Micellar Effects on Heteroaromatic Compounds. Part I. Nucleophilic Substitution of 2-Chloroquinoxaline with Hydroxide Ion

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The reaction between 2-chloroquinoxaline and hydroxide ion in water is catalysed by cationic micelles of hexadecyltrimethylammonium bromide (HTAB) and retarded by anionic micelles of sodium dodecyl sulphate (NaDS). The binding constants between substrate and micelles are 4200 for HTAB and 6200 for NaDS at 25°. Differences in micellar catalytic effects on nitroaromatic and ' aza ' heteroaromatic substrates are discussed in terms of a difference in polarity between respective transition states.

MANY data concerning both nitro-activated and ' aza- ' activated nucleophilic aromatic substitution are available in the literature.[1] Furthermore, the effect of micelles on the rate of nitro-activated nucleophilic aromatic substitution has been thoroughly studied,[2] but no data on ' aza- 'activated substrates appear to be available.

In view of the possibility that micelles might interact differently with the two types of activated system, we have investigated the reaction between hydroxide ion and 2-chloroquinoxaline † in water at 25° in the presence of a cationic (hexadecyltrimethylammonium bromide, HTAB) and of an anionic surfactant (sodium dodecyl sulphate, NaDS).

EXPERIMENTAL

Materials.—Hexadecyltrimethylammonium bromide (HTAB), m.p. 235—237°, was prepared by the reaction of trimethylamine with 1-bromohexadecane in absolute ethanol[3] and purified as described by Duynstee and Grunwald,[4] as was sodium dodecyl sulphate (NaDS).

2-Chloroquinoxaline, m.p. 46—47°, was prepared by treating 2-quinoxalone[5] with phosphoryl chloride. Deionized and degassed water was used in the preparation of solutions.

Sodium hydroxide was prepared from Normex solutions (C. Erba) and was standardized by titration with standard acid before use.

Kinetics.—The reaction of 2-chloroquinoxaline was followed spectrophotometrically at 25° directly in the spectrophotometer by measuring the appearance of 2-quinoxalone at 362 nm using a Monospec apparatus. The temperature of the cell compartment was maintained within ±0·05 °C. The concentration of 2-chloroquinoxaline was 1×10^{-4} mol l^{-1} and that of sodium hydroxide 0·05 mol l^{-1}. Graphically calculated first-order rate constants were converted into second-order rate constants.

Solubility Measurements.—The solubility of 2-chloroquinoxaline in the surfactant solutions was determined, after equilibration, by hydrolysis to 2-quinoxalone. Solutions containing solid 2-chloroquinoxaline were shaken periodically, and after several days the solid was filtered off. One portion (1 ml) of the solution was made up to 10 ml with N-NaOH to hydrolyse completely the 2-chloroquinoxaline, then this solution (1 ml) was made up to 10 ml with 0·0127M-sodium borate and the amount of 2-quinoxalone was determined from the absorbance at 362 nm.

Determination of Critical Micelle Concentration.—Results by Bunton and Robinson[6] have been confirmed within experimental errors and used throughout: HTAB ($7{\cdot}8 \times 10^{-4}$ mol l^{-1}, $3{\cdot}2 \times 10^{-4}$ mol l^{-1} ‡), NaDS ($6{\cdot}4 \times 10^{-3}$ mol l^{-1}, $2{\cdot}5 \times 10^{-3}$ mol l^{-1} ‡). C.m.c.s measured in the presence of the substrate are substantially identical with those measured in pure water.

RESULTS

Kinetics.—The effect of a charged surfactant on the second-order rate constant, k_2, for the reaction between 2-chloroquinoxaline and sodium hydroxide in water is simple. The rate increases sharply with concentrations of HTAB (cationic surfactant) above the c.m.c. to a maximum at a surfactant concentration of *ca.* 7×10^{-3} mol l^{-1} (Table). Addition of NaDS (anionic surfactant) decreases the reaction rate (Table).

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† The choice of the substrate was mainly dictated by the fact that its reaction can be easily followed at 25°, at which temperature the critical micellar concentration (c.m.c.) and the aggregation number (N) of the surfactants are well known.

‡ In the presence of 0·05M-NaOH

[1] J. Miller, 'Aromatic Nucleophilic Substitution,' Elsevier, New York, 1968.

[2] E. J. Fendler and J. H. Fendler, *Adv. Phys. Org. Chem.*, 1970, **8**, 271; C. A. Bunton and L. Robinson, *J. Amer. Chem. Soc.*, 1970, **92**, 356, and preceding papers.

[3] D. Attwood, P. M. Elworthy, and S. B. Kayne, *J. Phys. Chem.*, 1970, **74**, 3529.

[4] E. F. Duynstee and E. Grunwald, *J. Amer. Chem. Soc.*, 1959, **81**, 4540.

[5] A. H. Gowenlock, G. T. Newbold, and F. S. Spring, *J. Chem. Soc.*, 1945, 622.

[6] C. A. Bunton and L. Robinson, *J. Amer. Chem. Soc.*, 1968, **90**, 5972.

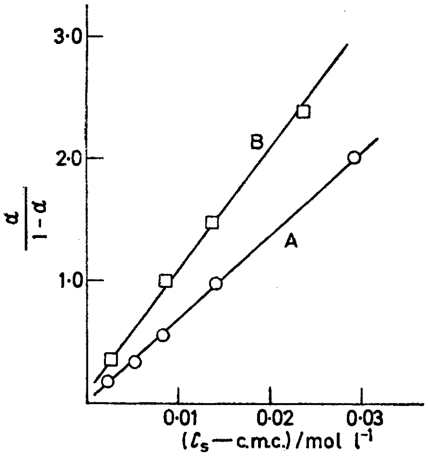
Incorporation of Substrate.—Solubility measurements were used to determine the amount of 2-chloroquinoxaline incorporated by the micelles. If we consider only concentration of detergent well above the c.m.c. and also assume that incorporation of the substrate into the micelle does not change the c.m.c. (see Experimental section) we can calculate the binding constants between substrate and micelles, plotting $\alpha/(1-\alpha)$ against C_s − c.m.c. according to equation (1),[6] where N is the aggregation number [for HTAB *ca.* 61 (ref. 7) and for NaDS *ca.* 62 (ref. 8)], α is the amount of substrate present in the micelle determined from the relative solubilities in surfactant solution and water, and C_s is the total concentration of detergent. The Figure shows plots of $\alpha/(1-\alpha)$ against C_s − c.m.c. for HTAB and NaDS. The values of K, obtained from the Figure and N values from the literature (see above), are: for the incorporation of 2-chloroquinoxaline into HTAB, *ca.* 4200, and into NaDS, *ca.* 6200.

$$K/N = \alpha/[(1-\alpha)(C_s - \text{c.m.c.})] \qquad (1)$$

Micellar effects on the reaction between hydroxide ion and 2-chloroquinoxaline[a]

C_s/mol l^{-1} [b]	HTAB	NaDS	C_s/mol l^{-1} [b]	HTAB	NaDS
	1·26	1·26	0·0075		0·83
0·001	2·50	1·23	0·008	5·20	
0·002	3·10		0·009	5·10	
0·0025		1·21	0·01	4·85	0·70
0·003	3·35		0·02	4·10	
0·004	3·95		0·025		0·43
0·005	4·75	0·99	0·03	3·70	
0·006	5·20	0·94	0·04	3·28	
0·007	5·30		0·05	2·96	0·26

[a] Values of $k_2 \times 10^4$/l mol^{-1} s^{-1} at 25°. [b] Molar surfactant concentration.

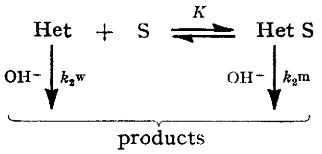


Effects of surfactants on the solubility of 2-chloroquinoxaline in water at 25°: A, HTAB; B, NaDS

DISCUSSION

Kinetics.—The qualitative behaviour is simple and consistent with other results.[6] The substrate is more readily attacked when incorporated into a cationic micelle (HTAB), whereas the opposite is true for incorporation into an anionic micelle (NaDS).

Anionic Micelles.—Kinetic behaviour in the presence of NaDS has been analysed by using the treatment previously applied to similar systems.[9] According to the Scheme, where Het = 2-chloroquinoxaline,



SCHEME

S = surfactant, K = binding constant, and k_2^{w} and k_2^{m}, respectively, are the second-order rate constants in water and in micelles, and with the usual approximations,[9] we can write equation (2), where k_2 is the observed second-order rate constant.

$$\frac{1}{k_2^{\text{w}} - k_2} = \frac{1}{k_2^{\text{w}} - k_2^{\text{m}}} + \frac{1}{k_2^{\text{w}} - k_2^{\text{m}}}\,\frac{N}{K(C_s - \text{c.m.c.})} \qquad (2)$$

Equation (2) fits the results well and the value of K/N determined kinetically from this equation is 110, which is close to the value (100) calculated from solubility measurements. The closeness of the value of $k_2^{\text{w}} - k_2^{\text{m}} = 1{\cdot}22 \times 10^{-4}$ l mol^{-1} s^{-1} [obtained from the intercept of the plot of $1/(k_2^{\text{w}} - k_2)$ *vs.* $1/(C_s - \text{c.m.c.})$] to the value $k_2^{\text{w}} = 1{\cdot}26 \times 10^{-4}$ l mol^{-1} s^{-1} obtained in the absence of detergent, shows that the reaction of 2-chloroquinoxaline is very slow when the substrate is incorporated in the anionic micelles.

The reliability of equation (2) is further confirmed by the closeness of the line calculated by using K/N = 100 (obtained from solubility data) to the experimental line.

Cationic Micelles.—In the presence of HTAB the form of the plot of k_2 against concentration is qualitatively explicable in terms of electrostatic effects and hydrophobic binding of the substrate to the micelles; the rate decreases after the maximum is reached possibly because of the increased counterion concentration.[10] For an alternative explanation of the last effect see ref. 6.

The quantitative treatment successfully applied in the case of the reaction of 1-chloro-2,4-dinitrobenzene with hydroxide ion in the presence of HTAB, based on equation (3), where 'a' is an additional term introduced to fit the results, is not valid in our case, probably because 'a' is not a true constant over the very large range of surfactant concentration. Therefore we were unable to obtain the true value of k_2^{m}.

$$k_2 = \frac{k_2^{\text{w}} + k_2^{\text{m}}(K/N)(C_s - \text{c.m.c.})}{1 + (K/N)(C_s - \text{c.m.c.}) + (a/N^2)(C_s - \text{c.m.c.})^2} \qquad (3)$$

If we consider the ratio k_2/k_2^{w} at the rate maximum,

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[7] E. W. Anacker, R. M. Rush, and J. S. Johnson, *J. Phys. Chem.*, 1964, **68**, 81.

[8] K. J. Mysels and L. H. Princen, *J. Phys. Chem.*, 1959, **63**, 1696.

[9] F. M. Menger and C. E. Portnoy, *J. Amer. Chem. Soc.*, 1967, **89**, 4698.

[10] R. B. Dunlap and E. H. Cordes, *J. Amer. Chem. Soc.*, 1968, **90**, 4395.

we obtain a value of *ca.* 4, considerably smaller than the corresponding value for the 1-chloro-2,4-dinitrobenzene reaction (k_2/k_2^w *ca.* 60). These different micellar catalytic effects can be associated mainly with the general conclusion that electronic charge in the transition state for nucleophilic substitution with charged reagents is less localized on 'aza-'groups than on nitro-groups,[11] *i.e.* cationic micellar catalysis is less effective in stabilising a less dipolar transition state, and in our case this situation certainly applies.

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[11] G. Illuminati, *Adv. Heterocyclic Chem.*, 1963, **3**, 285.