

Polarography of Quinazoline

THE polarographic behaviour of quinazoline displays special features which are not shown by the related compounds quinoxaline, phthalazine and 1,5-naphthyridine.

The anomaly is found in the pH -dependence of the limiting current. In neutral and alkaline solution the wave has the height of a normal two-electron wave. Between pH 6 and pH 1.5 the wave splits into two and the sum of the height of these two waves diminishes to less than 10 per cent of the height in neutral solution. In more acid solution the height of the waves increases and in 40 per cent perchloric acid ($H_0 \sim 2.5$) it reaches approximately the height found in alkaline solution.

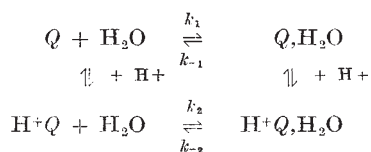
Whereas the wave-height of quinazoline at pH 6 is proportional to the square-root of the height of the mercury reservoir (diffusion controlled wave), the wave-height at pH 1.5 is independent of the height of the mercury reservoir, indicating that the wave-height is mainly governed by the rate of a chemical reaction.

4-Methylquinazoline and 2,4-dimethylquinazoline do not show this dependence of wave-height on pH ; nor do 4-methoxy-, 4-mercapto-, 4-methylmercapto-, 4-chloroquinazoline, and 3,4-dimethylquinazolinium iodide. 3-Methylquinazolinium iodide, however, shows a similar feature in all solutions where the polarograms can be measured before hydrolysis of the ring.

Quinazoline also displays anomalies in other respects. The base strength ($pK_a = 3.5$) is higher than expected (1.5, ref. 1) and the ultra-violet spectrum of the cation shows a hypsochromic shift compared with that of quinazoline. These anomalies have been explained by assuming that quinazoline in acid solution adds water with formation of an abnormal cation, 4-hydroxy-3,4-dihydroquinazolinium ion.

A dependence of wave-height on pH , similar to that of quinazoline, is found in the polarography of pyridine aldehydes^{2,3}. This is attributed to the fact that the aldehyde groups in the protonated pyridine aldehydes at pH near unity are mainly in the hydrated state, which is not reducible.

The polarographic behaviour of quinazoline is thus explained by assuming that the reducible species in acid solution is the normal quinazolinium ion, whereas the abnormal cation, 4-hydroxy-3,4-dihydroquinazolinium ion, is not reducible. According to this the polarography of quinazoline (Q) is governed by the following equilibria and the rate of these reactions:



with the four equilibrium constants:

$$K_1 = (Q, H_2O)/(Q)(H_2O) \quad (1)$$

$$K_2 = (H^+Q, H_2O)/(H^+Q)(H_2O) \quad (2)$$

$$K_3 = (Q)(H^+)/(H^+Q) \quad (3)$$

$$K_4 = (Q, H_2O)(H^+)/(H^+Q, H_2O) \quad (4)$$

The wave-height at $pH > 2.5$ is chiefly determined by the equilibrium concentration of the reducible, unprotonated quinazoline. This is shown by the fact that a similar curve with inflexion at the same pH (3.6) is found, when the extinction at 310 $m\mu$ of quinazoline is plotted against pH . The absorption at 310 $m\mu$ is mainly caused by quinazoline, whereas the abnormal cation has very little absorption at 310 $m\mu$.

At pH 1 the wave-height is essentially governed by the rate of the dehydration of the irreducible, abnormal

cation to the reducible, normal cation. The rate is the sum of an uncatalysed and an acid-catalysed reaction rate. The acid-catalysed dehydration is mainly responsible for the increase in wave-height between pH 0 and H_0 about -2. In more acid solution the equilibrium concentration of the normal cation increases, and this, together with the presence of some unhydrated, doubly-protonated cation, is also of importance for the wave-height.

The assumption of the irreducibility of the abnormal cation is substantiated by the fact that 3-methyl-4-hydroxy-3,4-dihydroquinazoline is polarographically irreducible and only yields an anodic wave.

4-Chloroquinazoline is polarographically reducible and yields two two-electron waves in neutral solution. By controlled potential reduction the first wave was shown to be caused by a reduction to quinazoline. In acid solution at 25° C the compound is rapidly hydrolysed to the irreducible 4-quinazolone, but at -5° to -10° C the compound is stable enough for polarographic investigation in 40 per cent alcohol. At pH 1, 4-chloroquinazoline yields a two-electron wave followed by two one-electron waves; the sum of the heights of the one-electron waves is equal to the height of the two-electron wave. The two one-electron waves are found at the same potentials as those of quinazoline, but the wave-height of quinazoline under the same conditions is very much smaller. This indicates that the quinazolinium ion formed in the reduction of 4-chloroquinazoline is reduced before it has time to be hydrated.

From (3) and (4) it follows that:

$$pH = pK_3 + \log (Q)/(H^+Q) = pK_4 + \log (Q, H_2O)/(H^+Q, H_2O) \quad (5)$$

The experimental results show qualitatively that $(Q) \gg (Q, H_2O)$ and $(H^+Q) \ll (H^+Q, H_2O)$, and thus at the experimentally determined:

$$pK_A(3.6) (Q) \simeq (H^+Q, H_2O) \quad (6)$$

Introducing (1), (2) and (6) into (5) one gets:

$$pK_A = pK_3 + \log (H_2O) + \log K_2 = pK_4 + \log (H_2O) + \log K_1 \quad (7)$$

pK_3 has been estimated to be 1.5 (ref. 1) and pK_4 has been measured at 7.77 (ref. 4). From these the values $K_1 \simeq 1.5 \times 10^{-6}$ and $K_2 \simeq 2$ are obtained. According to this estimate about 99 per cent of the protonated quinazoline is present as the abnormal cation. From this value and the ratio of the limiting current at pH 1.3 and the diffusion current at pH 7 (and assuming the same diffusion coefficients for the different forms of quinazoline) one can calculate⁵ the rate of the dehydration at pH 1.3; $k_{-2} = 0.2 \text{ sec}^{-1}$. The value of k_{-1} at pH 10 has been found⁴ by a method of flow technique to be 0.077 sec^{-1} .

The uncertainty of the estimate of k_{-2} is mainly due to the difference between pK_2 and the estimated value 1.5. pK_2 is probably equal to or greater than pK of pyrimidine (1.3); spectroscopic data (concentration of normal cation ~ 0 per cent)⁴ seem to exclude more than 2 per cent of the normal cation in the equilibrium at pH about 1. This means that k_{-2} with a high probability has a value between 0.1 and 0.4 sec^{-1} at pH 1.3.

HENNING LUND

Department of Chemistry,
University of Aarhus,
Aarhus C, Denmark.

¹ Albert, A., Armarego, W. L. F., and Spinner, E., *J. Chem. Soc.*, 2689 (1961).

² Volke, J., *Experientia*, **13**, 274 (1957).

³ Tirouflet, J., and Laviron, E., *C.R. Acad. Sci., Paris*, **247**, 217 (1958).

⁴ Armarego, W. L. F., *J. Chem. Soc.*, 561 (1962).

⁵ Koutceky, J., *Coll. Czech. Chem. Commun.*, **18**, 597 (1953).