^1$ for QOH $\rightleftarrows$ F1 can also be determined from these data as $k_3K_a{}^2/k_{-3}K_a{}^4$, and it has a value of 240 (310).

The equilibrium constant for F1 $\rightleftarrows$ $QO^- + H^+$ can also be calculated as $k_{-3}K_a{}^4/k_3$ and has a value of 13.56 (expressed as $pK_a{}^{F1}$). This is the equilibrium reaction being observed in strong base, and a value of this constant can also be obtained spectroscopically (Figure 5). For the experiments starting with a constant concentration of quinazolinium ion, the absorbance values A_b of Figure 4 are the ones of importance. The equilibrium constant is then given by $[H^+](A_b - A_b{}^{acid})/(A_b{}^{base} - A_b)$, where $A_b{}^{acid}$ and $A_b{}^{base}$ refer to values obtained when the equilibrium lies completely to the acid (F1) and base (QO^-) sides of the equilibrium. Although the curve in Figure 5 was not extended into sufficiently concentrated base to provide the latter, a value is available since this is equal to the initial absorbance reading $A_a{}^{base}$ which refers to QO^-. A value of $pK_a{}^{F1}$ of 13.59 can then be calculated, in excellent agreement with the value obtained above from the kinetic analysis.[15]

The absorbance values A_c of Figures 4 and 5 define an acidity constant $[H^+](A_c - A_c{}^{acid})/(A_c{}^{base} - A_c)$, and with $A_c{}^{base} = A_a{}^{base}$ a $pK^F{}_a$ value of 13.72 is obtained. This now refers to the equi-

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[14] This is apparent from the extension of curve c of Figure 2 to lower pH. In pH 10 buffer, from which the formanilide was isolated, the half-life for equilibration of F1 and F2 is short relative to the ov [illegible] required for extraction.

[15] For the experiments starting with formanilide, this equilibrium constant is given by $[H^+](A_{b^1} - A_{b^1}{}^{acid})/(A_{b^1}{}^{base} - A_{b^1})$. In this case, however, $A_{b^1}{}^{base}$ is not available.

librium of pseudobase anion and both isomers of formanilide, (F1 + F2) $\rightleftarrows$ QO$^-$ + H$^+$. The difference between this value and that based on A_b can be used to calculate the ratio at equilibrium of the two formanilide isomers:

$$\frac{[\mathrm{F2}]}{[\mathrm{F1}]} = \frac{K_a^{\mathrm{F1}}}{K_a^{\mathrm{F}}} - 1 \qquad (6)$$

for which a value of 0.35 is calculated. This shows good agreement with the value of 0.33 obtained from the NMR spectrum of the formanilide (Figure 3). From pK_a^{F1} and pK_a^{F} we obtain pK_a^{F2} = 13.13 for the equilibrium F2 $\rightleftarrows$ QO$^-$ + H$^+$.

Finally we can turn to the rate constants associated with profile c. This process is only observed in concentrated base and represents an equilibrating mixture of F1 and QO$^-$ proceeding to equilibrium with F2, so that the following expression can be derived:

$$k_{\mathrm{obsd}}(\mathrm{c}) = \left\{\frac{(1 + (K_a^{\mathrm{F1}}/K_a^{\mathrm{F2}}))[\mathrm{H}^+] + K_a^{\mathrm{F1}}}{[\mathrm{H}^+] + K_a^{\mathrm{F1}}}\right\}\frac{k_{-5}K_a^{6}}{[\mathrm{H}^+]} \qquad (7)$$

Since the constants K_a^{F1} and K_a^{F2} are available from the analysis above, a value of $k_{-5}K_a^6 = 1.05 \times 10^{-13}$ M s^{-1} can be obtained from the experimental data, and a value of $k_5 = 1.42$ s^{-1} can also be determined from $k_{-5}K_a^6/K_a^{\mathrm{F2}}$ (see Scheme I). It will be noted from Figure 2 that the values of k_{obsd}(c) vary in an approximately linear fashion with hydroxide ion concentration. Although this is not apparent from the form of eq 7, this arises because the bracketed term in the equation does not vary greatly (1.34–1.15) over the pH range studied (12–14).

Transformation d. As observed in a previous study,[8] there is a further irreversible change, resulting in formation of the *o*-aminobenzamide A. This material has been isolated form the oxoquinazolinium ion by hydrolysis in concentrated base and can also be prepared by a separate route.[8] The reaction forming this product is considerably slower than those discussed above, and in fact it only occurs at a reasonable rate of 25 °C in quite concentrated base (see curve d in Figure 2). The following scheme best satisfies the limited rate data obtained for this reaction:

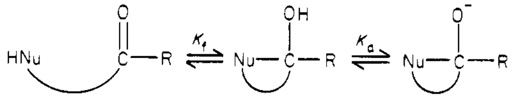
$$\mathrm{QO}^- \rightleftarrows \mathrm{F} \xrightarrow[k_8[\mathrm{OH}^-]^2]{k_7[\mathrm{OH}^-]} \mathrm{A} \qquad (8)$$

The formanilide, in equilibrium with pseudobase anion, undergoes hydrolysis by reactions which are first order and second order in hydroxide ion.[16] Values of $k_7 = 2.5 \times 10^{-5}$ M^{-1} s^{-1} and $k_8 = 6.1 \times 10^{-4}$ M^{-2} s^{-1} provide the best fit to the experimental data.

Discussion

From the UV evidence provided above there can be little doubt that the pseudobase QOH derived from the quinazolinium ion Q$^+$ is observed in weakly basic solutions. This observation represents a further example where a tetrahedral intermediate has been generated from a reactive precursor (cf. ref 5). However, a noteworthy feature of the present system is that in strongly basic solutions the anion of the intermediate, QO$^-$, is stable relative to the ring-opened form, F, so that the anion can be observed spectrally. Furthermore, since the manifold of Q$^+$, QOH, QO$^-$, and F can be entered from either end, the present system provides a unique instance where a tetrahedral intermediate and its anion can be observed in equilibrium with their acyl precursor, i.e., in the reaction for which they are actually the tetrahedral intermediates.[17]

The reason why the anionic intermediate can be observed in the quinazolinium ion system is that the equilibrium between the neutral intermediate and its breakdown product does not favor the latter to too large an extent, even though the neutral intermediate cannot be detected at equilibrium. Because of the relatively high acidity of the intermediate, a high concentration of hydroxide ion can shift the equilibrium toward the intermediate in its ionized form. In terms of the general equilibrium (eq 9),



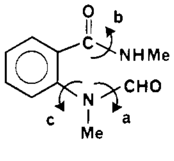
(9)

S **TOH** **TO$^-$**

the concentration of TO$^-$ can be defined in terms of the equilibrium constant [TO$^-$][H$^+$]/[S], the product of K_f and K_a. Thus a relatively acidic tetrahedral intermediate coupled with a not too unfavorable equilibrium between the neutral species S and TOH will give rise to a situation where TO$^-$ is observable in base. In principle, of course, some high concentration of base will always shift the equilibrium toward TO$^-$, but if we set 1 M hydroxide as a limit, K_fK_a must be $\geq 10^{-15}$ for there to be at least 10% TO$^-$ at equilibrium in this solution. If pK_a = 11, a not unreasonable value for a tetrahedral intermediate (see below), then K_f must be greater than 10^{-4}. Although formation constants of this order of magnitude are common at the carbonyl level of oxidation,[18] at the acyl level they are generally much smaller.[5h-j,19] It is interesting to note in this context that in the diphenylimidazolinium ion system (eq 1),[7] K_f(**3** $\rightleftarrows$ **4**) = 5.8×10^{-8}, so that the tetrahedral anion **5** cannot be observed in equilibrium with its ring-opened form.

A tetrahedral intermediate TOH is an alcohol, but the presence of two additional electronegative atoms causes it to be considerably more acidic than a simple alcohol.[20] The effect will be larger for oxygen atoms than for nitrogen atoms.[20] In the pseudobase QOH however, there are other electron-withdrawing groups in the molecule as well, and these undoubtedly also contribute to an enhanced acidity. A number of other pseudobase anions have been observed,[3] although none are of the tetrahedral intermediate type. Values of pK_a for their formation range from 9.7–15.[3]

Finally we can comment on the formation and presence of the two isomeric forms of the formanilide. Some precedents for this can be noted. Halliday and Symons,[21] in a study of the base hydrolysis of *N,N'*-dimethylformamidine, observed a kinetically controlled formation of the *cis-N*-methylformamide product, with this then undergoing a slow rearrangement to the trans isomer. Capon and Cuthbert,[9] in their study of the diphenylimidazolinium ion (eq 1), observed the two geometrical isomers of the anilide product (**3**) with the kinetically controlled ratio differing from the thermodynamically controlled ratio. In the present case the situation is complex and we are not certain of the actual structures of the two isomers. There may be substantial barriers to rotation about three bonds, as indicated in structure **8**. Barriers in amides



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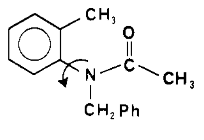

9

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(16) (a) First-order and second-order terms in hydroxide ion are usually observed in the base hydrolysis of anilides.[16b] (b) Biechler, E.; Taft, R. W. *J. Am. Chem. Soc.* **1957**, *79*, 4927–4931. Eriksson, S. O. *Acta Pharm. Suec.* **1969**, *6*, 139–162. Drake, D.; Schowen, R. L.; Jayaraman, H. *J. Am. Chem. Soc.* **1973**, *95*, 454–458.

(17) Several examples are known of molecules which can be regarded as being stable tetrahedral intermediates, but these generally have structural features resulting in stabilization of the tetrahedral form or destabilization of the carbonyl form.[5d]

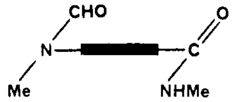
(18) (a) A shift in equilibrium toward the tetrahedral anion has been observed in the equilibration of a hydroxy aldehyde with its cyclic hemiacetal form[18b] and in the hydration and methanolysis of benzaldehydes.[18c] (b) Harron, J.; McClelland, R. A.; Thankachan, C.; Tidwell, T. T. *J. Org.* Chem. **1981**, *46*, 903–910. (c) Bover, W. J.; Zuman, P. *J. Am. Chem. Soc.* **1973**, *95*, 2531–2536. Greenzaid, P. *J. Org. Chem.* **1973**, *33*, 3164–3167. Bell, R. P.; Sorensen, P. E. *J. Chem. Soc., Perkin Trans. 2* **1976**, 1594–1598. Arora, M.; Cox, B. G.; Sorensen, P. E. *Ibid.* **1979**, 103–107.

(19) Guthrie, J. P. *J. Am. Chem. Soc.* **1973**, *95*, 6999–7003. Guthrie, J. P. *Ibid.* **1974**, *96*, 3608–3615. Guthrie, J. P. *Can. J. Chem.* **1977**, *55*, 3562–3574. Guthrie, J. P.; Cullimore, P. A. *Ibid.* **1980**, *58*, 1281–1294.

(20) (a) See the pK_a estimates for tetrahedral intermediates by Guthrie[19] and Fox and Jencks.[20b] (b) Fox, J. P.; Jencks, W. P. *J. Am. Chem. Soc.* **1974**, *96*, 1436–1449.

(21) Halliday, J. D.; Symons, E. A. *Can. J. Chem.* **1978**, *56*, 1463–1469.

(a and b), for example, lie in the range 14–21 kcal/mol; the barrier to rotation about the indicated bond in **9** is 20 kcal/mol.[22] Space-filling molecular models also reveal a further complication in the present case, in that it appears impossible for the two side chains to be coplanar with the benzene ring. This gives rise to four extreme situations, structures **10–13**, where substantial barriers to their interconversion must exist. Since only **10** can cyclize to pseudobase, one possible interpretation is that the rapid cyclization reaction observed represents the direct cyclization of **10**, while the slower reaction represents isomerization of one of the other species to **10**, which then cyclizes. This explanation is highly unlikely however, since this isomerization should be slow and pH independent, not fast and hydroxide ion dependent as is observed. For this reason we propose that the two atropisomers F1 and F2 are the two rotamers about the NMe–CHO bond in **10**. These cyclize, as anions, producing different conformers of QO^- (eq 10 and 11). The free energies of the transition states for these two cyclizations differ by only about 2 kcal/mol. This may be due to slightly different orientations of lone-pair electrons,[23] although in principle both reactions may be visualized as having proper lone-pair orientation. It is more likely that the difference is associated with pseudoequatorial and pseudoaxial oxygen atoms of the two different conformations of the pseudobase anion (eq 10 and 11). In the latter case the pseudoaxial $-O^-$ must have an unfavorable interaction with the π orbitals of the benzene ring, resulting in destabilization of the transition state of the reaction shown in eq 11.



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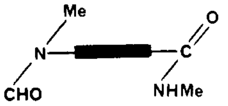

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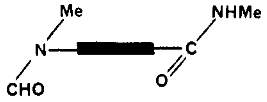

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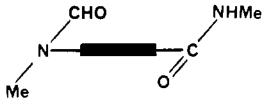

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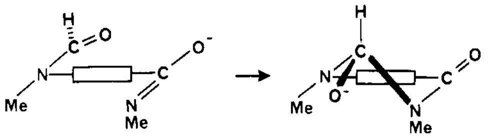
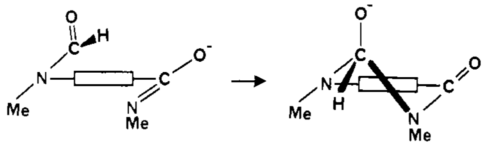


(10)



(11)

These arguments are necessarily tentative because of the complexity of the system. However, it does appear mandatory that the interconversion of the atropisomers F1 and F2 occurs via cyclization to the pseudobase anion QO^- and not by simple bond rotation, as is normally the case.[22]

Conclusion

We have identified a system in which one can generate a tetrahedral intermediate *and* its anion from a cationic precursor and from acyl precursors. From analysis of four distinct pH–rate profiles, we have obtained rate constants for the kinetically significant forward and backward steps. Equilibration of the acyl precursors (F1 and F2) occurs via the tetrahedral intermediate anion at high pH. In stronger base the anion becomes favored and is observable.

As a final point we note that the present study substantiates our earlier proposal[8] that Q^+ reacts with bromine via QOH. An alternative, that reaction occurs via a ring-opened form,[3] is precluded since ring opening of QOH is slow relative to its formation and reaction with bromine.

Experimental Section

The quinazolinium ion Q^+ as its iodide salt (3,4-dihydro-1,3-dimethyl-4-oxoquinazolinium iodide) and *o*-(methylamino)-*N*-methylbenzamide (A) were available from a previous study.[8] *o*-(Formylmethylamino)-*N*-methylbenzamide (F) was obtained by dissolving the cation Q^+ (0.25 g) in 50 mL of 0.001 M HCl and adding sufficient carbonate buffer to give a pH of 10.2. After the mixture was stirred for 10 min, the solution was extracted with ether, the extract was dried ($MgSO_4$), and the ether was removed on a rotary evaporator to give a white solid; mp 77–80 °C (NMR, see Figure 3).

Kinetic and spectral measurements were made on a Unicam SP 1800 spectrophotometer and a Durrum-Gibson stopped-flow spectrophotometer.[5f] An Aminco DW-2 spectrophotometer with stopped-flow accessory was also used.[24] The output voltage of the DW-2 (proportional to absorbance, $(2V/A)$) was captured on a Biomation 805 transient recorder (8-bit resolution, 2048 points). The stored trace was viewed on an oscilloscope, and if it was acceptable it was transferred serially at 9600 baud, using a Datos 305 interface to an Apple II microcomputer. Every 20th point was extracted and displayed by the Apple (100 points); the infinity value was taken as the average of the last 10 points. The rate constant for the run was calculated from 20–40 points spanning about 90% reaction.

The reported rate constants (Table S1) were obtained as the average of 3–8 runs and differed by <5%. Individual first-order rate constants were obtained from least-squares analysis of $\ln (A - A_\infty)$ or $\ln (A_\infty - A)$ vs. time. In those cases where A_∞ values could not be obtained because of interference from a subsequent reaction, the rate constants were obtained by the Kezdy–Swinbourne method[25] or the Guggenheim method.[25]

Acknowledgment. We are grateful to the Natural Sciences and Engineering Research Council of Canada for operating grants to O.S.T. and R.A.M. The work was also facilitated by a team grant to Professor M. J. Kornblatt and O.S.T. from the Quebec Ministry of Education (FCAC program).

Registry No. Q^+, 57573-54-3; QOH, 83561-68-6; F, 83561-69-7; A, 32212-33-2.

Supplementary Material Available: Table S1 containing the first-order rate constants plotted in Figure 2 (2 pages). Ordering information is given on any current masthead page.

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(22) Jackman, L. M. In "Dynamic Nuclear Magnetic Resonance Spectroscopy"; Jackman, L. M., Cotton, F. A., Eds.; Academic Press: New York, 1975; Chapter 7.

(23) (a) Unlike the case of Halliday and Symons,[21] lone-pair orientation[23b] does not appear to be a factor. (b) Deslongchamps, P. *Tetrahedron* **1975**, *31*, 2463–2490.

(24) Tee, O. S.; Paventi, M. *J. Org. Chem.* **1980**, *45*, 2072–2076. Tee, O. S.; Thackray, D. C.; Berks, C. G. *Can. J. Chem.* **1978**, *56*, 2970–2976.

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