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THE INFLUENCE OF AMPHIPHILIC COMPOUNDS ON IONIC ORGANIC REACTIONS IN AQUEOUS SOLUTION†

K. G. VAN SENDEN‡ and C. KONINGSBERGER
Laboratory of Organic Chemistry, Technical University, Eindhoven, The Netherlands

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Abstract—The effects of a cationic amphiphilic compound on the rates of a proton- and an hydroxyl ion-catalysed reaction have been investigated. Even at very low concentrations, such a compound retards the proton-catalysed hydrolysis of benzylidene aniline, and this effect increases with increasing concentration of the cationic compound. Conversely, the hydroxyl ion-catalysed hydrolysis of benzylidene acetophenone is accelerated at low concentrations of cationic compound; however, at higher cationic concentrations, the reaction is retarded.

These effects are qualitatively explained by considering the effect of a cationic compound on the electrostatic forces between the reactant ions and on the steric shielding of the reaction site.

INTRODUCTION

FROM investigations carried out by Robinson,[1] Schöpf,[2] Haley and Maitland[3] and others it is well known that many organic reactions of the ionic type occur smoothly under physiological conditions in aqueous solutions. However, up to now this reaction medium has found little practical application, owing to the very low solubility of most organic compounds in water.

Guided by the idea that detergent salts might solubilize the reactants in this medium, a new research project was started in this field. Similar investigations on emulsion polymerization have clearly indicated that amphiphilic compounds could be used to accelerate reactions and increase yields.

The amphiphilic compound chosen was the cationic cetyltrimethylammonium bromide (CTAB), which is completely ionized in aqueous solution. In order to differentiate between solubilization and charge effects, a proton-catalysed and a hydroxyl ion-catalysed reaction was investigated in the presence of this amphiphilic compound.

The molecules involved in these two reactions had to be sterically similar to each other in order to ensure that the only major difference between the reactions was the charges on the reactant species. Finally it was necessary that reaction rates could be measured by one of the standard techniques.

The reactions which fulfilled our requirements best were the hydrolysis of benzylidene aniline, a proton-catalysed reaction, and the hydrolysis of benzylidene acetophenone, a hydroxyl ion-catalysed reaction.

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† Taken from a dissertation submitted by K. G. van Senden, in partial fulfilment of the requirements for the Ph.D. degree, November 1960.

‡ Present address: Unilever Research Laboratory, Vlaardingen, The Netherlands.

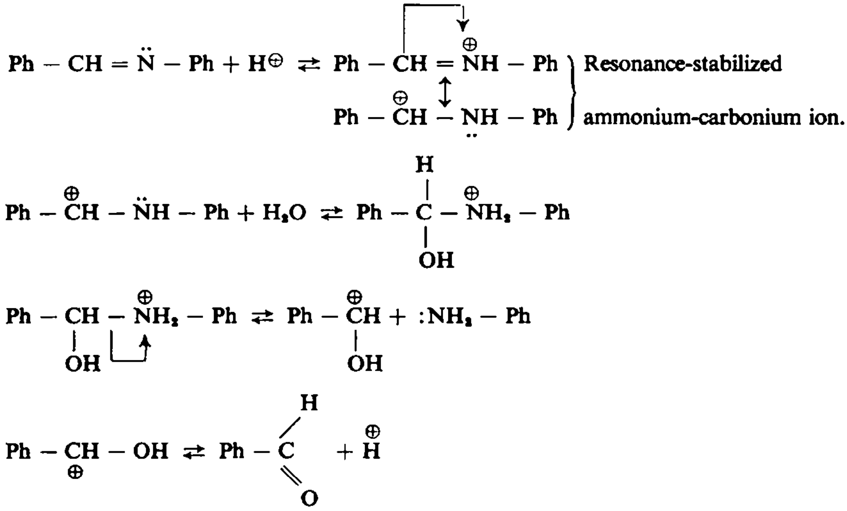
[1] R. Robinson, *J. Chem. Soc.* **111**, 876 (1917).

[2] C. Schöpf, *Angew. Chem.* **50**, 779 (1937); *Ibid.* **50**, 797 (1937).

[3] A. C. Haley and P. Maitland, *J. Chem. Soc.* 3155 (1951).

Mechanism of hydrolysis of benzylidene compounds

Benzylidene aniline. On theoretical grounds, the following mechanism is proposed for the hydrolysis of benzylidene aniline.



$$\mathrm{Ph-CH=\ddot{N}-Ph + H^{\oplus} \rightleftarrows Ph-CH=\overset{\oplus}{N}H-Ph \;\updownarrow\; Ph-\overset{\oplus}{C}H-\ddot{N}H-Ph}$$

$$\mathrm{Ph-\overset{\oplus}{C}H-\ddot{N}H-Ph + H_2O \rightleftarrows Ph-\underset{OH}{\overset{H}{C}}-\overset{\oplus}{N}H_2-Ph}$$

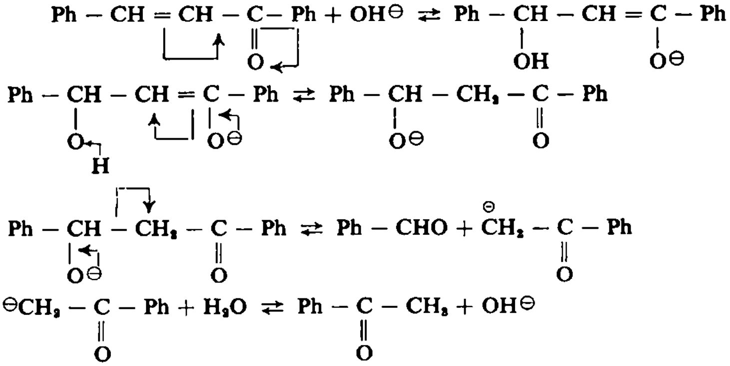
$$\mathrm{Ph-\underset{OH}{C}H-\overset{\oplus}{N}H_2-Ph \rightleftarrows Ph-\underset{OH}{\overset{\oplus}{C}H} + :NH_2-Ph}$$

$$\mathrm{Ph-\underset{\oplus}{C}H-OH \rightleftarrows Ph-C(H){=}O + \overset{\oplus}{H}}$$

The hydrolysis starts by protonation of the tertiary nitrogen atom to give a resonance-stabilized ammonium–carbonium ion. This is more electrophilic than the neutral molecule and is therefore attacked much more quickly by water. In excess water hydrolysis occurs, whilst at low water concentrations the reverse of the protonation reaction is faster than the reversible hydrolysis of the carbonium ion.

This mechanism is supported by the investigations of Willi and Robertson[4] and Holleck and Kastening.[5] Although the work of both groups was carried out in mixed solvents (50:50 and 30:70 methanol–water), their findings are in broad general agreement with the above mechanism.

Benzylidene acetophenone. The following mechanism can be given for the hydrolysis of benzylidene acetophenone.



$$\mathrm{Ph-CH=CH-\underset{\|\atop O}{C}-Ph + OH^{\ominus} \rightleftarrows Ph-\underset{OH}{C}H-CH=\underset{O^{\ominus}}{C}-Ph}$$

$$\mathrm{Ph-\underset{O-H}{C}H-CH=\underset{O^{\ominus}}{C}-Ph \rightleftarrows Ph-\underset{O^{\ominus}}{C}H-CH_2-\underset{\|\atop O}{C}-Ph}$$

$$\mathrm{Ph-\underset{O^{\ominus}}{C}H-CH_2-\underset{\|\atop O}{C}-Ph \rightleftarrows Ph-CHO + \overset{\ominus}{C}H_2-\underset{\|\atop O}{C}-Ph}$$

$$\mathrm{{}^{\ominus}CH_2-\underset{\|\atop O}{C}-Ph + H_2O \rightleftarrows Ph-\underset{\|\atop O}{C}-CH_3 + OH^{\ominus}}$$

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[4] A. V. Willi and R. E. Robertson, *Canad. J. Chem.* 31, 361, 493 (1952); A. V. Willi, *Helv. Chim. Acta* 39, 1193 (1956).

[5] L. Holleck and B. Kastening, *Z. Elektrochem.* 60, 127 (1956); B. Kastening, L. Holleck and G. A. Melkonian, *Ibid.* 60, 130 (1956).

The reaction starts with the addition of an hydroxyl ion at a carbon atom of benzylidene acetophenone—an hydroxyl ion-catalysed reaction. Hydrolysis takes place in excess water.

Support for this proposed mechanism was found by Coombs and Evans,[6] who studied the formation of benzylidene acetophenone in 90% ethanol solutions to which a small quantity of sodium ethoxide was added. One of their proposed mechanisms is in good agreement with the one we postulate here on purely theoretical grounds.

EXPERIMENTAL

Materials and methods

Benzylidene aniline and benzylidene acetophenone. Benzylidene aniline was synthesized according to Vogel[7], m.p., 52°; lit.[8], 51–52°. (Found: C, 85·1; H, 6·0; N, 7·9. Calc. for C, 86·19; H, 6·08; N, 7·73%.) The IR spectrum was identical with that of Witkop *et al.*[8] Benzylidene acetophenone was synthesized according to Vogel[10], m.p., 57°; lit.[9], 56–57°. (Found: C, 85·6; H, 6·4; O, 7·9. Calc. for C, 86·50; H, 5·81; O, 7·68%.)

The IR spectrum was identical with that in Sadtler.[10]

Cetyltrimethylammonium bromide. This compound was obtained from British Drug House and crystallized three times from EtOH–ether. (Found: C, 62·6; H, 11·7; N, 3·9; Br, 21·7. Calc. for C, 62·56; H, 11·52; N, 3·84; Br, 21·95%.) IR spectrum and analysis of the alkyl chain by gas chromatography are described elsewhere.[11] Only those samples shown by gas chromatography to be at least 99% pure were used for the final experiments.

Other chemicals. All other chemicals were obtained from Merck, analytical grade.

Determination of the reaction order and rate constants. In order to obtain swift dissolution of benzylidene aniline or benzylidene acetophenone in water, the compound was dissolved first in water-free MeOH; 1 ml of this solution was added to 499 ml buffer solution with vigorous shaking. A 1 cm quartz cell was filled with this solution and placed in a Cary model 14 PM 50 spectrometer with the cell compartment thermostatted at 25°. This already contained the reference cell with buffer solution. A record of extinction versus time was made. The time for the total operation from mixing till the start of the record never exceeded 3 min.

By the method given by Koning and van Senden,[12] the reactions were shown to be uncomplicated first-order with respect to benzylidene aniline or benzylidene acetophenone.

The gross rate constants of these pseudo unimolecular reactions were calculated by the method of least squares from the spectroscopic data according to the method described previously.[13]

The concentrations of benzylidene aniline and benzylidene acetophenone were always of the order of 10^{-4} mole/l.

Experimental results and interpretation

Influence of the methanol concentrations on the hydrolysis rate constants. In order to obtain rapid homogeneous solution, a small quantity of MeOH was added to the reaction medium. All reaction media used for correlation purposes contained 0·2%MeOH.

Table 1 shows the gross rate constants, k_h^*, of the hydrolysis of benzylidene aniline in the presence of cetyltrimethylammonium bromide and increasing concentrations of MeOH.

[6] E. Coombs and D. P. Evans, *J. Chem. Soc.* 1295 (1940).

[7] A. I. Vogel, *Practical Organic Chemistry* p. 625. Longmans Green, London (1951).

[8] E. Witkop, J. B. Patrick and H. M. Kissman, *Chem. Ber.* **85,** 949 (1952).

[9] A. I. Vogel, *Practical Organic Chemistry* p. 681. Longmans Green, London (1951).

[10] Sadtler Standard Spectra, No. 2723, Philadelphia, Midget Ed. (1959).

[11] K. G. van Senden, *Rec. Trav. Chim.* **84,** 1459 (1965).

[12] H. N. Koning and K. G. van Senden, *Rec. Trav. Chim.* **81,** 1024 (1962).

[13] K. G. van Senden and H. N. Koning, *Rec. Trav. Chim.* **81,** 49 (1962).

TABLE 1. THE INFLUENCE OF THE PERCENTAGE METHANOL IN THE REACTION MEDIUM ON THE HYDROLYSIS OF 2 × 10^{-4} M (18·12 mg/l) BENZYLIDENE ANILINE IN BORIC ACID-BORAX BUFFER SOLUTION pH 9·0 AT 25°, TO WHICH CETYLTRIMETHYLAMMONIUM BROMIDE (CTAB) ARE ADDED

M CTAB	% Methanol	$10^3 \times k_h^*$ min^{-1}	
0·01	0·2	2·72	2·75 2·69
	1·0	2·84	2·80 2·88
	2·0	2·93	2·86 3·00
	4·0	3·41	3·46 3·36
0·05	0·2	0·62	0·63 0·61
	1·0	0·64	0·61 0·67
	2·0	0·73	0·74 0·73
	4·0	0·77	0·77 0·78

By extrapolation from these values, the gross rate constants in MeOH free water were calculated to be 2·70 × 10^{-3} min^{-1} for 10^{-2} molar CTAB and 0·60 × 10^{-3} min^{-1} for 5 × 10^{-2} molar CTAB.

The influence of 0·2% MeOH in the reaction medium on the k_h^* values is hence within the experimental error, and may be neglected.

Influence of the concentration of amphiphilic compound on the hydrolysis rate constants. The relation between the gross rate constants of hydrolysis of benzylidene

TABLE 2. HYDROLYSIS OF BENZYLIDENE ANILINE IN BORIC ACID-BORAX BUFFER SOLUTION pH 9·0 AT 25°, TO WHICH 0·2% METHANOL AND DIFFERENT CONCENTRATIONS CETYLTRIMETHYLAMMONIUM BROMIDE (CTAB) ARE ADDED

10^3 × M CTAB	$10^3 \times k_h^*$ min^{-1}		10^3 × M CTAB	$10^3 \times k_h^*$ min^{-1}	
0·0	56·5	55 58	20·0	1·53	1·54 1·52
0·5	34·5		30·0	0·97	0·98 0·97
1·0	21·8		40·0	0·75	0·76 0·75
3·0	8·48		50·0	0·62	0·64 0·61
5·0	5·42		60·0	0·52	0·52 0·52
7·0	3·88		70·0	0·44	0·45 0·44
9·0	3·13		100·0	0·34	
10·0	2·72	2·75 2·69			

TABLE 3. HYDROLYSIS OF BENZYLIDENE ACETOPHENONE IN $\frac{1}{10}$N NaOH SOLUTION AT 25°, TO WHICH 0·2% METHANOL AND DIFFERENT CONCENTRATIONS CETYLTRIMETHYLAMMONIUM BROMIDE (CTAB) ARE ADDED

$10^3 \times$ M CTAB	$10^3 \times k_h^*$ min^{-1}		$10^3 \times$ M CTAB	$10^3 \times k_h^*$ min^{-1}	
0·00	6·24		6·00	16·27	
0·05	6·83		7·00	15·23	
0·10	7·00	6·95 7·05	8·00	14·46	
0·15	8·58		9·00	13·87	
0·20	11·28	11·27 11·29	10·00	13·39	
0·25	13·55		20·00	9·20	
0·30	18·20		30·00	7·09	
0·40	19·20		40·00	5·85	
0·50	20·76	20·74 20·79	50·00	5·06	
0·70	22·83		60·00	4·26	
0·90	22·97		70·00	3·79	
1·00	23·59		100·00	2·77	
1·20	23·96		110·00	2·59	
1·50	23·69		120·00	2·58	2·56 2·60
2·00	23·86		130·00	2·42	2·40 2·44
3·00	22·04		140·00	2·27	2·25 2·30
4·00	19·33		150·00	2·20	
5·00	17·85		160·00	2·13	

aniline and the concentration of CTAB present is shown in Fig. 1, which summarizes the results presented in Table 2.

The effect of CTAB on the rate constant for the hydrolysis of benzylidene acetophenone is quite different, as shown in Table 3.

The results are summarized in Fig. 2 and 3, which indicate that the overall-rate constant for the hydrolysis passes through a maximum on increasing the cationic concentration.

In a preliminary communication,[14] similar figures are given from experiments conducted with CTAB at concentrations above the critical micelle concentration. Similar effects are described by Fullington and Cordes,[15] Herries *et al.*[16] and others.

To give an interpretation of these phenomena, we have to consider what influences a cationic amphiphile can have on the processes generating the species involved in the rate-determining steps of these hydrolysis.

There appear to be two effects which the cationic can exert, and their relative magnitudes depend on the concentration. The first, which we may term the charge effect, predominates at concentrations below the critical micelle concentration. Both the organic substrates and the cationic amphiphile have a predominantly lipophilic

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[14] K. G. van Senden and C. Koningsberger, *Tetrahedron Letters* No. 1, 7 (1960).

[15] J. G. Fullington and E. H. Cordes, *Proc. Chem. Soc.* 224 (1964).

[16] D. G. Herries, W. Bishop and E. M. Richards, *J. Phys. Chem.* 68, 1842 (1964).

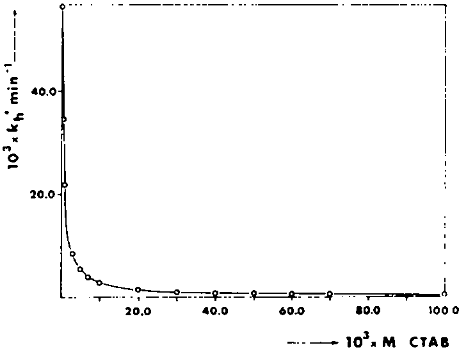

Fig. 1. Gross-rate constants for the hydrolysis of benzylidene aniline as a function of CTAB concentration in a boric acid-borax buffer solution pH 9·0, containing 0·2% methanol at 25°.

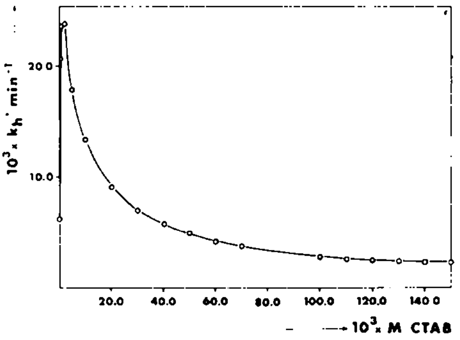

Fig. 2. Gross-rate constants for the hydrolysis of benzylidene acetophenone as a function of CTAB concentration in 0·1N NaOH solution, containing 0·2% methanol at 25°.

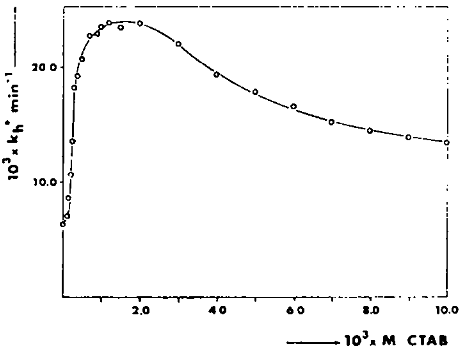

Fig. 3. Gross-rate constants for the hydrolysis of benzylidene acetophenone as a function of CTAB concentration in 0·1N NaOH solution, containing 0·2% methanol at 25°.

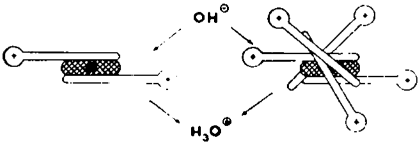

Fig. 4. Schematical representation of aggregation of amphiphilic ions with benzylidene aniline or benzylidene acetophenone at:

(a) low concentration and

(b) high concentration of amphiphile.

The black spot indicates the reactive site.

nature; in aqueous solution, therefore, we would expect aggregation of substrate and cationic amphiphile to occur, resulting in a positively charged species.

In order to start the proton-catalysed hydrolysis, this aggregate must be protonated: this process will be opposed by the electrostatic repulsions between the two cations so that the equilibrium

$$\begin{bmatrix}\text{Benzylidene aniline}\\ \text{(cationic)}\end{bmatrix}^{n\oplus} + H^{\oplus} \rightleftarrows \begin{bmatrix}\text{Reactive carbonium}\\ \text{(ion-cationic)}\end{bmatrix}$$

will be further to the left than that involving *no* charge repulsion in the absence of cationic amphiphile (see p. 1302)

$$\begin{matrix}\text{Benzylidene aniline}\\ \text{(zero charge)}\end{matrix} + H^{\oplus} \rightleftarrows \begin{bmatrix}\text{Reactive carbonium}\\ \text{(ion)}\end{bmatrix}$$

Hence the proton-catalysed hydrolysis is retarded by cationic amphiphilic compounds, and this effect should increase as the concentration of cationic amphiphile and the positive charge on the aggregate increase.

Conversely to start the hydroxyl ion-catalysed hydrolysis of benzylidene acetophenone, the positively charged aggregate must react with an OH^- ion; since now the charge interaction is *attractive*, the equilibria involving production of the reactive carbanion will be further to the right and the reaction will be catalysed (see p. 1302).

In both reactions, increasing the cationic concentration will result in the development of cationic micelles around the organic substrates; this we would expect to become important around the critical micelle concentration, and to result in steric hindrance to the approach of any ionic species (irrespective of its charge) and also of the water needed for the last steps in the reaction. In the case of the proton-catalysed hydrolysis this steric retarding effect should assist the charge repulsion effect already operating at lower concentrations. (These two stages are shown schematically in Fig. 4.)

However, in the case of the hydroxyl ion-catalysed hydrolysis, this screening effect will *oppose* the catalytic effect so that the rate constant should pass through a maximum as the cationic concentration is increased. As Figs. 1 and 2 show, that this is indeed the case.

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