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Synthesis of 2-(4-Nitrophenoxy)quinoxaline and its Reactions with Hydroxide Ion in Micellar Systems

Angela Cuenca,* Cesidio Bruno and Antonieta Taddei

Departamento de Química, Universidad Simón Bolívar
Apartado 89000, Caracas 1080-A, Venezuela

ABSTRACT: The synthesis of 2-(4-nitrophenoxy)quinoxaline (3) is described. The reaction of (3) with hydroxide ion was studied in the presence and absence of micellar systems. Cationic micelles of cetyltrimethylammonium chloride and bromide (CTACl and CTABr) and tetradecyltrimethylammonium chloride and bromide (MTACl and MTABr) speed the reaction of (3) with hydroxide ion. The second-order rate constants at the micellar pseudophase are smaller than the second-order rate constant in water.

Reaction rates and equilibria in water are affected by micellar systems.[1] Several models are available which quantitatively describe the effects of ionic micelles on reaction rate.[2-7] Most of the kinetic results are interpreted by using the pseudophase model[1-7] in which micelles and water are treated as distinct, but uniform reaction media. The pseudophase ion-exchange model (PIE)[2-5] provides a quantitative description of aqueous micellar effects on reaction rates and its advantages and limitations have been discussed previously.[1,3,8-11] The PIE model involves the assumption that the fractional charge neutralization of the micellar head groups, β, does not change as the surfactant concentration is changed or as reactive reactive counterion, *e.g.*, OH^- or F^- is added. This assumption fails when the only anions in the solution are very hydrophilic, especially at high concentration.[12,13] In these systems the data can be fitted by a mass-action model,[12] which assumes that β increases with increasing $[OH^-]$ (or $[F^-]$), equation 1:

$$D_n + OH_W^- \overset{K'_{OH}}{\rightleftharpoons} OH_M^- \qquad (1)$$

$$K'_{OH} = [OH_M^-]/\{[OH_W^-]([D_n] - [OH_M^-])\} \qquad (2)$$

where K'_{OH} is the counterion binding constant, D_n is the micellized surfactant, D_n = [D] - c.m.c., and $\beta = [OH_M^-]/[D_n]$. When two ions compete for the micellar head groups, it is possible to define independent equilibria for each of them, so that for OH^- as reactive ion and X^- as the micelle counterion, the equilibrium constants K'_{OH} and K'_X can be written as equation 3 and 4:[6,14]

$$K'_{OH} = [OH_M^-]/([D_n] - [OH_M^-] - [X_M^-])([OH_T^-]-[OH_M^-]) \qquad (3)$$

$$K'_X = [X_M^-]/([D_n] - [OH_M^-] - [X_M^-])([X_T^-] - [X_M^-]) \qquad (4)$$

where the subscript T denotes the total concentration.

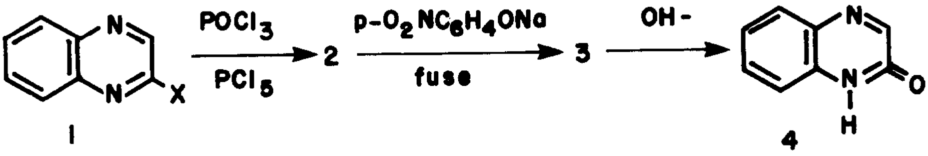
The PIE and mass-action-like models fit the experimental data equally well in dilute OH^-. An alternative treatment[15] for interactions of ions and ionic micelles assumes that electrostatic interactions will bring counterions toward the micellar surface and repel co-ions; ion distribution around spherical, cylindrical, or ellipsoidal micelles can be estimated by solving the Poisson-Boltzmann equation which has been used successfully to describe the thermodynamic behavior of ionic micelles.[15,16]

Nucleophilic heteroaromatic substitution reactions on aza-activated substrates have been extensively studied in water and organic solvents.[17,18] However, the information relative to the effect of colloidal systems upon nucleophilic aromatic substitution reactions on quinoxaline derivatives is limited.[19]

Quinoxaline derivatives are widely used as pharmaceutical and agricultural chemicals.[20] They are, in general, comparatively easy to prepare, and numerous derivatives have been prepared in work designed to produce biologically active materials.[20,21] 2-Chloro-quinoxaline reacts readily with nucleophiles (amines and aryloxides) to give the corresponding 2-substituted quinoxalines.[22]

In this report a route for the synthesis of the novel heterocyclic compound, 2-(4-nitrophenoxy)quinoxaline (3) (Scheme 1) is presented and its basic hydrolysis in water and under micellar conditions was investigated.

The effect of added inert salts upon the reaction of (3) with OH^- in the presence and absence of surfactant was studied. The surfactants were cetyltrimethylammonium bromide and chloride ($C_{16}H_{33}N^+Me_3X^-$; X = Br, Cl; CTABr and CTACl), and tetradecyltrimethylammonium bromide and chloride ($C_{14}H_{29}N^+Me_3X^-$; X = Br, Cl; MTABr and MTACl).



1, X = OH; 2, X = Cl; 3, X = p-$O_2NC_6H_4O$

Scheme 1

RESULTS AND DISCUSSION

Synthesis of 2-(4-nitrophenoxy)quinoxaline (3). - The synthesis of 2-(4-nitrophenoxy)quinoxaline (3) is shown in Scheme 1. The displacement of chloride ion with 4-nitrophenoxide ion was carried out when a mixture of 2-chloroquinoxaline (2) and the pre-formed sodium aryloxide were fused together. No cyclised products were obtained as by-products.

Reactions in water. - In water, 2-(4-nitrophenoxy)quinoxaline reacts with OH^- to produce 2-quinoxalone (4) (Scheme 1). The reaction was followed over a range of $[OH^-]$ from 0.003 M to 0.02 M. Repetitive scanning of the reaction mixture showed that no intermediate built up during reaction. The second-order rate constant (k_w) value is 3.98×10^{-4} $M^{-1}s^{-1}$. Added salts (0.02 M NaBr and NaCl) reduce k_w by approximately 5-7%. Br^- is more effective at inhibiting the reaction than Cl^-. We could not further increase

[salt] due to solubility problems.

Reactions in micelles.- Figure 1 shows the pseudo-first order rate constants, k_ψ, *vs.* surfactant concentration profiles for reaction of (3) with 0.02 M OH^- in the presence of MTAX (X = Cl, Br) and CTAX (X = Cl, Br). First-order rate constants increase with increasing [surfactant] and go through maxima, and are lower when the surfactant counterion is Br^- rather than Cl^-. These results are typical for micellar-assisted bimolecular reactions and are explained by pseudo-phase models that consider distribution of both reactants between water and micelles.[1-7] The rate maxima move towards lower surfactant concentration with increasing length of the *n*-alkyl group of the cationic surfactant.

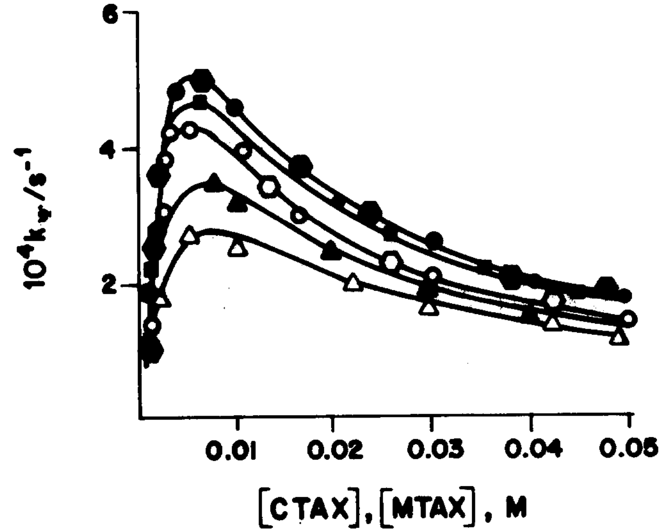
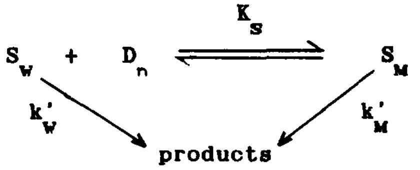


Fig. 1. Reaction of 2-(4-nitrophenoxy)quinoxaline (3) with 0.02 M OH^- in CTAX (●,○), CTAX + 0.02 M NaCl (■) and MTAX (▲, △). Solid symbols X = Cl, open symbols X = Br. (⬣, ⬡) Reaction followed in CTACl, by observing the formation of p-nitrophenoxide ion. Lines are calculated.

Figure 1 shows the effect of added 0.02 M NaCl on the reaction of (3) with 0.02 M OH^- in CTACl. In diluted electrolyte, added Cl^- ion inhibited the reaction of (3) with ^-OH in CTACl by competing with the reactive anion for the micelle.

Quantitative Treatment.- The kinetic analysis follows Scheme 2,[7] where S is the substrate, K_S, is the substrate binding constant, and k'_W and k'_M are first-order rate constants in aqueous and micellar pseudophase, respectively given by[3-5]



Scheme 2

$$k'_W = k_W [OH^-_W] \tag{5}$$

$$k'_M = k_M [OH^-_M]/[D_n] = k_M m^s_{OH} \tag{6}$$

$$\beta = m^s_X + m^s_{OH} = \text{constant} \tag{7}$$

In equations 5 and 6 k_W and k_M are second-order rate constants, but k_M is defined in terms of the mole ratio of bound OH^- to micellized surfactant.

The variations of k_ψ with surfactant concentration were treated quantitatively by means of the PIE model based on equation 8 where competition between OH^- and halide ion X^- is written as:

$$K^{OH}_X = [OH^-_W][X^-_M]/[OH^-_M][X^-_W] \tag{8}$$

The first-order rate constant, k_ψ, is given by equation 9:

$$k_\psi = (k_W [OH^-_W] + k_M K_S m^S_{OH} [D_n])/(1 + K_S [D_n]) \tag{9}$$

The parameters in equation 8 and 9 can be estimated by fitting experimental rate constant-surfactant profiles to these equations (Figure 1). The rate constants for reaction in water, k_W, were direcly measured. Table 1 shows the estimated rate constants in the micellar pseudophase.

The parameter values used in calculations were $K^{OH}_{Cl} = 4$ and $K^{OH}_{Br} = 8$. Solid lines in Figure 1 represents the values of k_ψ calculated using equation 9. The fit of theory and experiment is reasonably good and fitted values of k_M are within 5%. The effect of added salt in CTACl fits the model without introduction of further adjustable parameters. The variation of k_ψ with [surfactant] was predicted for assumed values of β and K^{OH}_X, provided that these parameters are constant over a range of surfactant concentration. The second-order rate constant, k_M, of reactions in the micellar pseudophase have the dimensions of reciprocal time, because the

Table 1. Parameters that Best Fit the Kinetic Results for Sustrate (3) in Micelles.[a]

Surfactant	10^4 c.m.c. M	10^4 k_M s^{-1}	K_S M^{-1}	β	10^4 k_2^m s^{-1}	k_2^m/k_W
MTACl	72	15.3	6500	0.75	2.14	0.54
MTABr	30	12.7	6500	0.75	2.53	0.64
CTACl	11	18.1	8000	0.8	2.49	0.62
CTACl[b]	9.0	17.8	8200	0.8	1.78	0.45
CTABr	8.0	17.0	8000	0.8	2.38	0.60

[a] At 25.0 °C and 0.02 M NaOH. [b] With 0.02 M NaCl.

concentration of OH^- is written as a mole ratio.[2,12a,14] This choice of units allows an unambiguous definition of concentration in the micellar pseudophase, but k_M cannot then be compared directly with second-order rate constants in water, k_W, the units of which are generally mol^{-1} L s^{-1}. We can compare the second-order rate constants for reaction in the micellar and aqueous pseudophases (k_M and k_W) by defining the volume element of reaction in the micelles, which we assumed to be that of the Stern layer, with a molar volume, V_M, of ca. 0.14 L mol^{-1}.[3,4] Therefore, the second-order rate constant, k_2^m, is given by[23,24]

$$k_2^m = k_M V_M \tag{10}$$

For many ion-molecule reactions second-order rate constants at the micellar surface appear to be very similar to those in water.[2,25-27] However, there are some exceptions to this generalization where the rate constants in micellar solutions are larger than the rate constant in water.[28] The k_2^m/k_W values obtained for the reaction of 2-(4-nitrophenoxy)-quinoxaline with OH^- in the presence of the cationic surfactants are shown in Table 1. The determined second-order rate constants in the micellar pseudo phase are smaller than the second-order constants in water. Under the conditions used here, dilute OH^-, we can ascribe the observed rate enhancements for the nucleophilic heteroaromatic substitution of (3) with OH^- in the presence of cationic micelles, to concentration of reactants at the colloidal surface.

EXPERIMENTAL

General Methods. - Melting points are uncorrected. Unless otherwise indicated, all reagents and solvents were purchased from Aldrich or Merck and used without further purification. Silica gel TLC plates (Merck silica gel 60 F_{254}) were used to monitor reactions. The surfactants were commercial samples (MTABr and CTABr) recrystallized from EtOH-Et_2O or prepared by quaternization of N-alkyl-N,N-dimethylamine (alkyl = $C_{14}H_{29}$ and $C_{16}H_{33}$). The purity of surfactants was tested by means of surface tension measurements and there were no minima in plots of surface tension of the purified surfactants against -log [surfactant].

IR spectra were recorded on a Perkin-Elmer 1430 spectrophotometer as KBr plates. ^{1}H-NMR spectra were recorded in a Bruker AM-300 apparatus with TMS as an internal reference in CDCl solutions. Chemical shifts are given in ppm (δ). Mass spectra were obtained on a Hewlett-Packard 5971A spectrometer at 70 eV and peak abundances are quoted as percentage of the base peak. Elemental analysis was performed by Galbraith Laboratories, Inc., Knoxville, TN.

Synthesis of 2-chloroquinoxaline (2). - Compound (2) was prepared from 2-hydroxyquinoxaline following the proven method reported by Castle and Onda.[22a] All spectral data are consistent with reported values.[29]

Synthesis of 2-(4-nitrophenoxy)quinoxaline (3). 2-Chloroquinoxaline (2) was added slowly to a fused mixture of *4*-nitrophenol (8 g, 575 mmol) and KOH (2 g, 356 mmol). The mixture was heated at fusion temperature for one hour and was monitored by TLC (ether-chloroform 6:4) until the reaction was completed. The reaction mixture was washed with KOH 10% solution and filtered. The expected product was recrystallized in hot acetone to afford (3), M.p. 153 °C (1,70 g, 56.7 %). IR (KBr) 3120, 3080, 1625, 1500, 1350, 1320, 1300, 1200, 1000, 860 and 760 cm^{-1}; ^{1}H-NMR 300 MHz (CDCl): δ = 7.50 (d, 2H, H-2', H-6', J = 10 Hz), 7.64-7.80 (m, 3H, H-5, H-6, H-7), 8.08-8.14 (m, 1H, H-8), 8.29 (d, 2H, H-3', H-5', J = 10 Hz), 8.76 (s, 1H, H-3). MS, m/z (relative intensity) 267 (M^+, 100), 129 (59), 102 (59), 75 (14). Anal. Found: C, 62.97; H, 3.25; N, 15.46; requires for $C_{14}H_9N_3O_3$; C, 62.90; H, 3.40; N, 15.72

Kinetics. - All reactions were run at 25.0 °C with a Cary 219 spectrometer. The reaction was followed by observing the appearance of 2-quinoxalone (4) at 362 nm. Some of the reactions were also followed by observing the appearance of nitrophenoxide ion at 405 nm; rate constants obtained by both methods were within ± 2% (Figure 1). The substrate (6-8 x 10^{-5} M stock solution in acetonitrile), was added to the reaction mixture so that the final amount of acetonitrile in the reaction mixture was 0.1%. The spontaneous water reaction made only a minor contribution and we neglected it in the analysis. All reactions followed first-order kinetics for at least four half-lives. First-order rate constants, k_ψ, are in reciprocal seconds and are the averages of at least three separate runs with a maximum deviation of 5%.

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