Mechanism of Alkaline Cyclization of 2-(Substituted benzamido)benzamides to 4-Quinazolinones

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The title amides cyclize rapidly to the corresponding quinazolin-4-ones in aqueous alkaline solution at 25 °C; the pseudo-first-order rate constants fit the empirical equation $k_{obs} = k_{max}[OH^-]/(K_m + [OH^-] + [OH^-]^2K_{m'})$ where $K_{m'}$ is essentially zero for all except the 4-nitro species. The value of K_m measures the ionization of the neutral amide **1** to *nonproductive* conjugate base **2**. Studies of the cyclization in alkali of 2-benzamido-*N*-methylbenzamide (**1i**) and 2-(N-methylbenzamido)benzamide (**1j**) indicate that **7** carries over 99% of the reaction flux and that the tautomer **8** does not contribute significantly. The ratio k_{max}/K_m is a composite rate constant first order in **1** and first order in $[OH^-]$. The value of the Hammett ϱ for k_{max}/K_m (0.67) is consistent with the above scheme where decomposition of **7** is rate limiting.

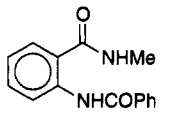
Introduction

4(3*H*)-Quinazolinones are well known for their pharmacological activity,[1-4] and methods of synthesis of these useful heterocycles have been reviewed by Armarego[1,2a] and Taylor and Shvo.[2b] Although quinazolinones have been studied for many years, their synthesis often requires relatively extreme conditions. High yields have been obtained for the preparation of quinazolinones from 2-amidobenzonitriles with alkaline hydrogen peroxide. The reaction probably involves formation of an amide from the action of the hydroperoxy anion on the nitrile which then cyclizes in a specific base-catalyzed dehydration step.[5-7] The synthesis of quinazolinones from acetanthranils by reacting with amines in aqueous media is also thought to involve the 2-(acylamido)benzamide.[8] Meyer and Wagner[9] confirmed the existence of a 2-benzamidobenzamide intermediate in the reaction of anthranilic acid with benzamide. A facile synthesis of quinazolinones involves reaction of 2-(acylamido)-benzonitriles with strong acid followed by strong base.[10] Direct synthesis of 4-quinazolinones from 2-(acylamido)-benzamide in alkali was reported by Partridge and Butler.[11]

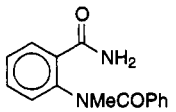
Amides often react sluggishly with nucleophiles in aqueous solution, and it is therefore of interest to study the kinetics of the facile alkaline-catalyzed cyclization of a series of 2-(substituted benzamido)benzamides **1a–h**, 2-benzamido-*N*-methylbenzamide (**1i**), and 2-(*N*-methylbenzamido)benzamide (**1j**) in order to elucidate the mechanism (Scheme 1) of this useful synthetic procedure.

Experimental Section

Materials. 2-Benzamidobenzamides **1a–h** (Table 1) were prepared by stirring the corresponding benzonitrile (1 g, from



1i



1j

a previous study[12]) overnight with HCl (5 M, 25 mL). The resultant suspension was then filtered and recrystallized from methanol.

4(3*H*)-Quinazolinones were prepared by stirring a solution of the corresponding 2-benzamidobenzamide (1 g) in KOH solution (1 M, 25 mL) for 2 h after which the pH was adjusted to pH 7.[11] The resultant precipitate was isolated and recrystallized from aqueous methanol to give a high yield of the 4-quinazolinone. 2-(*N*-Methylamino)benzamide and 2-amino-*N*-methylbenzamide were prepared by the method of Clark and Wagner[13] from *N*-methylisatoic anhydride and isatoic anhydride, respectively, by stirring with the appropriate amine. The aminobenzamides were then treated with benzoyl chloride in pyridine solvent to yield the 2-benzamidobenzamides **1j** and **1i**, respectively, in good yield. Recrystallization from ethanol gave analytically pure materials (Table 1).

The *N*-methyl-4-quinazolinone from **1i** was prepared by the method of Partridge and Butler[11] by refluxing the benzamide (1.5 g) in 5% aqueous NaOH (60 mL) with 10 mL of ethanol for 1.5 h. The product was recrystallized from ethanol. In the case of **1j** the reaction was complete in about 15 min without reflux and at pH 9–10.

The purity of the products was checked by TLC on Kieselgel plates, using MeOH/benzene eluent, by NMR, IR, and elemental analysis (see Table 1), and the structural identities of the compounds were checked by comparing melting points with literature values (where possible) and by NMR and IR spectroscopy.

Other materials, such as buffer components, were of analytical reagent grade; water employed in the kinetic studies was double distilled from glass. TLC plates of aluminium foil coated with silica gel (Merck Kieselgel 60 F254) were obtained from Aldrich.

Methods. Kinetics were measured by adding a stock solution of the benzamidobenzamide in dioxane (50 μL, ca. 0.1 mM) on the flattened tip of a glass rod to a solution of KOH (2.5 mL) at the required strength in a silica cell in the thermostated cell compartment of a Pye-Unicam SP800 or Perkin-Elmer Lambda 5 spectrophotometer. The progress of the reaction was monitored by repetitive scanning of the UV spectrum, and the wavelength 300 nm was chosen to study the kinetics of each member of the series **1a–h** between 0.1 and 1 M at 25 °C; the ionic strengths were maintained at 1 M

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Table 1. Physical and Analytical Data for 2-(Substituted benzamido)benzamides and 4(3*H*)-2-(Substituted phenyl)quinazolin-4-ones[a]

		found				calcd		
	mp/°C (lit. mp)	N	C	H	formula	N	C	H
2-(Substituted benzamido)benzamides								
1a, parent	218–9 (218)[b]	11.66	70.09	4.79	$C_{14}H_{12}N_2O_2$	11.66	69.68	5.04
1b, 4-methoxy	210–12	10.28	66.55	5.29	$C_{15}H_{14}N_2O_3$	10.36	66.66	5.22
1c, 4-methyl	201–2 (204–5)[c]	10.94	70.65	5.52	$C_{15}H_{14}N_2O_2$	11.01	70.86	5.55
1d, 3-methyl	203–5	10.99	70.94	5.68	$C_{15}H_{14}N_2O_2$	11.01	70.86	5.55
1e, 4-chloro	182–3 (200.5)[c]	10.28	61.44	3.78	$C_{14}H_{11}ClN_2O_2$	10.20	61.21	4.04
1f, 3-chloro	184–6	10.23	61.39	3.95	$C_{14}H_{11}ClN_2O_2$	10.20	61.21	4.04
1g, 3-nitro	229–30 (230)[c]	14.11	59.00	3.86	$C_{14}H_{11}N_3O_4$	14.75	58.94	3.86
1h, 4-nitro	235–6 (235–6)[c]	14.53	58.80	3.62	$C_{14}H_{11}N_3O_4$	14.75	58.94	3.86
2-Benzamido-*N*-methylbenzamide (**1i**)	155–6 (158–60)[e]	11.06	70.77	5.49	$C_{15}H_{14}N_2O_2$	11.01	70.86	5.55
2-(*N*-Methylbenzamido)benzamide (**1j**)	130–2	11.02	71.17	5.39	$C_{15}H_{14}N_2O_2$	11.01	70.86	5.55
4(3*H*)-2-(Substituted phenyl)quinazolin-4-ones								
parent	236–7 (238),[d,f] (236)[b]							
methoxy	252–3 (247)[b,f]	11.19	71.57	4.41	$C_{15}H_{12}N_2O_2$	11.1	71.42	4.79
4-methyl	243–4 (241),[b,f] (241–2)[c]							
3-methyl	219–20	11.84	76.26	5.07	$C_{15}H_{12}N_2O$	11.86	76.25	5.12
4-chloro	296–7 (306)[c]							
3-chloro	300–2	10.90	65.31	3.26	$C_{14}H_9ClN_2O$	10.91	65.51	3.53
3-nitro	>300 (>300, 354)[f]							
4-nitro	>300 (354),[c] (365)[f]							
3-Methyl-2-phenyl-4(3*H*)-quinazolinone	135–6 (136–8)[e]							
1-Methyl-2-phenyl-4(1*H*)-quinazolinone	163–64	12.33	75.98	5.01	$C_{15}H_{12}N_2O$	11.86	76.25	5.12

[a] Literature compounds were characterized only by melting point and spectroscopic data except where indicated. [b] Stephen, H.; Wadge, G. *J. Chem. Soc.* **1956**, 4420. [c] Zentmyer, D. T.; Wagner, E. C. *J. Org. Chem.* **1949**, *14*, 967. [d] Tavernier, B. H.; de Cat, A. H. Belg. Pat. 565,656, 1958; *Chem. Abstr.* **1960**, *54*, 15037g. [e] Jackman, G. B.; Petrow, V.; Stephenson, O. *J. Pharm. Pharmacol.* **1960**, *12*, 529. [f] Smith, T. A. K.; Stephen, H. *Tetrahedron* **1957**, *1*, 38.

with added KCl. The optical density (A_t) was recorded as a function of time with a Servoscribe recording potentiometer, and pseudo-first-order rate constants were obtained from linear plots of $\log(A_{infinity} - A_t)$ versus time. The final spectrum for a specimen run for each benzamidobenzamide was checked against the spectrum of an authentic sample of the corresponding quinazolinone. The identity of the product isolated from the reaction of 2-benzamidobenzamide in basic solution was checked by TLC (MeOH/benzene and Kieselgel plates) using 2-phenyl-4(3*H*)-quinazolinone as standard. The benzamidobenzamide concentration in the product analysis study was set at 100 mg per 20 mL of the solvent and the reaction allowed to run at 25 °C for a time period calculated from the kinetic data to ensure completion. The product was extracted with chloroform and then subjected to TLC analysis.

Results

The products of the reaction of 2-(substituted benzamido)benzamides **1a–j** in alkaline solution were shown to be the corresponding 4-quinazolinone by product isolation in the case of the parent and by UV-spectral analysis under the kinetic conditions and comparison with the spectra of the material synthesized unambiguously (Table 1).

The rate constants for the cyclizations for **1a–j** obeyed good pseudo-first-order kinetics up to greater than 90% of the total reaction. The data are recorded in Table 2 for varying concentrations of hydroxide ion concentration. The pseudo-first-order rate constants (k_{obs}) possessed a nonlinear dependence on hydroxide ion concentration (eq 1). A small value of k_{obs} was observed at 50 °C at pH 9.0 for **1a** (essentially zero $[OH^-]$ concentration); the values of k_{obs} at $[OH^-] = 0$ were zero within experimental error at 25 °C for **1a–h**. The parameter K_m is essentially a

$$k_{obs} = k_{max}[OH^-]/(K_m + [OH^-]) \quad (1)$$

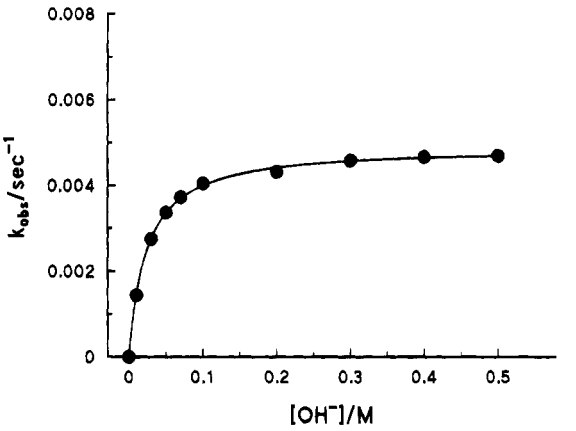


Figure 1. Dependence on hydroxide ion concentration of the rate constants for reaction of 2-(3-chlorobenzamido)benzamide. Data and conditions are as given in Table 2. Line is calculated from eq 1 with parameters from Table 2.

composite ionization constant for the neutral benzamidobenzamide. The kinetics of the cyclization of the 4-nitrobenzoyl derivative **1h** exhibit a decrease in rate constant as the hydroxide ion concentration increases above 0.1 M, and this is considered to be due to a second ionization (K_m') to yield an unreactive dianion **4**. In this case the empirical rate law for the kinetics follows eq 2.

$$k_{obs} = k_{max}[OH^-]/(K_m + [OH^-] + [OH^-]^2K_m') \quad (2)$$

Figure 1 illustrates the dependence of the observed rate constants on hydroxide ion concentration for the 3-chlorobenzamide species (eq 1), and that for the 4-nitrobenzamide species (eq 2) is illustrated in Figure 2.

The parameters k_{max} and K_m are recorded in Table 2 but K_m' is not known with reasonable accuracy except

Table 2. Reaction of 2-(Substituted benzamido)benzamides in Aqueous Alkali[a]

[OH]/M	4-MeO (1b)	4-Me (1c)	3-Me (1d)	parent (1a)	4-Cl (1e)	3-Cl (1f)	3-NO_2 (1g)	4-NO_2 (1h)	(1i)[b]	(1j)[c]
0	0	0	0	0	0	0	0	0		
0.01						1.44	1.79			
0.015										
0.02	1.36	1.29	1.40					3.84		
0.03				2.03	2.60	2.75	3.67			
0.035										
0.04	2.11	1.99	2.15					4.86		15
0.05				2.68	3.24	3.36	4.22			
0.06	2.89	2.73	2.55					5.33		25
0.07				3.24	3.43	3.72	4.34			
0.08	3.04	3.14	3.05					5.41		32
0.1	3.30	3.36	3.16	3.47	3.98	4.04	4.51	5.59	0.256	37
0.012										44
0.14							4.46			54
0.15										59.1
0.16										
0.2	4.01	3.94	3.96	4.46	4.41	4.31	4.41	5.44	0.291	
0.3	4.26	4.24	4.21	4.65	4.51	4.57	4.39	5.34	0.359	
0.4	4.51	4.46	4.52	5.02	4.41	4.65	4.31	5.11	0.418	
0.5	4.49	4.53	4.53	5.12	4.41	4.68	3.88			
k_{max}[a] × 1000/s^{-1}	5.20 ± 0.26	5.33 ± 0.3	4.89 ± 0.19	5.33 ± 0.26	5.34 ± 0.22	4.95 ± 0.080	5.64 ± 0.00026	6.78 ± 0.13		
K_m/M	0.0544 ± 0.004	0.0599 ± 0.007	0.0519 ± 0.0045	0.0491 ± 0.0055	0.0326 ± 0.0036	0.0237 ± 0.0012	0.0178 ± 0.0027	0.0147 ± 0.001		
K_m/M^{-1}								0.745 ± 0.076		
r	0.9987	0.9987	0.9992	0.9990	0.9989	0.9996	0.9952	0.9996		

[a] Conditions: 25 °C, ionic strength maintained at 0.5 M with KCl stock solution. Pseudo-first-order rate constants have the units 10^{-3} s^{-1}. [b] 50 °C; k_{OH} = 5.54 ± 0.48 × 10^{-4} M^{-1} s^{-1} and k_0 = 1.93 ± 0.13 × 10^{-4} s^{-1}. [c] 25 °C; k_{OH} = 0.361 ± 0.014 M^{-1} s^{-1}. This amide exhibited a k_{obs} value of 2.29 × 10^{-4} s^{-1} at pH 9.5 and 50 °C.

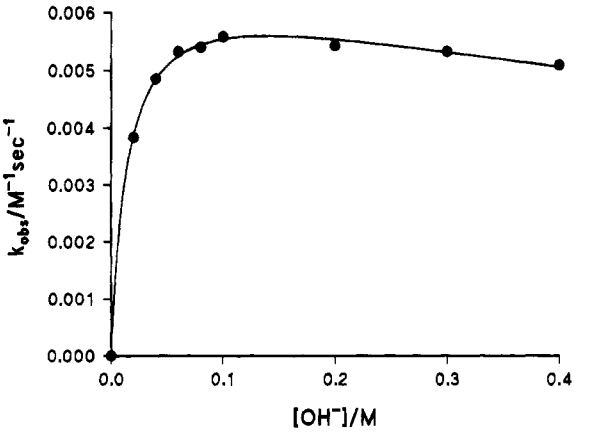


Figure 2. Dependence on hydroxide ion concentration of the rate constants for reaction of 2-(4-nitrobenzamido)benzamide. Data and conditions are as given in Table 2. Line is calculated from eq 2 with parameters from Table 2.

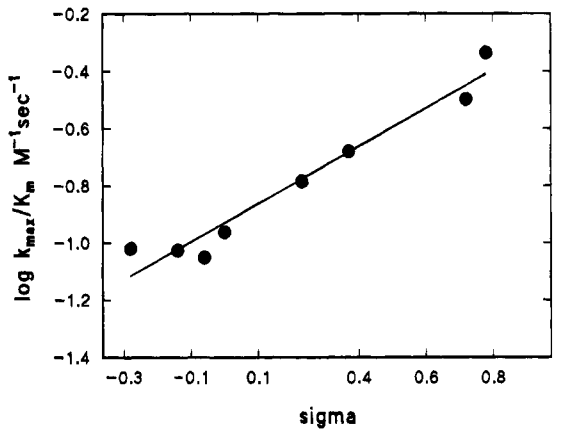


Figure 3. Hammett σ dependence for the cyclization of 2-benzamidobenzamides catalyzed by hydroxide ion (k_{max}/K_m). Data and conditions are from Table 2; the line is calculated from eqs 3 and 4.

for the 4-nitro-substituted species. The data for k_{max}/K_m and K_m fit Hammett equations (eqs 3 and 4). Second-

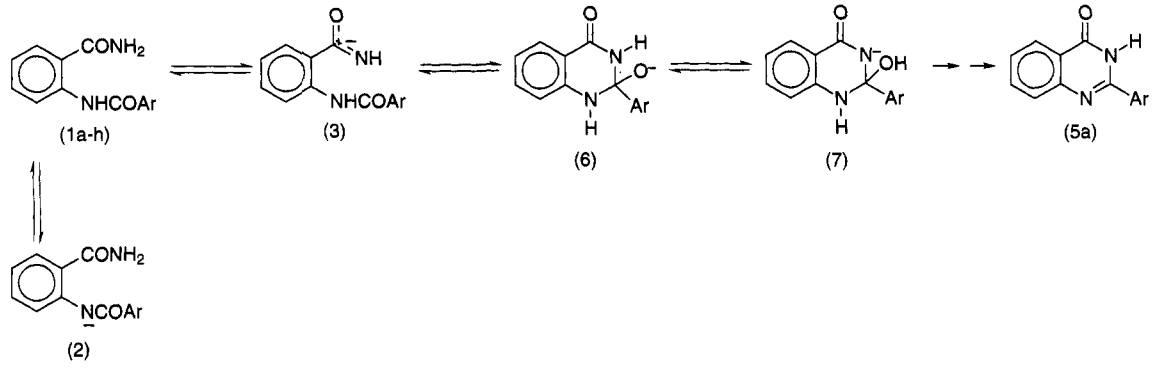
$$\log k_{max}/K_m = 0.67 \pm 0.06\sigma - 0.93 \pm 0.03 \; (r = 0.9572) \quad (3)$$

$$\log K_m = -0.59 \pm 0.06\sigma - 1.35 \pm 0.02 \; (r = 0.9731) \quad (4)$$

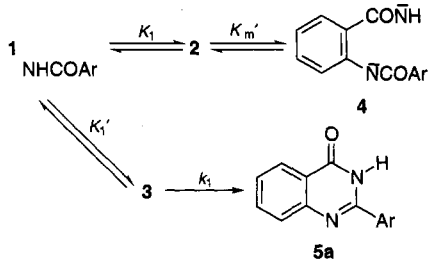
order rate constants (k_{OH}) for the alkaline cyclization of **1i** and **1j** are also given in Table 2.

Synthesis of 4-(3*H*)-quinazolinones was attempted via the method of Showell,[10] but unless treatment under alkaline conditions was employed only the acylamidobenzamide was isolated. The function of the base is not simply to neutralize the HCl which was used to react with the 2-acylamidonitrile reactant but is necessary to complete the reaction. The product we obtained under conditions where alkali is used only as a neutralizing agent was the 2-acylamidobenzamide, and indeed the reaction gave an excellent synthesis of these amides. The amides are relatively stable to acid and require a slightly more prolonged treatment in alkali than simple basification in order to achieve the quinazolinone product. The product of the cyclization of species **1a**–**h** is likely to be the 2-aryl-4(3*H*)-quinazolinone tautomer **5a** rather than

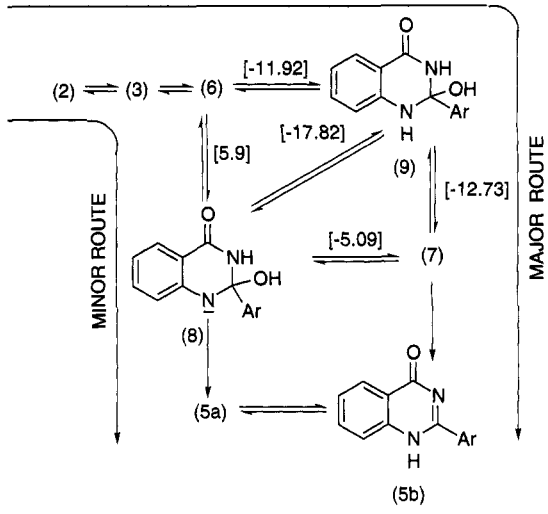
Scheme 1



Scheme 2



Scheme 3



the 4(1*H*) isomer **5b**; Hagiwara, Kurihara, and Yoda[14] showed by UV, IR, and NMR spectroscopic techniques that 2-substituted 4(3*H*)-quinazolinones were the preferred tautomers. Hearn, Morton, and Simpson[15] showed that the 4(1*H*) tautomers were the least favored.

Discussion

The empirical rate law of eq 1 can be derived from the mechanism given in Scheme 2 neglecting the ionization of the monoanion **2**. Qualitatively, the inclusion of the K_m' term gives rise to a dependence on hydroxide ion concentration involving a decrease in reactivity at higher concentrations of hydroxide ion due to formation of the unreactive dianionic species **4**.

The calculated value of pK_a (see appendix) for the ionization of **1a** to **2** (12.69) is close to that (12.70) calculated from the kinetically determined parameter $pK_a = pK_w - pK_m$ and confirms that the major ionized component is not **3** but is **2** which cannot give **5a** and is thus a nonproductive anion. The ϱ value for K_m is consistent with the ionization of an NH group adjacent to a carbonyl function adjacent to the aryl function. The ionization of **1** to **3** is expected to have a negligable ϱ value against the variation of substituents in the benzoyl group.

The overall rate equation assuming equilibrium between **1** and the two ionized species **2** and **3** may be deduced from Scheme 2 to be eq 5 (it is also assumed

$$k_{obs} = k_1K_1[OH^-]/(K_1 + K_{1'})([OH^-] + K_1K_1/(K_1 + K_{1'})) \quad (5)$$

that the second ionization is not important, except in the case of the 4-nitro species). Thus, $k_{max} = k_1K_1/(K_1 + K_{1'})$ and $K_m = K_{1'}K_1/(K_1 + K_{1'})$. Simplification is possible because K_m is essentially equal to K_1 so that $K_1 < K_{1'}$ and hence $k_{max} = k_1K_1/K_{1'}$. (The parameters $K_{1'}$ and K_1 are, respectively, equal to $K_w/K_{a'}$ and K_w/K_a; K_w, K_a, and $K_{a'}$ are, respectively, the ionic product of water and the ionization constants of **1** to give **3** and **1** to give **2**.) The reaction of **3** to give **5** thus has a rate constant $k_1 = k_{max}K_1/K_m$, and since $K_{1'}$ is expected to be independent of substituent in the aryl group the ϱ value for k_1 is the same as that for k_{max}/K_m (0.67).

The tetrahedral intermediate first formed in cyclization is **6**, but this is required to tautomerize to **7** and **8** (Scheme 3) prior to giving the product. The absence of buffer catalysis is consistent with rapid transfer of proton between the tautomeric forms **6**, **7**, and **8**. The expulsion of an hydroxide ion is assisted by the relatively high internal nucleophilicity of the nitrogen anions in **7** or **8** expected from their high basicities (pK_a's of the conjugate acids are calculated to be 15.4 and 17.82, respectively), by the fact that the reaction is intramolecular and because of the stability of the final product.

The (methylbenzamido)benzamides **1j** and **1i** have, respectively, second-order rate constants of 0.361 M^{-1} s^{-1} at 25 °C and 5.54 × 10^{-4} M^{-1} s^{-1} at 50 °C. The second-order rate constant for **1j** (where position 1 is blocked) is close to that of **1a** (the parent); thus, the tautomer **8** is not a major contributor to the reaction flux (Scheme 3). This is confirmed by consideration of the apparent second-order rate constant (k_{cat}/K_m) for **1i** (where the 3-position is blocked) which is some 200-fold smaller even at the higher temperature which is required to obtain the observed rate constant. The ratio of the rate constants for **1j**–**i** indicates that the proportion of reaction flux through **8** is about 0.15% of the total. The various

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pK_a values calculated from the free energy equations enable the equilibrium constants (pK_e) to be calculated for the tautomeric equilibria in Scheme 3; the figures given in brackets refer to $-\log K_a$ or $-\log K_e$ and the equilibrium constants are defined for reaction left to right or top to bottom. Consideration of the calculated pK_a values indicates that species **7** is the most thermodynamically stable of the triad of tautomers **6**, **7**, and **8** as well as taking the major part of the reaction flux; it is present at a concentration some $10^{5.09}$-fold greater than that of **8** in the case of the parent species (see Appendix for an appreciation of the confidence limit on this equilibrium constant).

The work of Shames and Byers[16] and of Kirsch and co-workers[17] indicates that the ρ value for formation of a tetrahedral intermediate from a nucleophile and a substituted benzoyl species is about 2. The observed ρ value of 0.67 indicates that either the transition state for a rate-limiting step **3**−**6** is earlier than in most reactions at a benzoyl group or, most probably, that the rate-limiting step is subsequent to formation of **7** and involves a component of electron withdrawal. It is unlikely that the equilibria between **6**, **7**, and **8** will have significant ρ values as the positioning of the negative charge relative to the substituent change does not alter very much, and we therefore conclude that decomposition of **7** is rate limiting. The proposed rate-limiting step involves expulsion of hydroxide ion, and the substituents "see" an overall low buildup of negative charge comprising electron buildup in the formation of **7** and electron withdrawal in its decomposition. It is therefore possible to compute the Hammett ρ for the decomposition of **7**; assuming formation of **6** has a ρ of 2 and the equilibrium between **6** and **7** has a negligible ρ value then the overall ρ of 0.67 means that the ρ for decomposition of **7** is −1.33. This value of ρ is consistent with substantial fission of the 2-C−OH bond of **7** in the transition state because the decomposition of **7** to **5b** is expected to have a $\rho_{equilib}$ value of about 2. The substantial extent of bond fission is reasonable considering that the hydroxide ion is a poor leaving group.

The breakdown of **7** to **5b** as the rate-determining step and taking the major part of the reaction flux are interesting results in view of the fact that **7** is substantially more thermodynamically stable than **8**. The higher basicity of N3 of **8** compared with that of N1 in **7** is not sufficient to cause the reaction flux to be taken by **8**. This means that the rate constant for expulsion of hydroxide ion has a less than unit dependence on the basicity of the nitrogen. Although **8** is expected to be more reactive than **7** it is simply not present in suffient quantity for this route to compete with expulsion from **7**.

It is recognized that once the bicyclic tetrahedral intermediate is formed from the dianion **4** then expulsion of the hydroxide ion would be very rapid (it is assumed that the intervening proton transfer step will be fast). The simplest explanation of the unreactivity of the dianion is electrostatic repulsion between the anionic nucleophile and anionic electrophile in **4** which dramatically retards formation of the tetrahedral intermediate. Benzamides **1** with substituents other than the 4-nitro group do not suffer any retardation in rate at high alkalinity due to the weaker acidity of these species than **1h**.

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Appendix

Calculation of pK_a Values. The pK_a values of the various tautomeric parent (Ar = Ph) species **1a**, **6**, **7**, and **8** may be calculated using techniques described by Fox and Jencks[18] and Perrin, Dempsey, and Serjeant.[19] The pK_a of species **9** may be calculated from the Taft equation for the alcohol ($R_1R_2R_3COH$) (eq 6)

$$pK_a = C_1 - 1.42\sum\sigma^* \quad (6)$$

assuming that the ρ^* value (1.42) is the same for primary as for tertiary alcohols.[19] Primary alcohols have pK_a's governed by eq 7[19] so that substituting σ^* for hydrogens

$$pK_a = 15.9 - 1.42\sigma^* \quad (7)$$

(+0.49) into eq 6 gives $pK_a = C_1 - 1.42(2 \times 0.49) - 1.42\sigma^* = C_1 - 1.39 - 1.42\sigma^*$ and thus $C_1 = 17.29$. The derived value of C_1 is close to that obtained by Guthrie.[20] Substituting values for C_1 and σ^* into eq 6 (PhCONH, 1.68; Ph, 0.75; PhNH, 1.35) gives pK_a = 11.92 for the alcohol of **9**. The value of σ^* for PhNH− is not available and may be calculated from eq 6 and the experimental pK_a of 1,3-diphenyl-2-hydroxyimidazolidine (12.75).[21]

The pK_a of the amido NH of species **9** is calculated from the Taft equation (8) for the analogue **10**. Equation 9[19]

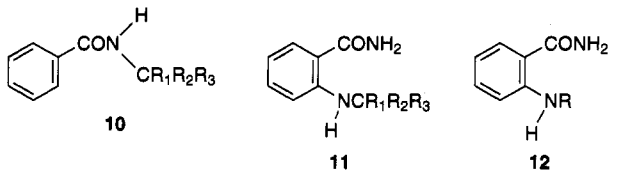
$$pK_a = C_2 - 1.24\sum\sigma^* \quad (8)$$

$$pK_a = 22.0 - 3.1\sum\sigma^* \quad (9)$$

correlates the pK_a of the amido species RNHCONPh; the pK_a of **10** ($R_1 = R_2 = R_3 = H$) is thus calculated to be 15.18 (σ^* values from ref 19). Substituting into eq 8 for species **10** ($R_1 = R_2 = R_3 = H$) gives $C_2 = 17.00$. The pK_a of the amido NH of **9** is then calculated to be 12.73 by substituting σ^* values for Ph, OH, and PhNH and the value of C_2 into eq 8.

The pK_a of the anilino NH group of **9** may be calculated from the Taft equation (10) for the standard amine **11**

$$pK_a = C_3 - 1.32\sum\sigma^* \quad (10)$$



10 **11** **12**

the value of the ρ^* (−1.32) is obtained from Fox and Jencks.[18] The pK_a of 2-carboxamidoaniline (20.21) is obtained from the pK_a of the corresponding anilinium species via eq 11 derived from the data of Stewart and

$$pK_a = 18.0 - 0.60pK_a\text{anilinium} \quad (11)$$

(16) Shames, S. L.; Byers, L. D. *J. Am. Chem. Soc.* **1981**, *103*, 6170.
(17) Kirsch, J. F.; Clewell, W.; Simon, A. *J. Org. Chem.* **1968**, *33*, 127.
(18) Fox, J. P.; Jencks, W. P. *J. Am. Chem. Soc.* **1974**, *96*, 1436.
(19) Perrin, D. D.; Dempsey, B.; Serjeant, E. P. *pK_a Predictions for Organic Acids and Bases*; Chapman and Hall: London, 1981.
(20) Guthrie, J. P. *J. Am. Chem. Soc.* **1978**, *100*, 5892.
(21) Robinson, D. R. *J. Am. Chem. Soc.* **1970**, *92*, 3138.

O'Donnell.[22] Assuming the effect of R on the pK_a in analogue **12** is given by eq 12,[18] then substituting for $\sigma^* = 0.49$ gives $C_4 = 20.86$. The value of C_4 equals the pK_a

$$pK_a = C_4 - 1.32\sigma^* \quad (12)$$

of **11** when $R_1 = R_2 = R_3 = H$; thus, $C_3 = 20.86 + 1.32(0.49 + 0.49 + 0.49) = 22.80$. Substituting σ^* for R_1 = OH, R_2 = Ph, and R_3 = NHCOPh[19] and C_1 into eq 10 gives 17.82 as the pK_a of the anilino group of **9**.

(22) Stewart, R.; O'Donnell, J. P. *Can. J. Chem.* **1964**, *42*, 1694.

The pK_a's of **1** for the formation of **2** and **3** may be calculated from eq 9 using the appropriate σ^* values to be, respectively, 12.69 and 13.61.

The errors in the estimates of the pK_a values are discussed in the monograph authored by Perrin, Dempsey, and Serjeant and are probably accurate to better than 0.5 pK units. Further manipulation as in the estimation of the equilibrium constants will naturally increase the uncertainty, and it is only safe to consider large differences. The equilibrium constant for the tautomerization between **8** and **7** is probably accurate to less than 1 logarithmic unit, and the conclusion that **8** is substantially less stable than **7** is sound.