Polarographic study of 3,5-dioxopyrazolidines

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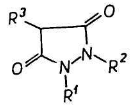
The polarographic properties of 3,5-dioxopyrazolidines (Ketazon, Fenylbutazon, Trimetazon) studied by means of A.C. and S.W. techniques are described. At the frequency of 120 c.p.s. the relationship between the height of double waves and pH has been investigated. The change in the ratio of the heights of double waves is a function of pH and is explained by the dissociation of the enol form of the investigated substances. The concentration dependence is of exponential character. The wave height decreases with temperature and the wave disappears in nonaqueous medium. This indicates that the waves under investigation are adsorption waves.

The substances of the group of 3,5-dioxopyrazolidines are of continuing interest because of their outstanding antirheumatic properties. The physicochemical properties of these compounds have been studied mainly analytically [1—6].

As the investigated derivatives of 1,2-diphenyl-3,5-dioxopyrazolidine are not active in direct current polarography (D.C.), the alternating current polarography (A.C.) [7] and square wave polarography (S.W.) [8] have been used (Scheme 1).



$R^1 = R^2$	R^3	Name
C_6H_5	$CH_3COCH_2CH_2$	Ketazon
C_6H_5	$(CH_3)_3CCOCH_2CH_2$	Trimetazon
C_6H_5	$CH_3CH_2CH_2CH_2$	Fenylbutazon

Scheme 1

Alternating current polarography is also suitable for the investigation of adsorption processes (tensammetry) at a dropping mercury electrode [9, 10]. In aqueous medium both reduction and adsorption processes take place. In nonaqueous medium the reduction processes are enhanced while the adsorption processes are suppressed [11— 13].

Experimental

Chemicals: Ketazon, Trimetazon, Fenylbutazon (all Spofa), Britton—Robinson buffer solution, ethanol, methanol, pyridine (all UV Merck), LiCl, anal. grade, *p*-hydroxyazobenzene, $ZnSO_4 \cdot 7H_2O$, anal. grade (all Lachema).

Instruments: D.C. polarograph OH-102, A.C. adapter OH-993, S.W. polarograph OH-104 (all Radelkis), pH-meter pHM-26 (Radiometer).

a) pH Dependence of the wave height

Ketazon (6×10^{-4} M) in Britton—Robinson (BR) buffer solution (pH 8.03) was investigated polarographically using A.C. technique in three-electrode arrangement (dropping mercury electrode, saturated calomel electrode, and mercury bottom). The pH value varied by adding the standard BR solution to the sample. The pH was measured and the polarographic wave was recorded. Trimetazon and Fenylbutazon were processed in the same way. At the frequency of 120 c.p.s. all three substances showed two pairs of waves (Figs. 1 and 2). The ratio of the heights of double waves changes

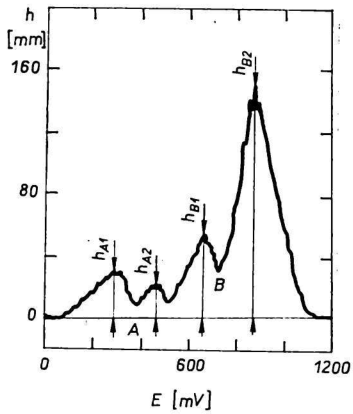


Fig. 1. Ketazon (A.C. polarogram), 6×10^{-4} M in BR buffer solution, pH 6.89, $S = 2 \times 10^{-10}$ A, $f = 120$ c.p.s., $U_s = 20$ mV.

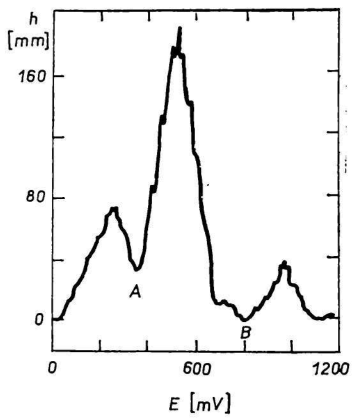


Fig. 2. Ketazon (A.C. polarogram), 6×10^{-4} M in BR buffer solution, pH 5.66, $S = 2 \times 10^{-10}$ A, $f = 120$ c.p.s., $U_s = 20$ mV.

with pH (Fig. 3). The pH dependence of the arithmetic mean of the corresponding parts of double wave (h_{A1}, h_{A2} or h_{B1}, h_{B2}) was plotted. A similar change in the wave heights was also observed in the S.W. polarography. Both double waves reach the same height at a pH characteristic of the individual substances: Ketazon at pH 6.12, Trimetazon at pH 6.85, Fenylbutazon at pH 7.11. A small shift of the E_s value (summit potential) of double waves appears with a change in the pH value.

b) Concentration dependence of the wave height

This relationship was investigated in BR solution at pH 8.56 and $E_s \doteq -1$ V. The curve representing the concentration dependence of the wave height shows an exponential character over the concentration range from 5×10^{-3} to 5×10^{-4} M and approaches tangentially the value of 160 mm. The change in concentration brings about a shift in E_s.

$$c = 5 \times 10^{-3}\ \text{M}, \qquad E_s = -1.00\ \text{V};$$

$$c = 5 \times 10^{-4}\ \text{M}, \qquad E_s = -0.86\ \text{V}.$$

c) Temperature dependence of the wave height

The wave height of Ketazon (1×10^{-3} M in BR solution; pH 7.48) was recorded by means of A.C. technique in the temperature range from 20 to 60°C. The temperature dependence of the waves of *p*-hydroxyazobenzene (2×10^{-3} M in BR solution; pH 8.65; organic reducible substance), Zn^{2+} (2×10^{-3} M in BR solution; pH 5.22; inorganic reducible substance), and pyridine (1×10^{-3} M in BR solution; pH 7.48; substance adsorbed at the mercury electrode) was also recorded. The temperature dependence of the height of Ketazon wave shows a falling tendency like that of pyridine (Fig. 4).

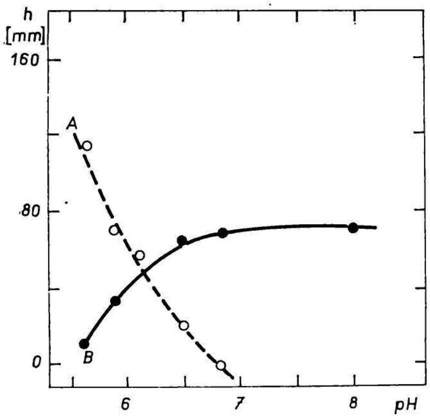


Fig. 3. pH Dependence of the height of double waves (A.C. polarogram). Ketazon, 6×10^{-4} M in BR buffer solution.

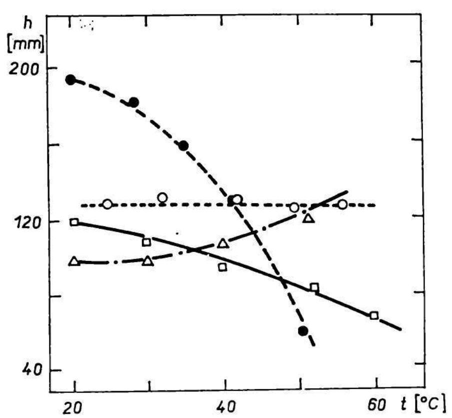


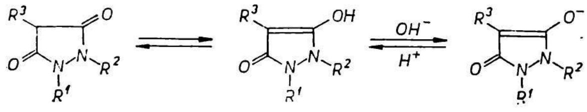
Fig. 4. Temperature dependence of the height of double waves.
□ Ketazon; ○ Zn^{2+}; ● pyridine; △ *p*-hydroxyazobenzene.

The polarographic properties of Ketazon were investigated in water-free methanolic medium. Ketazon (1×10^{-3} M) dissolved in methanol containing 0.1 N-LiCl as supporting electrolyte showed no polarographic activity either in the A.C. or in the S.W. polarography.

Results and discussion

The investigated 3,5-dioxopyrazolidines are not active in the D.C. polarography. In the A.C. polarography they appear to be slightly active at 60 c.p.s. but at 120 c.p.s. they exhibit well developed double waves. The minimum between two waves of the double wave at 120 c.p.s. [14] corresponds to the maximum of the single wave at 60 c.p.s. Two pairs of double waves exhibited by 3,5-dioxopyrazolidines correspond to two single waves. This has also been confirmed by S.W. technique.

For all substances under investigation it was established that the ratio of the heights of double waves varies with pH (Figs. 1 and 2). The double waves reach the same height at a pH, which is characteristic of each substance: Ketazon 6.12, Trimetazon 6.85, and Fenylbutazon 7.11. This phenomenon may be explained by the assumption that the active form is not ionized in acid medium while the ionized enol form of 3,5-dioxopyrazolidines occurs in alkaline medium (Scheme 2).



Scheme 2

The above sequence indicates that Ketazon is most acidic while Fenylbutazon is least acidic. The order of the apparent pK' values determined in water is similar: Ketazon 3.67, Trimetazon 3.98 [16], and Fenylbutazon 4.52 [17]. The curve representing the concentration dependence of the height of double wave is of exponential character. However, a similar dependence is manifested in A.C. polarography by the majority of organic substances which are reducible or adsorbable [15]. The temperature dependence of the wave height of Ketazon shows a falling tendency similarly as is the case with pyridine, which manifests itself only by an adsorption wave (Fig. 4).

Based on these results as well as on the fact that Ketazon is not polarographically active in water-free medium it may be assumed that the investigated 3,5-dioxopyrazolidines exhibit adsorption waves. According to pH the ionized, non-ionized, or both forms may be active.

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