

Kinetics of the Reversible Addition of Water to Substituted Quinazolines and Some Triazanaphthalenes

By J. W. Bunting and D. D. Perrin, Department of Medical Chemistry, John Curtin School of Medical Research, Australian National University, Canberra

A rapid-reaction technique has been used to study the pH-dependence of the reversible addition of water across the 3,4-double bond of some substituted quinazolines and 1,3,5-, 1,3,7-, 1,3,8-, and 1,4,6-triazanaphthalene. The pH-rate profiles for the hydration and dehydration reactions have been calculated from the observed pseudo-first-order rate constants. Substituent effects are discussed.

IN aqueous solutions, the quinazoline cation rapidly undergoes reversible covalent hydration across the C(4),N(3)-double bond, so that whereas the neutral molecule is almost entirely "anhydrous," at equilibrium the cation is predominantly that of the "hydrated" species, 3,4-dihydro-4-hydroxyquinazoline.¹ This phenomenon of covalent hydration across C=N bonds occurs in several other nitrogen-containing heterocycles, including pteridine and its 2- and 6-hydroxy-derivative, 1,3,5-, 1,3,6-, 1,3,7-, 1,3,8-, and 1,4,6-triazanaphthalene, 1,4,5,8-tetra-azanaphthalene, and 8-azapurine. Qualitative² and quantitative¹ aspects of this type of reaction have been discussed. More recently, equilibrium constants and true pK_a values for some substituted quinazolines have been published.³ We now report results of a kinetic study of the reversible hydration of some of these compounds over a pH range.

Similar studies, but over a more restricted time scale, have been made for reversible hydration following cation formation by pteridine,⁴ some of its methyl derivatives,⁴ and 1,3,8-triazanaphthalene.⁵ Hydration of pteridine has also been studied polarographically.⁶ Armarego⁷ measured rates of dehydration of a series of substituted hydrated quinazolines at one pH value, and Lund⁸ used polarography to obtain the rate constants and to show that the dehydration of the hydrated quinazoline cation over the range H_+ -2 to pH 1.5 is hydrogen-ion catalysed. Lund also examined⁸ the dehydration of the cation of 3,4-dihydro-4-hydroxy-3-methylquinazoline from H_+ -2 to pH 6. With these exceptions, most of the previous measurements have been concerned with the behaviour of hydroxy-derivatives where, at equilibrium, the neutral molecule is mainly hydrated and the anion is mainly anhydrous. In all examples so far studied, the hydration-dehydration reaction is catalysed by hydrogen and hydroxide ions and follows a first-order rate equation.

The present methods and calculations followed closely those described earlier.⁹ The heterocyclic substances used were provided by Dr. W. L. F. Armarego.

RESULTS

True pK_a values (pK_a^X), equilibrium pK_a values, and K_1 , the equilibrium ratio of "hydrated" to "anhydrous"

cations for most of the substances studied, have been published.³ The remainder are in Table 1.

Kinetics for the hydration and dehydration reactions of quinazoline and 2-methylquinazoline have been studied over the pH range 0-13 at 20°. The observed pseudo-first-order rate constants, k_{obs} , together with the rate constants for hydration, k_h , and dehydration, k_d , calculated from them, are given in Table 2. The values of k_h and k_d were obtained by use of the relations (1) and (2), derived as described previously.¹⁰

$$k_h = k_{obs} \cdot \frac{K_1(a_{H^+}) + K_2K_a^X}{(K_1 + 1)(a_{H^+}) + (K_2 + 1)K_a^X} \quad (1)$$

$$k_d = k_{obs} \cdot \frac{(a_{H^+}) + K_a^X}{(K_1 + 1)(a_{H^+}) + (K_2 + 1)K_a^X} \quad (2)$$

In all the quinazolines so far studied, K_2 , the equilibrium ratio of "hydrated" to "anhydrous" neutral molecules, is negligible.¹¹

Over the pH range 4-12, where the anhydrous species exist predominantly as the neutral molecules, the pH-rate profiles for the hydration of quinazoline and 2-methylquinazoline can be described by equations of the form (3)

$$k_h = b(a_{H^+}) + c + d/(a_{H^+}) \quad (3)$$

where $b = 200$, $c = 7.0 \times 10^{-7}$, $d = 3.5 \times 10^{-16}$, and $b = 525$, $c = 3.0 \times 10^{-6}$, and $d = 4.0 \times 10^{-16}$, respectively. Minima in the rate profiles occur at pH 8.76 and 9.06. Similar curves have been found for 1,3,8-triazanaphthalene,⁵ and pteridine and its methyl derivatives.⁴ At lower pH values, cation formation becomes appreciable, and another term, $a(a_{H^+})^2$, has to be included in equation (3). For quinazoline and 2-methylquinazoline $a = 1.1 \times 10^3$ and 5.6×10^4 , respectively. The complete pH-rate profile for hydration of quinazoline is shown in the Figure.

The successive terms in k_h are interpreted as follows:

Strongly acid solution: attack of H_2O on dication

Weakly acid solution: attack of H_2O on monocation

Neutral solution: either attack of OH^- on monocation

or attack of H_2O on neutral molecule

Alkaline solution: attack of OH^- on neutral molecule

From the pK_a value of quinazoline dication, -5.5,¹² and the above value of a , a rate constant of $3.9 \times 10^6 \text{ sec}^{-1}$ is

⁵ Y. Inoue and D. D. Perrin, *J. Chem. Soc.*, 1963, 5166.

⁶ J. Komenda and D. Laskafeld, *Coll. Czech. Chem. Comm.*, 1962, 27, 199.

⁷ W. L. F. Armarego, *J. Chem. Soc.*, 1962, 561.

⁸ H. Lund, *Acta Chem. Scand.*, 1964, 18, 1984; *Nature*, 1964, 204, 1087.

⁹ J. W. Bunting and D. D. Perrin, *J. Chem. Soc. (B)*, 1966, 433.

¹⁰ Y. Inoue and D. D. Perrin, *J. Phys. Chem.*, 1962, 66, 1689.

¹¹ W. L. F. Armarego, personal communication.

¹² A. Albert, W. L. F. Armarego, and E. Spinner, *J. Chem. Soc.*, 1961, 2689.

¹ D. D. Perrin, *Adv. Heterocyclic Chem.*, 1965, 4, 43.

² A. Albert and W. L. F. Armarego, *Adv. Heterocyclic Chem.*, 1965, 4, 1.

³ J. W. Bunting and D. D. Perrin, *J. Chem. Soc. (B)*, 1966, 436.

⁴ Y. Inoue and D. D. Perrin, *J. Chem. Soc.*, 1963, 2648.

calculated for the attack of a water molecule on the quinazoline dication. In less acid solutions, the possibility that reaction proceeds by attack of an hydroxide ion on the anhydrous dication can be excluded because the required rate constant of about $10^{20} \text{ l. mole}^{-1} \text{ sec}^{-1}$ ($= bK_{\text{al}}^{\text{X}}K_{\text{a2}}^{\text{X}}/K_{\text{w}}$

Table 3. Similar behaviour is reported in the analogous hydration-dehydration reactions across $\text{C}=\text{N}$ bonds in Schiff bases derived from weakly basic amines.¹⁴

The pH-rate profile for dehydration of hydrated quinazoline is also shown in the Figure. The rate constant

TABLE 1
Acid dissociation constants, and equilibrium ratios, of quinazoline cations

Quinazoline	Temp.	True $\text{p}K_{\text{a}}$ ($\text{p}K_{\text{al}}^{\text{X}}$)	λ (m μ)	pH range	Eqm. $\text{p}K_{\text{a}}$	λ (m μ)	pH range	K_1^a
Unsubstituted	4.3°	2.01 ± 0.02^b	242 ^c	1.0—2.7 ^d	3.89 ± 0.03^b	<i>e</i>	—	75
	12.1	1.97 ± 0.06	242	1.0—2.7	3.66 ± 0.02	<i>e</i>	—	48
	20.0	1.95 ± 0.05	242	1.0—2.7	3.51 ^f	—	—	35
	29.5	1.94 ± 0.08	242	1.0—2.7	3.43 ± 0.01	<i>e</i>	—	30
2-Me	20.0	3.00 ± 0.07	242	2.2—4.0	4.52 ^g	—	—	32
4-CONH ₂	20.0	0.50 ± 0.05	245	0.2—1.4	3.40 ± 0.02	317	2.5—4.1	790
4-CONH ₂ -2-Me	20.0	1.57 ± 0.07	245	0.8—2.4	4.41 ± 0.04	322	3.4—5.0	690
4-CONH ₂ -2,6-Me ₂	20.0	1.79 ± 0.05	250	1.0—2.8	4.21 ± 0.04	333	3.4—5.0	260
4-CONH ₂ -6-F-2-Me ...	20.0	1.03 ± 0.04	245	0.4—1.9	4.18 ± 0.03	334	2.8—4.8	1410

^a Ratio of [hydr. cat.]/[anhyd. cat.]. ^b Maximum deviation. ^c Analytical wavelength. ^d pH range over which $\text{p}K_{\text{a}}$ calculated. ^e Measured potentiometrically. ^f W. L. F. Armarego, *J. Chem. Soc.*, 1962, 561. ^g A. Albert, W. L. F. Armarego, and E. Spinner, *J. Chem. Soc.*, 1961, 2689.

TABLE 2

First-order rate constants (sec^{-1}) for hydration and dehydration of quinazoline and 2-methylquinazoline at 20°

(i) Quinazoline: 228 m μ ; $2.5 \times 10^{-4}\text{M}$ (pH < 4), $2.0 \times 10^{-5}\text{M}$ (pH 4—10), $2.5 \times 10^{-4}\text{M}$ (pH > 10)								
pH	k_{obs}	k_{h}	k_{d}	pH	k_{obs}	k_{h}	k_{d}	
0.5	6.01	5.84	0.173	4.39	0.0606	0.00684	0.0535	
0.7	4.44	4.31	0.130	4.98	0.0583	0.00185	0.0563	
0.9	3.79	3.68	0.115	6.12	0.0560	0.000136	0.0560	
1.10	3.00	2.90	0.0954	6.45	0.0583	0.0000680	0.0583	
1.30	2.31	2.23	0.0783	6.92	0.0541	0.0000232	0.0541	
1.47	2.08	2.00	0.0766	7.43	0.0435	0.00000745	0.0435	
1.65	1.99	1.91	0.0818	8.03	0.0242	0.00000204	0.0242	
1.82	1.48	1.41	0.0700	8.55	0.0182	0.00000116	0.0182	
2.00	1.14	1.07	0.0646	8.95	0.0244	0.00000143	0.0244	
2.15	1.04	0.972	0.0716	9.43	0.0311	0.00000175	0.0311	
2.30	0.902	0.805	0.0765	9.80	0.0544	0.00000302	0.0544	
2.65	0.433	0.370	0.0635	9.88	0.0652	0.00000359	0.0652	
2.82	0.347	0.279	0.0671	10.41	0.150	0.00000825	0.150	
3.00	0.265	0.197	0.0685	10.80	0.325	0.0000179	0.325	
4.00	0.0815	0.0192	0.0622	11.52	2.02	0.000111	2.02	
4.01	0.0666	0.0154	0.0508	12.0	4.47	0.000246	4.47	
(ii) 2-Methylquinazoline: 230 m μ ; $3.6 \times 10^{-4}\text{M}$ (pH < 4 or > 11), $2.4 \times 10^{-5}\text{M}$ (pH 4—11)								
pH	k_{obs}	k_{h}	k_{d}	pH	k_{obs}	k_{h}	k_{d}	
1.0	6.06	5.86	0.185	6.46	0.0182	0.000204	0.0182	
1.30	2.90	2.81	0.0894	6.87	0.0184	0.0000824	0.0184	
1.70	1.61	1.56	0.0510	7.40	0.0188	0.0000270	0.0188	
2.02	1.14	1.10	0.0386	8.03	0.0159	0.00000735	0.0159	
2.25	0.873	0.843	0.0309	8.50	0.0179	0.00000470	0.0179	
2.72	0.570	0.543	0.0258	8.95 ^a	0.0240	0.00000474	0.0240	
2.93	0.428	0.405	0.0234	9.01	0.0350	0.00000680	0.0350	
3.34	0.244	0.222	0.0220	9.40	0.0294	0.00000613	0.0294	
3.74	0.113	0.0937	0.0192	10.00	0.0358	0.00000591	0.0358	
3.89	0.0794	0.0494	0.0171	10.37	0.0716	0.0000117	0.0716	
4.00	0.0767	0.0572	0.0196	10.91	0.181	0.0000292	0.181	
4.40	0.0361	0.0184	0.0163	11.39	0.628	0.000102	0.628	
4.91	0.0233	0.00633	0.0167	12.0	2.29	0.000371	2.29	
5.43	0.0187	0.00199	0.0167	12.5	6.56	0.00106	6.56	
5.73	0.0174	0.000980	0.0164	13.0	16.4	0.00266	16.4	

^a Extrapolated to zero borate concentration.

would be so very much greater than that for a diffusion-controlled reaction (*ca.* $10^{11} \text{ l. mole}^{-1} \text{ sec}^{-1}$)¹³

In near-neutral solutions, general acid-base catalysis of hydration and dehydration was found. Thus, for 2-methylquinazoline solutions at pH 8.95, the observed rate constant varied with borate concentration as shown in

¹³ E. F. Caldin, "Fast Reactions in Solution," Blackwell, Oxford, 1964, p. 13.

can be expressed by an equation (4) similar to that for the hydration, where $a_1 = 2.0 \times 10^7$, $b_1 = 3.6 \times 10^6$, $c_1 =$

$$k_{\text{d}} = a_1(a_{\text{H}^+})^2 + b_1(a_{\text{H}^+}) + c_1 + d_1/(a_{\text{H}^+}) \quad (4)$$

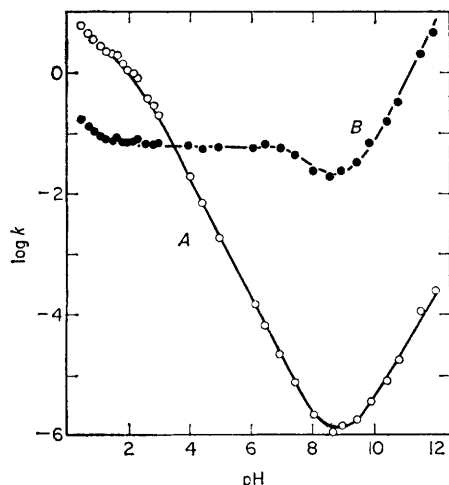
1.3×10^{-2} , and $d_1 = 6.4 \times 10^{-12}$ for quinazoline, and $a_1 =$

3.5×10^8 , $b_1 = 3.3 \times 10^6$, $c_1 = 1.9 \times 10^{-2}$, and $d_1 =$

¹⁴ E. H. Cordes and W. P. Jencks, *J. Amer. Chem. Soc.*, 1963, 85, 2843.

2.5×10^{-12} for 2-methylquinazoline. These terms are attributed to the loss of a molecule of water from the dication, the monocation, and the neutral molecule, and the loss of OH^- from the anion, respectively. Lund had suggested⁸ that in strongly acid solution dehydration proceeds by water-removal from the dication.

The pH-rate profiles in the Figure are very similar in shape to those for 1,3,8-triazanaphthalene.⁵



pH-Rate profiles at 20° for the reversible hydration of quinazoline: (A) $\log k_h$; (B) $\log k_d$; the curves are calculated by use of the constants given in the text

The constants in equations (3) and (4) have been evaluated on the basis of change in total concentration of anhydrous or hydrated quinazoline species. For comparative purposes it is preferable to express the rate constants in terms of

TABLE 3

Variation with borate concentration of rate constant, k_{obs} , for 2-methylquinazoline

Borate concn. (M)	(0)	0.0087	0.0174	0.0261
k_{obs} (sec. ⁻¹)	(0.0240)	0.0373	0.0520	0.0647

change in the kind of species believed to be directly concerned in the reaction. Thus, in weakly acid solutions this is the monocation (equation 5)



where X refers to the anhydrous, and Y to the hydrated, species. The first-order rate constants k_2 , k_{-2} , b , and b_1 are related by the identities (6) and (7).

$$k_2 = bK_{a1}^{\text{X}} \quad (6)$$

$$k_{-2} = b_1K_{a1}^{\text{Y}} = k_2/K_1 \quad (7)$$

In the absence of a knowledge of the $\text{p}K_a$ values of the dications, the reaction rates in strongly acid solutions must be expressed in terms of change in monocation concentrations (equations 8 and 9), where $k_1 = aK_{a1}^{\text{X}}$, and

$$-d[\text{XH}^+]/dt = k_1[\text{H}^+][\text{XH}^+] \quad (8)$$

$$-d[\text{YH}^+]/dt = k_{-1}[\text{H}^+][\text{YH}^+] \quad (9)$$

$$k_{-1} = a_1K_{a1}^{\text{Y}} = k_1/K_1.$$

Values of k_1 , k_{-1} , k_2 , and k_{-2} for a series of substituted

quinazolines and also some triazanaphthalenes (three of which were aza-analogues of quinazoline) are listed in Table 3, together with the pH ranges over which these constants were obtained. The pH-rate profiles appeared to be similar to those for quinazoline, and the rates could be represented by similar equations.

Although they have been obtained over a different pH range, the constants for 1,3,8-triazanaphthalene are in good agreement with values ($k_2 = \text{ca. } 24.8 \text{ sec.}^{-1}$, $k_{-2} = 0.032 \text{ sec.}^{-1}$) calculated from published⁵ results.

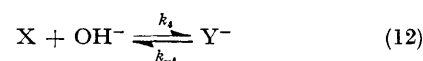
The 4-carbamoylquinazolines differed from the other quinazolines studies in their greater ease of formation of anions, by both the hydrated and the anhydrous species in alkaline solution. These anions could be distinguished from each other, and from the neutral species, by their ultraviolet spectra [for 4-carbamoylquinazoline, $\lambda_{\text{max.}} = 277 \text{ m}\mu$, $\log \epsilon = 3.82$ for the unstable hydrated anion (at pH 13; stopped-flow technique), and $\lambda_{\text{max.}} = 308 \text{ m}\mu$, $\log \epsilon = 3.48$ for the anhydrous anion (pH 15)]. Values of $\text{p}K_a^{\text{Y}}$ for anion formation by the hydrated neutral molecule were obtained by rapid-reaction measurements following addition of alkali to solutions of the (hydrated) cation, whereas equilibrated solutions afforded $\text{p}K_a^{\text{eqm}}$. From these values, and $\text{p}K_{a1}^{\text{X}}$, $\text{p}K_{a1}^{\text{Y}}$, and $\text{p}K_{a1}^{\text{eqm}}$ for the monocations, equilibrium ratios for hydrated to anhydrous species, and also $\text{p}K_a^{\text{X}}$ for anion formation, could be calculated.¹ Results are in Table 5.

Over the pH range 1–14, the pH-rate profile for reversible hydration of 4-carbamoylquinazolines, when expressed in terms of the neutral molecules as the reacting species, fitted the simple expressions (10) and (11). Values of

$$k_h = b(a_{\text{H}^+}) + d/(a_{\text{H}^+}) \quad (10)$$

$$k_d = b_1(a_{\text{H}^+}) + d_1/(a_{\text{H}^+}) \quad (11)$$

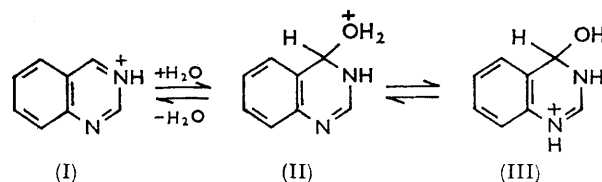
k_h and k_d were calculated from the equations for the hydration and dehydration of heterocyclic acids¹⁰ in pH regions where anion formation was important. The reactions in alkaline solution are assumed to be (12) with $k_4 = d/K_w$,



and $k_{-4} = d_1/K_a^{\text{Y}}$. Values of these constants are given in Table 6.

DISCUSSION

From the results we suggest the mechanism (I)–(III) for reversible hydration of the quinazoline cation.



The step (II) \rightleftharpoons (III) would involve a proton transfer to and from solvent water molecules. Because isoquinoline is a stronger base than quinoline, N(3) in quinazoline is probably slightly more basic than N(1), so that the anhydrous cation is probably a mixture of N(3)- and N(1)-protonated species in which the former predominates.

The making and breaking of C-O bonds (the actual addition and removal of the molecule of water) would be expected to be rate-determining steps, with the species (II) and (III) existing in dynamic equilibrium. The observed rate of the dehydration would thus depend, among other things, on the ratio [II]/[III]. A similar fast protonation step, with slow loss of water from the

molecule or a hydroxide ion on the protonated Schiff base.¹⁷ In alkaline solutions, hydroxide ion attacks the non-protonated Schiff base.¹⁷

The present value of k_{-2} (0.064 sec.⁻¹ at 20°) for quinazoline is in good agreement with that (0.10) obtained from Lund's data⁸ (at 25°?) by taking $K_1 = 35$.³

TABLE 4

First-order rate constants (sec.⁻¹) for hydration and dehydration of some substituted quinazolines and triazanaphthalenes at 20°

Compound	pH range	k_1	k_2	k_{-1}	k_{-2}
Quinazoline	1.0—3.6	—	0.84 ^a	—	0.011 ^a
	1.0—3.6	—	1.4 ^b	—	0.028 ^b
	0.5—7.0	12	2.3	0.35	0.064
	1.0—3.6	—	3.4 ^c	—	0.113 ^c
2-Me	1.0—7.0	56	0.53	1.7	0.016
4-Me	2.6—2.8	—	0.018	—	0.18
4-Et	2.0—3.0	—	0.052	—	0.071
4-Pr ^l	2.0—3.2	—	0.026	—	0.032
5-Me	0.8—3.5	16	1.1	0.92	0.058
6-Me	0.6—3.5	11	1.1	0.62	0.066
7-Me	0.3—3.0	6.4	0.43	1.9	0.13
8-Me	0.8—4.0	—	1.0	—	0.098
5-OMe	1.6—4.0	—	1.8	—	0.18
6-OMe	0.6—3.0	4.0	0.49	0.97	0.10
8-OMe	1.0—3.4	23	1.8	0.62	0.051
6-NO ₂	—	—	—	—	0.024 ^d
8-Cl	—	—	—	—	0.13 ^e
4-CONH ₂	0.4—5.0	—	0.116	—	1.47 × 10 ⁻⁴
4-CONH ₂ -2-Me	0.8—6.0	—	0.0510	—	7.40 × 10 ⁻⁵
4-CONH ₂ -2,6-Me ₂	1.0—6.0	—	0.0226	—	8.68 × 10 ⁻⁵
4-CONH ₂ -6-F-2-Me	0.6—6.0	—	0.0723	—	5.13 × 10 ⁻⁵
1,3,5-Triazanaphthalene	1.8—4.0	—	12.5	—	0.024
1,3,7-Triazanaphthalene	1.8—5.0	—	8.8	—	0.011
1,3,8-Triazanaphthalene	1.1—2.8	—	~22 ^f	—	~0.031
1,4,6-Triazanaphthalene	0.4—3.8	— ^g	0.015	— ^g	0.00010

^a At 4.3°. ^b At 12.1°. ^c At 29.5°. ^d Estimated from k_{obs} at pH = pK_{eqm} : at this pH (4.18), $k_h = k_d$. ^e Ditto, pH = 3.30. ^f Taking $pK_a^* = 1.0$ ^g Below pH 2 the rate constant was not strictly proportional to hydrogen-ion concentration, possibly because of di-hydrate formation [see T. J. Batterham, *J. Chem. Soc. (C)*, 1966, 999].

TABLE 5

Acid dissociation constants (for anion formation) and equilibrium ratios for hydrated and anhydrous 4-carbamoylquinazolines at 20°

Quinazoline	pK_a^Y	pK_a^{eqm}	pK_a^X	[Hydr. n.m.]/[Anhyd. n.m.] ^a	[Hydr. an.]/[Anhyd. an.]
4-CONH ₂	11.38 ± 0.09	13.76 ± 0.09	13.80	3.5 × 10 ⁻⁴	0.089
4-CONH ₂ -2-Me	11.45 ± 0.05	13.93 ± 0.04	14.03	6.9 × 10 ⁻⁴	0.26
4-CONH ₂ -2,6-Me ₂	11.44 ± 0.05	13.98 ± 0.08	14.03	2.8 × 10 ⁻⁴	0.11
4-CONH ₂ -6-F-2-Me	11.23 ± 0.06	13.73 ± 0.06	13.91	1.1 × 10 ⁻³	0.53

^a Personal communication from Dr. W. L. F. Armarego.

TABLE 6

Rate constants (sec.⁻¹) for the reversible hydration of 4-carbamoylquinazolines in alkaline solutions at 20°

Quinazoline	k_4	k_{-4}	pH _{min.}	Quinazoline	k_4	k_{-4}	pH _{min.}
4-CONH ₂	0.086	0.41	7.40	4-CONH ₂ -2,6-Me ₂ ...	0.038	0.30	7.85
4-CONH ₂ -2-Me	0.086	0.26	7.74	4-CONH ₂ -6-F-2-Me	0.110	0.14	7.49

O-protonated cation, is thought to occur in the acid-catalysed dehydration of aliphatic alcohols.¹⁵ The formation and hydrolysis of Schiff bases also proceed *via* a hydrated (carbinolamine) intermediate.¹⁶ In Schiff bases derived from aromatic amines the rate-determining hydration step in weakly acid or neutral solution is the nucleophilic attack of either a water

4-Methyl-substitution diminishes the rate of water addition to quinazoline 130-fold. With 4-carbamoylquinazoline the reduction is 20-fold. Steric factors arising from the need to change from a planar to a near-tetrahedral configuration about C(4) in passing from (I) to (II) probably contribute significantly to the reduction in rate when a large substituent is present on C(4).

¹⁵ D. V. Banthorpe, "Elimination Reactions," Elsevier, Amsterdam, 1963, p. 145.

¹⁶ W. P. Jencks, *Progr. Phys. Org. Chem.*, 1964, **2**, 63.

¹⁷ R. B. Martin, *J. Phys. Chem.*, 1964, **68**, 1369.

However, the relative basicities of N(1) and N(3) must also be considered because they are likely to be quite sensitive to substituent effects, as, also, is the electron-density at C(4). In 4-carbamoylquinazoline, unlike quinazoline itself, N(1) may be the more basic centre as a result of the electron-withdrawing effect of this substituent. If so, nucleophilic attack at C(4) would be expected to be further reduced, thereby at least partly offsetting the favourable inductive effect of the carbamoyl group on the electron-density at C(4).

On the other hand, whereas a 4-alkyl substituent increases the rate of dehydration, a 4-carbamoyl group considerably diminishes it. This may be owing to two effects. The electron-density at the oxygen atom (and hence the ease of *O*-protonation) depends on the electron-releasing or -withdrawing effect of the substituent on C(4). Thus, the methyl group would facilitate protonation while the carbamoyl group would retard it. Also, electron-release by the methyl group would make it easier to remove the water molecule from (II), whereas electron-withdrawal by the carbamoyl group would make it more difficult. The process (III) \rightleftharpoons (II) involves no stereochemical change at C(4).

The rate constants for the attack of a water molecule on the anhydrous cations (k_2 in Table 3) show some

general trends. Thus electron-donating groups in the benzene ring reduce the rate of hydration, while molecules with electron-withdrawing substituents in this ring (*e.g.*, 1,3,4-triazanaphthalenes) show an increased rate of hydration. However, no simple relationship is to be expected for substituent effects at different positions in quinazoline. Factors which cannot, at present, be discussed quantitatively include the variations in the relative basicity of N(1) and N(3) as the substituents are varied, and the resulting effects on the electron-density at C(4). Also, in the triazanaphthalenes, the nitrogen atom that undergoes protonation is probably not in the ring to which water addition occurs.³

The temperature range of the results for quinazoline in Table 4 enables a rough estimate to be made of the Arrhenius parameters for the hydration and dehydration of the quinazoline monocation. At 20° these values are $\Delta E_a = 9.3 \pm 0.5$ kcal.mole⁻¹ and $\Delta S^\ddagger = -27 \pm 2$ cal. deg.⁻¹ for hydration, and $\Delta E_a = 15.3 \pm 0.5$ kcal.mole⁻¹ and $\Delta S^\ddagger = -14 \pm 2$ cal. deg.⁻¹ for dehydration.

We thank Dr. W. L. F. Armarego for the heterocyclic compounds. One of us (J. W. B.) acknowledges a Commonwealth of Australia Postgraduate Scholarship.

[7/035 Received, January 10th, 1967]