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MICELLAR CATALYSIS OF ORGANIC REACTIONS. PART 36. NUCLEOPHILIC AROMATIC SUBSTITUTION REACTIONS IN HYDROXY FUNCTIONALIZED MICELLES WITH BULKY HEAD GROUPS

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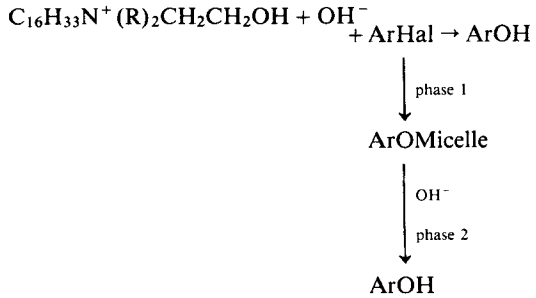
The reaction of several nitro activated aromatic halides with hydroxide ions was studied in the presence of hydroxy functionalized micelles containing bulky head groups, e.g. $C_{16}H_{33}N^+R_2CH_2CH_2OH\ Br^-$, where R = Me, Et, Bu. In a biphasic reaction, the aryl halide is first converted into an aryl mincellar ether which subsequently reacts with hydroxide ions to form the phenolic product. Despite the increased nucleophilicity of hydroxide ions as water is squeezed away from the micelle surface by the bulky head groups, no direct reaction of the aromatic substrate with hydroxide ion is detectable. In the second phase of reaction, the breakdown of the aryl micellar ether to form the phenolic product, the order of reactivity in the different micelles is dependent on the steric interactions between substituents *ortho* to the reaction centre and the head group of the micelle. For compounds having one substituent *ortho* to the reaction centre, the order of reactivity is Bu > Me > Et, whereas for 2-chloro-1,3-dinitrobenzene, which has two substituents *ortho* to the reaction centre, the order is Me > Et > Bu.

INTRODUCTION

The effects of cationic micelles containing bulky head groups on the hydroxydehalogenation of some activated aromatic substrates has been reported.[1] For 1-chloro-2,4-dinitrobenzene (**1**), a neutral substrate, it was found that the magnitude of catalysis by micelles of cetyltrialkylammonium bromide increased as the size of the alkyl groups in the micellar head group was increased from methyl to ethyl, propyl and butyl. However, for ionic substrates, e.g. sodium 2-chloro-3,5-dinitrobenzoate (**2**) and sodium 4-chloro-3,5-dinitrobenzoate (**3**), the magnitude of catalysis decreased as the size of the micellar head group was increased. This was explained by the decrease in polarity at the micelle surface, as water is squeezed away as a result of the increase in size of the head groups.

It is now of interest to determine the effect of increasing the size of the head group on the rate of reaction in the presence of a series of hydroxy functionalized micelles. Previous studies[2] have shown that such S_NAr reactions in the presence of hydroxy functionalized micelles proceed by a biphasic mechanism (Scheme 1). In the first phase, the aromatic substrate is partitioned between direct reaction with hydroxide ions to give the corresponding phenolic product (ArOH) and reaction with the micellar alkoxide ion to form an aryl micellar ether (ArOMicelle). In the second phase, the micellar ether is converted into the phenolic product by reaction with hydroxide ions. It is of interest to determine the effect of increasing head group size, first on the partitioning in phase 1 and second on the rate of decomposition of the micellar ether in phase 2.



Scheme 1. R = Me, Et, Bu and Hal = Cl for compounds **1–4** or F for compounds **1a**, **4a**, **5** and **6**

Specifically, it was of interest to determine the effect of increasing the size of the micellar head group the rates of both phases of reaction and on the percentage

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of trapping, i.e. the amount of aryl micellar ether produced in the first phase of reaction. In addition to substrate **1** above, we studied the reactions of 2-chloro-1,3-dinitrobenzene (**4**), sodium 2-fluoro-5-nitrobenzoate (**5**) and 4-fluoronitrobenzene (**6**).

RESULTS AND DISCUSSION

Observed first-order rate constants for the phase 1 reaction of compounds **1**, **4** and **5**, are given in Table 1 and those for the phase 2 reactions of 1-fluoro-2-4-dinitrobenzene (**1a**), 2-fluoro-1,3-dinitrobenzene (**4a**) and **5** in Table 2.

In biphasic reactions, it is important to ensure that the rates of each phase are obtained without interference from the other phase. For the chloro compounds (**1** and **4**), this was achieved in the case of phase 1 (formation of the aryl micellar ether) by using the isosbestic point of the phase 2 reaction as an analytical wavelength. In this way, any contribution of the phase 2 reaction was eliminated, since no change in absorbance occurs at this wavelength in the phase 2 reaction. Thus, any change in absorbance detected at this wavelength must be due only to the first phase of reaction.

For compound **5**, a fluoro compound, the analytical wavelength used, 300–305 nm (depending on the detergent), corresponded to the λ_{max} of the micellar ether. Since this compound had a fluoride leaving group, the phase 1 reaction was fast in comparison with the phase 2 reaction, which had an alkoxide ion as the leaving group.[3] Consequently, the phase 2 reaction of the fluoro substrates did not interfere with the observation of the phase 1 reaction. The phase 1/phase 2 rate ratio varied from 28 for R = Bu to 54 for R = Me and 64 for R = Et.

For the measurement of the rates of the phase 2 reaction, fluoro compounds were again used. In this way, the fast phase 1 reaction was complete before the phase 2 reaction became significant. Then the spectral changes of the phase 2 reaction, including the isosbestic points, could be measured without any contribution by the phase 1 reaction.

Formation of the aryl micellar ether—phase 1

For each substrate, in all micelles, the trapping, i.e. formation of the aryl micellar ether, was quantitative. The

Table 1. Observed pseudo-first-order rate constants [$10^3 \times k_1$ (s^{-1})] for the first phase of reaction, i.e. formation of the micellar ether

Substrate	[Detergent] (mM)	Me	Et	Bu
1 at 30·6 °C, 5 mM hydroxide	1	3·91	6·51	7·45
	2	9·37	13·1	14·4
	4	13·4	19·3	19·8
	8	15·9	20·3	24·6
	13·3	16·7	21·3	25·6
	16	16·9	22·2	26·2
	18	17·2	23·4	24·6
	20	15·4	19·8	22·5
Analytical wavelength (nm)		323	324	325·5
4 at 30·6 °C, 5 mM hydroxide	1	0·61	1·00	1·03
	2	1·36	1·65	1·61
	4	2·02	2·5	2·01
	8	2·28	2·87	1·59
	13·3	2·40	2·48	1·36
	16	2·43	2·20	1·31
	18	2·34	2·18	1·22
	20	1·90	1·98	1·08
Analytical wavelength (nm)		275	278	278
5 at 60·7 °C, 5 mM hydroxide	1	0·43	0·59	0·88
	2	0·91	0·97	0·96
	4	1·04	1·33	1·17
	8	0·93	1·28	0·95
	13·3	0·77	0·86	0·83
	16	0·71	0·84	0·68
	18	0·66	0·82	0·66
	20	0·64	0·72	0·63
Analytical wavelength (nm)		300	300	305

Table 2. Observed pseudo-first-order rate constants [$10^3 \times k_1$ (s^{-1})] for the second phase of reaction, i.e. decomposition of the micellar ether

Substrate	[Detergent] (mM)	Me	Et	Bu
1a at 30 °C, 5 mM hydroxide, 358 nm	0·5			4·31
	0·53			4·50
	0·56			4·81
	0·58			4·53
	0·60			4·42
	0·9		3·04	
	0·95		3·25	
	1	2·85	3·22	4·11
	1·1	2·87		
	1·25	2·64		
	1·5	2·58		
	2	2·42	3·04	4·02
	4	1·86	2·68	3·06
	8	1·35	1·99	1·86
	13·3	1·00	1·13	1·39
	16	0·87	0·95	1·25
	18	0·77	0·87	1·11
	20	0·70	0·80	1·06
4a at 30·6 °C, 5 mM hydroxide, 442 nm	0·5			1·67
	0·56			1·71
	0·6			1·69
	0·9		1·68	
	0·97		1·84	
	1·0	1·86	1·65	1·61
	1·1	1·89		
	2	1·68	1·55	1·24
	4	1·19	1·28	1·08
	8	0·84	1·02	0·69
	13·3	0·61	0·52	0·47
	16	0·46		
	20	0·43	0·39	
5 at 60·7 °C, 5 mM hydroxide, 414 nm	0·50			0·0222
	0·56			0·0203
	0·80			0·0177
	0·91	0·0108		
	1	0·0151	0·0092	0·0164
	1·5	0·0147	0·010	
	2	0·0137	0·014	0·0138
	4	0·0128	0·0092	0·0124
	8	0·0095	0·006	
	13·3	0·0075		

observed rates of the phase 1 reaction, were therefore rates of micellar ether formation. From Table 1, it can be seen that in all cases the rate increased as the detergent concentration was increased up to a maximum rate, which presumably corresponds to the concentration at which all of the substrate is solubilized by the micelles. Above this concentration the rate decreased, as a result of dilution of the reactants in the micellar pseudo-phase.

Because the alkoxide nucleophile in a hydroxy functionalized micelle is bound to individual detergent molecules, the pseudo-phase ion-exchange (PPIE) kinetic model is not appropriate for the treatment of rate data obtained in such micelles. We therefore report values of the observed rate of reaction in the presence of micelles. However, some conclusions can be drawn from consideration of the raw rate data obtained.

Solubilization of the substrates

The detergent concentration at which the optimum rate is observed gives an indication of how well the substrate

is solubilized by the micelle. The lower the concentration at which the optimum rate is observed, the better the substrate is solubilized by the micelle. The ionic substrate **5** is therefore solubilized more efficiently than the neutral substrates **1** and **4**. Further, for the ionic substrate the optimum rate is at 4 mM in all micelles. The driving force for the solubilization of this substrate is presumably an electrostatic attraction between the cationic micelle and the negative charge on the substrate. It appears that this electrostatic attraction is not affected by the size of the head group on the micelle, since the optimum rate is obtained at the same concentration in all of the micelles.

The neutral substrates **1** and **4** have optimum rates at higher detergent concentrations than for substrate **5** and are thus less well solubilized by these micelles. Solubilization of substrates **1** and **4** by the butyl micelle is marginally better than by either the methyl or ethyl micelle. Solubilization of these neutral substrates is presumably a result of hydrophobic interactions between the substrates and the micelles. Hence the hydrophobic interaction is apparently favoured by the larger head groups.

Magnitude of catalysis

Optimum rates of each reaction in each micelle are compared with rates in the presence of 1 mM detergent, because in the complete absence of detergent no micellar ether is formed and hence the rate of reaction in that case refers to the alternative direct reaction with hydroxide ion producing the phenolic product.

The magnitude of catalysis (i.e. $k_{\text{optimum}}/k_{1\text{ mM detergent}}$) for the reaction of the neutral substrates is slightly larger than for the reaction of the ionic substrate. The methyl micelle shows the greatest catalysis for the reactions of all compounds studied. However, for substrate **1**, which has only one *ortho* substituent group, the variation of catalysis by the different micelles is small (4·4–3·5), i.e. a decrease of 20% from the Me to the Bu micelle.

For substrate **4**, which has two *ortho* substituent groups, the variation of catalysis by the different micelles is larger (decreasing from 4·0 for Me to 1·9 for Bu, i.e. a decrease of 52%). It is possible that this larger decrease in the observed catalysis is a result of increased steric problems between a substrate having two *ortho* substituent groups and a nucleophile, the micellar alkoxide ion, which becomes bulkier as the size of the head group is increased.

For the ionic substrate **5**, the catalysis decreased by 46% from 2·4 for the Me micelle, down to 1·3 for the Bu micelle. Two explanations are possible for this decrease. First, although there is only one *ortho* substituent group in substrate **5**, it is the ionic carboxylate group which probably has considerable water of solvation about it, making it fairly large. Second, for this reaction an anionic intermediate is produced and this may be more sensitive to the polarity of its surroundings than the formally neutral intermediates, formed from the neutral substrates. The smaller catalysis is therefore consistent with a report that water is squeezed away from the micelle surface as the size of the head group is increased.[4]

A surprising feature of these reactions is that despite the increased nucleophilicity of hydroxide ions as water is squeezed away from the micelle surface, quantitative formation of the micellar ether occurs in the first phase of reaction, for all substrates and all detergents used. Hence the increase in the steric bulk of the micellar head group does not seem to retard the formation of the aryl micellar ether sufficiently to allow the direct reaction with hydroxide ion to compete effectively. Two possible reasons for this effect are first that the positive charge on the detergent molecule interacts favourably with an electron-rich substituent *ortho* to the reaction centre and second that the positive charge on the detergent molecule interacts favourably with the π-electron cloud of the benzene ring. We favour the latter explanation, since a high percentage of trapping was observed even for reactions with 4-fluoronitrobenze (**6**), which does not have any substituent *ortho* to the reaction centre.

Decomposition of the micellar ether – phase 2

For the decomposition of the aryl micellar ethers, the optimum rate is observed at the exact detergent concentration determined to be the critical micelle concentration (CMC) in neutral solution. This may be a coincidence, as it has been shown[5] that the CMC usually decreases when hydroxide ion is added to micellar solutions. However, it is consistent with the very effective solubilization of all of the aryl micellar ethers, the substrates for this phase of reaction, by the micelle. We therefore conclude that variation of the magnitude of catalysis is due to variation of the rate of reaction in the micellar pseudo-phase, rather than to differences in the binding constants of the various micellar ethers.

For the decomposition of the cationic micellar ether derived from substrate **1a**, the rate order is Bu > Et > Me. In this case, a neutral intermediate containing only one *ortho* substituent is produced. Charge is destroyed in the rate-determining step. In terms of the Hughes–Ingold solvent theory,[6] the reaction is favoured by a less polar solvent. The reaction is favoured by the micelle with the largest head groups, i.e. Bu, and this is consistent with water being squeezed out from the micelle surface as the size of the head group is increased. This results in a drier and hence a less polar Stern region for the micelle with the largest head group.

For the decomposition of the cationic micellar ether derived from substrate **4a**, the rate order is Me > Et > Bu. In this case, a neutral intermediate is again formed and charge is being destroyed in the rate-determining step. However, the intermediate has two *ortho* substituents. The reversal of this order of reactivity possibly reflects the greater steric hindrance in the reactions of substrate **4a** as the size of the micellar head group is increased.

For the decomposition of the formally neutral micellar ether, derived from substrate **5**, the rate order is Bu > Me > Et. In this case, an anionic intermediate with only one *ortho* substituent is formed. Charge is being dispersed in the rate-determining step and the reaction is favoured by the less polar environment of the butyl micelle, as it was for the reaction of substrate **1a**. It therefore appears that the variable steric interaction of substituents *ortho* to the reaction centre and the bulky head groups of the micelles are the major cause of the variations in the order of catalytic effects by the different micelles.

EXPERIMENTAL

Materials. 1-Chloro-2,4-dinitrobenzene, 1 -fluoro-2,4-dinitrobenzene, 2-chloro-1,3-dinitrobenzene and 4-fluoronitrobenzene were commercially available. 2-Fluoro-5-nitrobenzoic acid was available from previous work.[7] 2-Fluoro-1,3-dinitrobenzene was prepared from the corresponding chloro compound by the halide exchange method of Finger and Kruse[8] using nitrobenzene as solvent. 2-Chloro-1,3-dinitrobenzene (3·4 g, 0·017 mol) and potassium fluoride (2·57 g) were dried by azeotropic distillation with benzene and then freshly distilled nitrobenzene (25 g) was added and the mixture was heated at reflux for 10 h. After cooling to room temperature, the mixture was washed with hot toluene (200 ml) and filtered. The combined filtrate was concentrated on a Rotovap at water pump pressure (16 mmHg) (1 mmHg = 133·3 Pa) to remove toluene and nitrobenzene was removed by distillation under high vacuum (1 nmHg).The residue was cooled with ice and the precipitate was recrystallized, first from ethanol at low temperature (−96 °C) and second from benzene, to afford 2-fluoro-1,3-dinitrobenzene, m.p. 58 °C (lit.[9] m.p. 60 °C).

The detergents were all prepared by the quaternization of the appropriate *N,N*-dialkylethanolamine with cetyl bromide in propan-1-ol at reflux for 2 days (R = methyl) or 9 days (R = ethyl or butyl). The reaction mixture was then cooled to room temperature and the propanol was removed by evaporation under reduced pressure (16 mmHg). The residue was then recrystallized from ethanol and washed with dry diethyl ether to produce a white solid, m.p. 203–204 °C, lit.[10] m.p. 194–204 °C (R = Me); m.p. 79–80 °C, lit.[11] m.p. 80 °C (R = Et); m.p. 54–55 °C (R = Bu). $C_{26}H_{56}NOBr$ requires C 65·3 H 11·7, N 2·9, Br 16·7; found C 65·1, H 11·5, N 3·0, Br 16·4% (R = Bu). The identity of each of the detergents was further confirmed by electrospray mass spectral analysis. The electrospray mass spectra of these compounds were recorded on a VG Bio-Q triple quadrupole mass spectrometer (VG Bio Tech, Altringham, Cheshire, UK) using a mobile phase of 50% aqueous methanol containing 1% acetic acid. Principal ions at m/z 314·2 (R = Me), 342·1 (R = Et) and 398·1 (R = Bu) were observed. In each case the absence of the protonated *N,N*-dialkylethanolamine, the product of a possible competing elimination reaction, was also confirmed.

Distilled water was further purified using a Millipore Milli-Q system to achieve a resistivity of 18 MΩ cm.

Kinetics. Stock solutions (0·01 M) of the substrates were prepared in HPLC-grade acetonitrile. Stock solutions of NaOH (0·015 M) and the detergents (20 mM) were prepared in purified water. Rate measurements were carried out at the temperatures indicated in the tables in a cuvette kept at constant temperature in the cell compartment of a Varian Model 634 UV–visible spectrophotometer. Micellar solutions (2 ml) of the required concentrations were pipetted into a quartz cuvette. The substrate (18 μl) was added by microsyringe, the cuvette was shaken, allowed 15 min to reach temperature equilibrium in the jacketed cell compartment of a Varian Model 634 UV–visible spectrophotometer and the reaction was initiated by the addition of sodium hydroxide solution (1 ml) which had also been temperature equilibrated in the water-bath. The solution was again shaken and the absorbance was monitored at the analytical wavelength indicated in the tables by means of a National VP 6511 A X–T recorder. The temperature within the cuvette was measured with a Jenco Thermistor thermometer. Reactions were followed to infinity (ten half-lives) where possible, or alternatively for very slow reactions, and for consecutive reactions, an infinity value was calculated by using a computer program designed to give the best straight-line fit to data collected over at least two half-lives. Good agreement was obtained between rate constants and infinity measurements obtained by the two methods. Rate constants were all obtained in duplicate and average results (within ±2%) are presented in the tables.

Critical micelle concentrations. The critical micelle concentrations were determined in neutral solution at 30·0 °C using a platinum electrode and an Activon PT-301 conductivity meter. Aliquots of known detergent concentration (0·01 M) were added to purified water (30 ml) and the conductivity was measured as a function of detergent concentration.

Percentage of trapping. The percentage of micellar ether formation (trapping) was determined spectrophotometrically. The absorbance at the wavelength of maximum absorbance of the phenolic product was determined for the fluoro substrates initially when the fast phase 1 reaction was complete (A_0) and again when the phase 2 reaction was complete (A_∞). The percentage trapping was then determined as $(A_\infty - A_0) \times 100/A_\infty$.

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