

Note

Kinetics of hydrolysis of 2-methyl/phenyl-3-(2'-hydroxybenzalamino)-quinazolin-4(3H)-one

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Kinetics of hydrolysis of 2-methyl-3-(2'-hydroxybenzalamino)quinazolin-4(3H)-one (MHBQ) and 2-phenyl-3-(2'-hydroxybenzalamino)quinazolin-4(3H)-one (PHBQ) have been studied. Rate coefficients have been measured for the alkaline hydrolysis of MHBQ and PHBQ in 70% (v/v) dioxane-water at various temperatures. The enthalpies and entropies of activation have been evaluated. The hydrolysis of MHBQ and PHBQ follows first order kinetics in both the substrate and the base. The relative rates of hydrolysis and activation parameters have been used to suggest the mechanism of the reactions.

Quinazoline compounds are reported to be physiologically and pharmacologically active and find application in the treatment of several diseases like leprosy and mental disorder. These compounds have also been used as antibacterial, antifungal, antitubercular, anticonvulsant, antipyretic, antimoebic, insecticidal, herbicidal, anti-fertile and plant growth regulating agents¹⁻⁵. Some of these compounds are also known to induce sedation and have proved to possess hypnotic activity.

Even though quinazolines possess various applications in biological and pharmacological field, the investigations in general, particularly the studies of kinetics of hydrolysis on these compounds are very scanty. In view of this, the present work throws light on the kinetics of hydrolysis of these compounds. Such studies will provide detailed mechanism of these compounds when they act as drugs.

The chemistry of drug action and drug metabolism have acquired much importance in pharmaco kinetics because of the fact that synthetic drugs are used

enormously in which the drug action is due to the presence of hydrolysable groups like $-\text{CH}=\text{N}-$, $-\text{CO}-\text{N}-$, $-\text{CO}-\text{O}-$, etc. Hence, the studies on kinetics of hydrolysis of these sites in a variety of new and existing molecules assume importance. In the present note, an investigation on the mechanism of the alkaline hydrolysis of 2-methyl-3-(2'-hydroxybenzalamino)quinazolin-4(3H)-one (MHBQ) and 2-phenyl-3-(2'-hydroxybenzalamino)quinazolin-4(3H)-one (PHBQ) in 70-30% (v/v) dioxane-water are reported.

Experimental Section

All the chemicals used were of AnalaR grade. The procedures for the preparation of MHBQ and PHBQ are used as reported in the literature⁶. Melting points of the MHBQ and PHBQ after repeated recrystallization and drying under reduced pressure were in agreement with the reported values⁶. Structure and purity of the compounds were monitored by IR, NMR and mass spectral data. The solvent dioxane was purified as reported in the literature⁷. The products of the reactions as discussed in the results section were identified by comparing the UV spectra with standards under identical conditions.

Kinetic measurements

A Shimadzu Model UV-160A Ratio Recording Spectrophotometer was used for recording the spectra and for other kinetic measurements with its double walled cuvet holders thermostatted by an Insref model cryostatic circulating liquid bath with a temperature stability of $\pm 1^\circ\text{C}$ between 20° and 60°C. The spectra were scanned repetitively in the first instance to determine the best single wavelength for monitoring the kinetics. Kinetics were measured by observing the increase in absorbance as a function of time at 409 and 380 nm for MHBQ and PHBQ respectively. Appropriate reagent blanks were used as reference solutions. Reactions were initiated by adding an aliquot (1 mL) of the stock solution of the substrate to the NaOH solution (9 mL) in 70-30% dioxane-water in an iodination flask. An aliquot of the mixture was immediately transferred into the cuvet in the thermostatted cell compartment of spectrophotometer. Pseudo first order rate constants were ob-

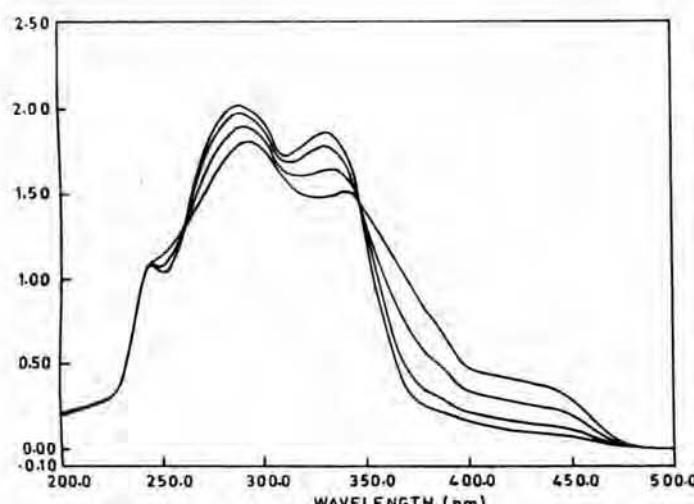
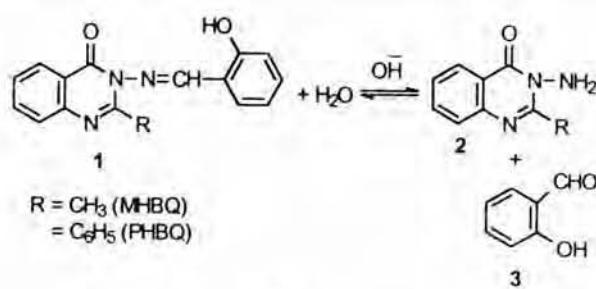


Figure 1—Repetitive spectral scans of PHBQ in 0.01 M NaOH at 25°C

Table I—Effect of [Substrate] on k_{obs} for hydrolysis of MHBQ and PHBQ

$[MHBQ] \times 10^4$ mol dm ⁻³	$k_{obs} \times 10^5$ (s ⁻¹)	$[PHBQ] \times 10^5$ mol dm ⁻³	$k_{obs} \times 10^5$ (s ⁻¹)
0.29	7.31	0.42	12.50
0.78	7.30	0.84	12.49
1.55	7.30	1.68	12.50
3.10	7.32	3.36	12.53
6.55	7.30	6.72	12.48

$[OH^-] = 3.67 \times 10^{-3}$ mol dm⁻³, Temp=40°C, Dioxane-Water 70-30% (v/v)



Scheme I

tained from the linear plots of $\log A_\alpha - A_t$ against time or by the use of curve fitting software. Here, A_α and A_t are absorbances of the reaction mixture at given time and residual respectively. The kinetic runs were reproducible within $\pm 5\%$.

Results

The time variant repetitive scan spectral profiles of PHBQ at pH 10 is shown in Figure 1. Isosbestic

points are observed in this and also in the spectra of MHBQ, studied. Hence, it may be suggested that there are only two absorbing species throughout the course of the reaction and that the mechanism might be uniform. The products of the hydrolysis reaction of substrate **1** were found to be 2-methyl/phenyl-3-aminoquinazoline-4(3H)-one **2** and salicylaldehyde **3** and the overall hydrolysis reaction may be represented stoichiometrically as shown in Scheme I.

To study the dependence of the rate of hydrolysis on [Substrate], the experiments were set-up under the conditions where $[OH^-] \gg [Substrate]$ in 70-30% (v/v) dioxane-water at constant temperature.

Effect of [Substrate]

The concentration of substrate has been varied from 0.39×10^{-4} to 6.55×10^{-4} M for MHBQ and 0.42×10^{-5} to 6.72×10^{-5} M for PHBQ at fixed concentration of hydroxide. Variation of $\log (A_\alpha - A_t)$ against time is linear ($R^2 = 0.999$). The pseudo-first order rate constants (k_{obs}) at different [Substrate] are presented in Table I. The data of rate constants are near constant with concentrations of the substrate indicating that the reaction follows first order kinetics with respect to the substrate.

Effect of $[OH^-]$

Kinetics runs have been carried out at different OH^- concentrations ranging from 0.23×10^{-3} to 3.67×10^{-3} M at fixed substrate concentration. The observed rate constants (k_{obs}) are collected in Table II. These constants increase linearly with the increase in $[OH^-]$. The variation of $\log k_{obs}$ against $\log [OH^-]$ is linear ($R^2 = 0.999$) with a slope of unity indicating the first order dependence in hydroxide ion. It is also supported by second order rate constants (k_2) (cf. Table II).

Effect of temperature

To study the effect of temperature on the rate of reaction, the reactions have been carried at different temperatures (20-60°C) in 70-30% (v/v) dioxane-water at fixed concentrations of substrate and hydroxide ion. The second order rate constants at different temperatures are given in Table III. Activation energy (E_a) has been calculated from the plot of $\log k_2$ versus $1/T$ (from the Arrhenius equation $\log k = \log A - E_A/2.303RT$). By making use of the Eyring Equation, the other Activation parameters of the hydrolysis

Table II—Effect of $[OH^-]$ on k_{obs} for hydrolysis of MHBQ and PHBQ

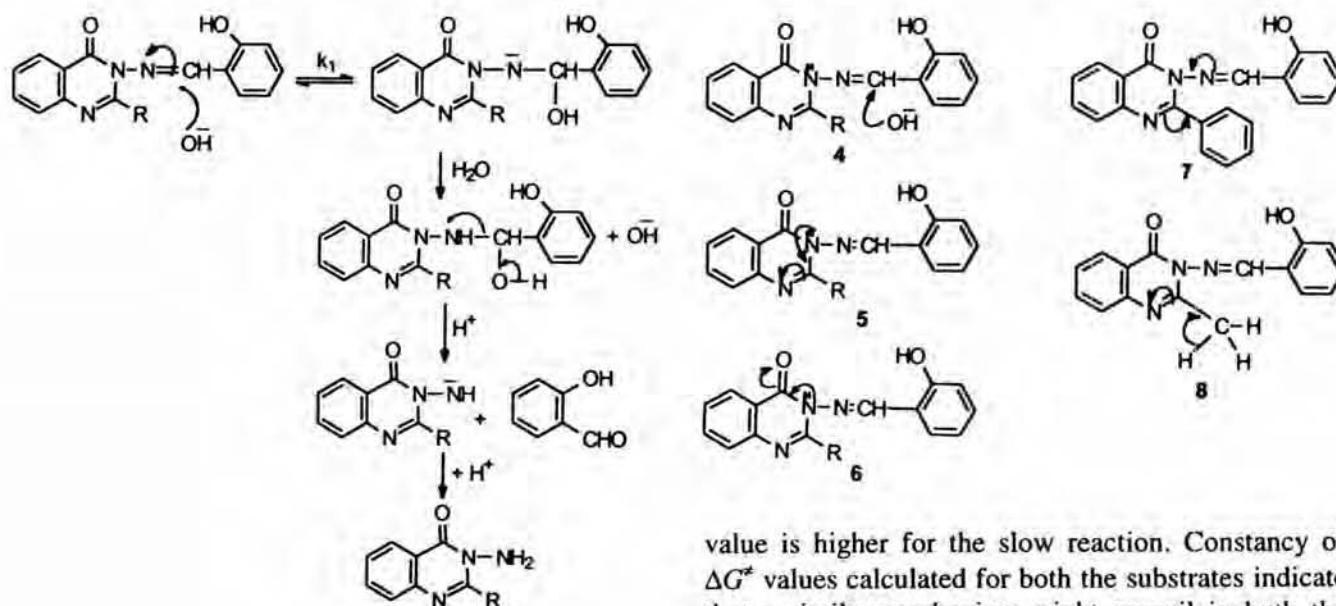
$[OH^-] \times 10^3$ mol dm $^{-3}$	MHBQ		PHBQ	
	$k_{obs} \times 10^3$ (s $^{-1}$)	$k_2 \times 10^2$ (A)	$k_{obs} \times 10^3$ (s $^{-1}$)	$k_2 \times 10^2$ (A)
0.23	0.46	2.00	0.79	3.44
0.45	0.90	2.00	1.56	3.47
0.92	1.83	1.99	3.13	3.46
1.83	3.66	2.00	6.26	3.42
2.75	5.49	2.00	9.48	3.52
3.67	7.32	1.93	12.53	3.41

[MHBQ]= 3.1×10^{-4} mol dm $^{-3}$, [PHBQ]= 3.36×10^{-5} mol dm $^{-3}$, Temp=40°C
Dioxane-Water 70-30% (v/v), (A)=dm 3 mol $^{-1}$ s $^{-1}$

Table III—Effect of temperature on k_2 and thermodynamic parameters at 40°C

Compd	$k_2 \times 10^3$ (dm 3 mol $^{-1}$ s $^{-1}$) at temp (°C)					E_a (A)	ΔH^\ddagger (A)	ΔS^\ddagger (B)	ΔG^\ddagger (A)
	20	30	40	50	60				
MHBQ	4.89	10.00	19.95	36.86	74.43	55.00	52.40	-110.5	87.1
PHBQ	9.30	16.48	34.17	67.30	97.42	49.74	47.14	-122.9	86.0

[Substrate]= 3.0×10^{-5} mol dm $^{-3}$, $[OH^-]=3.67 \times 10^{-3}$ mol dm $^{-3}$, Dioxane-Water 70-30% (v/v) (A)=kJ mol $^{-1}$ (B)=J K $^{-1}$ mol $^{-1}$



Scheme II

of MHBQ and PHBQ compounds were also evaluated⁸. These data are provided in Table III.

Discussion

The alkaline hydrolysis of MHBQ and PHBQ is of first order in both the substrate and the hydroxide ion. The rate of alkaline hydrolysis of PHBQ is greater than that of MHBQ. This is also supported by activation parameters (Table III). The activation energy

value is higher for the slow reaction. Constancy of ΔG^\ddagger values calculated for both the substrates indicate that a similar mechanism might prevail in both the substrates. The reaction pathway is shown in Scheme II for this hydrolysis reaction. Attack of the OH^- is proposed to be the rate-determining step, based on the kinetic data obtained.

The above mechanism of kinetics of hydrolysis of the compounds can be explained as follows. The electron deficiency of ring nitrogen will be transmitted through inductive effect to the exocyclic azomethine which polarises the $-HC=N-$ site to facilitate the attack of OH^- ion 4. Electron deficiency on the ring nitrogen is due to carbonyl polarization involving the lone pair on the ring nitrogen of 5. It is also due to

double bond polarization towards ring nitrogen which involves lone pair on the other ring nitrogen attached to $-N=C-$ moiety (str. 6).

The faster rate observed in PHBQ may be explained as follows. The electron deficiency on the ring nitrogen will be increased by the phenyl group due to electron withdrawing nature through inductive effect (see str. 7). However, methyl group decreases the electron deficiency through the hyperconjugation effect hence decreases the rate (see str. 8).

The rate law based on **Scheme II** is represented as:

$$\text{Rate} = k_2[\text{Substrate}][\text{OH}^-]$$

This rate expression clearly explains the observed results, i.e. first order each in [Substrate] and $[\text{OH}^-]$.

$$k_{\text{obs}} = k_2[\text{OH}^-] \text{ or } 1/k_{\text{obs}} = 1/k_2[\text{OH}^-]$$

Where k_{obs} is psuedo first order rate constant and k_2 , the second order rate constant. According to this equation, variation of $1/k_{\text{obs}}$ vs $1/[\text{OH}^-]$ should be linear passing through the origin. This has been found to be so, thus supporting the mechanism proposed.

Acknowledgement

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