

INVESTIGATION OF THE MECHANISM OF THE
POLAROGRAPHIC REDUCTION OF THE SYDNONEIMMONIUM
CATION

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The polarographic reduction of the sydnoneimmonium cation (I) was investigated in the case of 3- β -phenylisopropylsydnoneimine hydrochloride (sydnophen). The effect of the pH, alcohol concentration, ionic strength, and surface-active substances was studied, and the electrolysis was carried out at a controllable potential under various conditions. The cyclic voltamperograms were recorded. A mechanism for the reduction of I is proposed. Cleavage of the ring of I in the near-electrode space is observed in unbuffered media. The first direct proof of the existence of the unstable sydnoneimine base was obtained.

Sydnoneimines constitute a pseudoaromatic system and are classified as so-called mesoionic heterocyclic compounds. The aromatic sextet in mesoionic heterocycles is realized by partial ejection of one of the seven $2p_z$ electrons of the ring to the "exocyclic group" (for example, the oxygen atom in sydnones) or by complete ejection of the electron to the anion (as in sydnoneimine salts). It has been established that sydnones [1-3] and sydnoneimine salts [4] are capable of reduction on a dropping mercury electrode. The mechanism of the reduction of sydnones in aqueous alcohol media is determined by the pH of the medium: N-substituted α -amino acids are formed in acidic media with the consumption of six electrons, whereas four electrons participate in the reduction in neutral and alkaline media, and the reaction products are the corresponding substituted hydrazine- α -carboxylic acids [1-3]. Preliminary assumptions regarding the mechanism of the reduction of sydnoneimines have been expressed [4]. Inasmuch as 3-aralkyl- and 3-alkylsydnoneimines undergo the same type of reduction [4], we selected 3- β -phenylisopropylsydnoneimine hydrochloride (I) for a more detailed study of the polarographic behavior of this class of compounds. This choice is also determined by the fact that I is a psychotropic medicinal preparation (sydnophen)[5] and is the starting material in the synthesis of another preparation - sydnocarb [6].

The study of the polarographic behavior of I was carried out in aqueous and aqueous alcohol buffered and unbuffered media with $\text{pH} < 7$, inasmuch as the sydnoneimine base (II) formed in alkaline solutions is extremely unstable and is readily converted, with ring opening, to the N-nitroso derivative of the nitrile of an N-substituted α -amino acid (III) [7, 8].

A single distinctly expressed wave is observed in the reduction of I in buffered media containing 10% ethanol over the entire investigated pH range. At $\text{pH} > 3$, the discharge current of the base electrolyte is shifted to positive potentials as the concentration of I increases, and this is apparently associated with catalytic hydrogen evolution, inasmuch as the catalytic current falls as the buffer capacity of the solution and the proton concentration decrease. An increase in the percentage of the organic solvent (ethanol) also has the same effect, and this is characteristic for processes that are limited by the rate of the antecedent protonation reaction [9].

The magnitude of the $E_{1/2}$ value of the reduction wave of I is independent (Fig. 1) of the pH ($E_{1/2} = -0.88$ V for solutions containing 10% ethanol). This is apparently associated with the fact that the sydnoneimmonium cations (I) are extremely weak acids and the $\text{I} \rightleftharpoons \text{II} + \text{H}^+$ equilibrium is shifted practically

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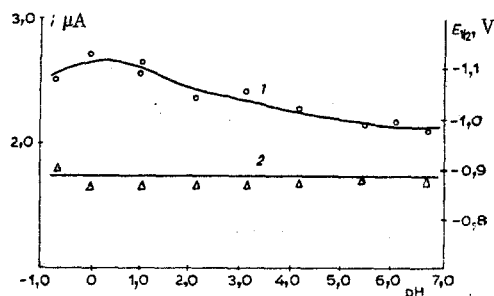


Fig. 1

Fig. 1. Dependence of i_{lim} (1) and $E_{1/2}$ (2) for the reduction of I on the pH (in 10% ethanol).

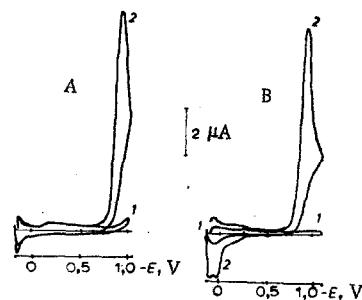


Fig. 2

Fig. 2. Cyclic voltamperograms of I in 10% ethanol (0.5 V/sec): A) in 0.1 M HClO_4 ; B) at pH 6.16; 1) base electrolyte; 2) 0.3 mM I.

completely to favor I over the investigated pH range. However, the addition of a second proton to mono-cation I was not observed even in concentrated acids [10].

The limiting current increases somewhat as the pH increases from -1.0 to 1.0. It again begins to decrease as the pH is increased further and takes on an almost constant value at $\text{pH} > 4$ (Fig. 1).

At all of the pH values the limiting current depends linearly on the concentration of I, and an increase in the percentage of ethanol from 10 to 50% in 0.1 N HCl and in a buffer solution with pH 6.75 leads to a decrease in the height of the wave in conformity with the change in the viscosity of the medium: $i_{lim} \cdot \eta^{1/2} = \text{const}$. From this it can be concluded that the limiting current has diffusion character in all of the investigated media.

In all likelihood, the reduction of I takes place in the adsorbed state. As the alcohol concentration increases, the adsorbability of I decreases, a first-order maximum develops on the wave, and the $E_{1/2}$ value is shifted to negative potentials; however, the latter effect is small, inasmuch as it may be compensated to a certain degree [11] by an increase in the activity of cation I.

Coulometric measurements in a buffer solution with pH 6.1 (10% ethanol) give $n = 4.2 \pm 0.1$, whereas $n = 5.1 \pm 0.1$ during electrolysis in 0.1 N HClO_4 in 10% alcohol. This result is in agreement with the ratio of the heights of the waves of reduction of I at pH 6.1 and in 0.1 N perchloric acid. An anode wave ($E_{1/2} = +0.03$ V) is observed on the polarogram after electrolysis of I at pH 6.1, whereas the products of electrolysis of I in acidic media are incapable of oxidation on a mercury electrode. An anode peak similarly appears during voltamperometry with triangular imposition of the pulse in neutral medium, whereas the anode peak is absent in acidic media (Fig. 2).

We turned our attention to the fact that a new small wave (this is shown in the case of the buffer solution with pH 4.8, 10% ethanol) appears in addition to the wave of reduction of I at more negative potentials ($E_{1/2} = -1.32$ V when $\mu = 0.1$) as the buffer capacity decreases considerably. In unbuffered aqueous KCl solutions this wave is expressed considerably more distinctly. Its height increases appreciably as the ionic strength of the solution increases (Fig. 3) and does not change with time. This phenomenon can be explained as follows. Inasmuch as the reduction of I is accompanied by the consumption of protons, alkalization of the near-space should occur in solutions with low buffer capacities and, especially, in unbuffered media; the alkalization effect should increase as the ionic strength increases as a result of a decrease in the $|\psi^A|$ potential [11]. Considering the instability of sydnoneimines in alkaline media, it can be assumed that partial opening of the sydnoneimine ring of I to give nitrosonitrile III occurs in the near-electrode space, and the wave at more negative potentials corresponds to the reduction of III. In fact, the addition of an equimolecular amount of NaOH to an unbuffered solution of I leads [7, 8] to disappearance of the wave of reduction of I with the simultaneous appearance of a wave of reduction of nitrosonitrile III, the $E_{1/2}$ value of which corresponds to the $E_{1/2}$ value of the second wave that appears in unbuffered media. The wave of reduction of nitrosonitrile III formed by the addition of alkali to a solution of I is half the wave of reduction of starting I, and the $E_{1/2}$ value of III is independent of the alkali concentration. Acidification of the alkaline solution with excess mineral acid, as one should have expected [12], led to quantitative cyclization of III to I.

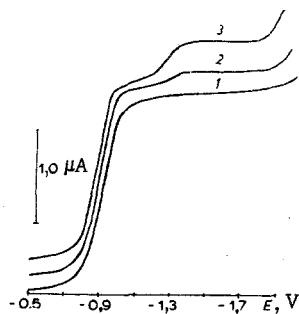


Fig. 3

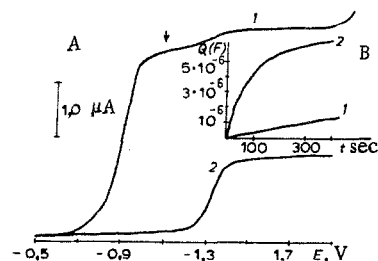


Fig. 4

Fig. 3. Polarograms of 0.5 mM I in KCl solutions of different concentrations: 1) 0.01 M; 2) 0.1 M; 3) 1.0 M.

Fig. 4. A) Polarograms of a 1.0 mM solution of I in a 0.1 M KCl base electrolyte: 1) before electrolysis; 2) after electrolysis. B) Change with time in the amount of electricity during electrolysis at 1.1 V: 1) 0.1 M KCl base electrolyte; 2) a 1.0 mM solution of I.

Of course, under polarographic reduction conditions alkalization occurs only in the near-electrode space, and the second wave that appears in unbuffered media is stable with time. Electrolysis in unbuffered media should bring about alkalization of the entire volume of the solution. Moreover, the concentration of I should decrease not only due to electrical reduction of I but also as a result of autocatalytic cleavage of I to III under the influence of hydroxide ions. In fact, in the electrolysis of 5 ml of a 1.0 mM solution of I in a 0.1 M KCl base electrolyte ($E = -1.1$ V) the wave of reduction of I vanishes completely after 200 sec, and only $5.6 \cdot 10^{-6}$ F is consumed (of the $20 \cdot 10^{-6}$ F necessary for the four-electron reduction of the amount of I used), but the wave of reduction of III increases sharply (Fig. 4). The concentration of I after electrolysis with this amount of electricity should have been 0.72 mM. The wave of reduction of III observed after electrolysis corresponds precisely to this concentration.

It has been shown [7, 8] that sydnoneimine base II is an intermediate in the formation of nitrositrile III from sydnoneimmonium cations I. However, even when the wave of reduction of nitrositrile III is seen on the polarograms of sydnophen, the wave of reduction of base II is not observed. We observe only a considerable increase in the slope of the wave of I as compared with the slope of the wave of I in acidic media.* This phenomenon can be explained as follows. Cation I undergoes reduction in unbuffered media at the potentials of the start of the wave. The concentration of base II, which is reduced with somewhat more difficulty than cation I, increases as the current and, consequently, the pH of the near-electrode layer increases. This also leads to the observed increase in the slope of the wave, but the process is complicated by the simultaneous conversion of II to nitrositrile III. This reaction is catalyzed by hydroxide ions, i.e., it is accelerated as the wave of reduction of sydnophen increases. When hydrochloric acid is added to a solution of KCl in concentrations lower than the concentration of I, reduction of only cations I proceeds initially along the trend of the wave as a consequence of the relative acidification of the near-electrode layer; and it is only after this that all of the H_3O^+ ions in this layer are depleted, and the protons are consumed through cation I and water. As a result, the near-electrode space becomes alkaline spasmodically. This jump is appreciable on the polarogram (Fig. 5) — the wave at this site is branched, and its upper portion corresponds to the same processes that also occur in KCl media — reduction both of cation I and of base II.

As the unbuffered solution is acidified, the wave of reduction of III decreases and then vanishes. Calculations by the latent-current method [13] provide evidence that four protons are consumed in the reduction of I.

The effect of the ionic strength of the solution on the reduction of I was studied. It followed from the theoretical premises [11] that the reduction of cation I should be hindered as the ionic strength increases. However, it was found that an increase in the KCl concentration from 0.01 to 1.8 M does not affect the $E_{1/2}$ value. This is apparently associated with the fact that the reduction of I proceeds in the adsorbed state. The adsorption of cation I reduces to a considerable degree the change in the $|\psi'|$ potential that should

*It should be noted that the slope of the wave of I also increases in buffered media as the pH increases.

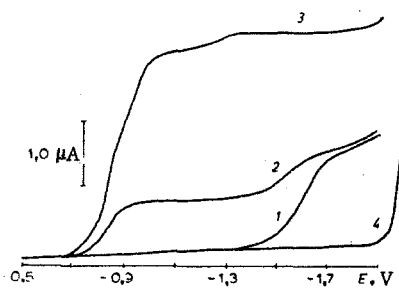


Fig. 5

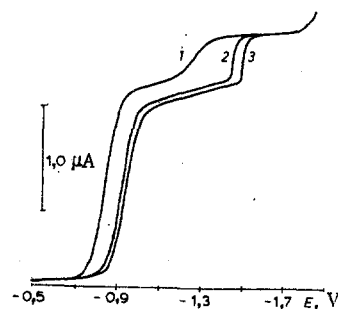


Fig. 6

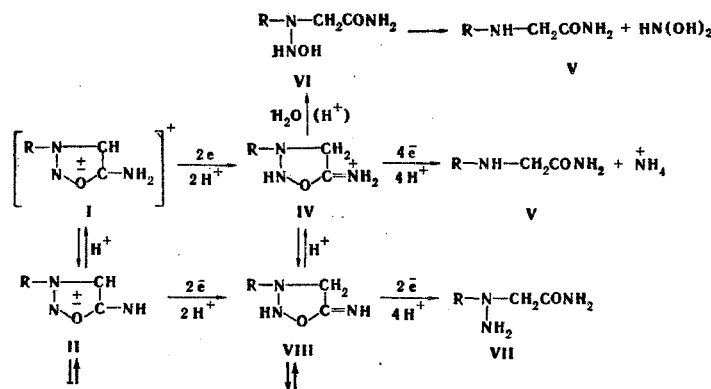
Fig. 5. Polarograms of I in 0.1 M KCl solution containing HCl: 1) 0.5 mM HCl; 2) 0.5 mM HCl + 0.26 mM I; 3) 0.5 mM HCl + 0.86 mM I; 4) 0.1 M HCl base electrolyte.

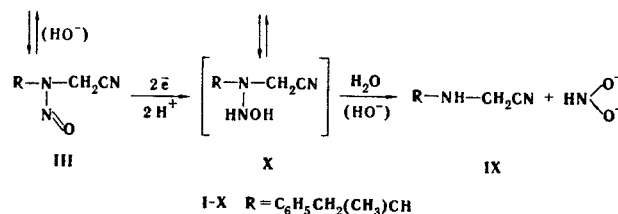
Fig. 6. Polarogram of a 0.5 mM solution of I in base electrolytes: 1) 1.0 M KCl; 2) 1.0 M KCl + 0.5 mM $(C_4H_9)_4NClO_4$; 3) 1.0 M KCl + 1.0 M $(C_4H_9)_4NClO_4$.

have occurred as the KCl concentration increases, and the change in the adsorbability of I is probably small as the ionic strength of the solution increases. To confirm this conclusion we added tetrabutylammonium perchlorate to an unbuffered KCl solution. At the investigated potentials the tetrabutylammonium ion, added to the solution in approximately equimolecular amounts with respect to cation I, is capable of displacing the latter from the electrode surface. As a result, a shift in the wave of reduction of I to negative potentials is observed (by 77 mV when 0.5 mM tetrabutylammonium perchlorate solution in 1.0 M KCl is added and by 59 mV when 0.5 mM tetrabutylammonium perchlorate solution in 0.1 M KCl is added). In this case the slope of the wave of reduction of I increases somewhat, and its height also decreases. The latter phenomenon, as in the case of an increase in the KCl concentration, can be explained by an increase in the alkalization of the near-electrode space. However, when the tetrabutylammonium cation is present even in low concentrations (0.5 mM), the reduction of nitrositrile III is completely suppressed because of the strong surface activity of this cation. The wave of reduction of III appears only when the potential of desorption of the tetrabutylammonium cations is reached. As a result, this wave has an unusual form (the current reaches the limiting value sharply spasmodically), and it is shifted to the negative potential region as the concentration of the tetrabutylammonium ion increases (Fig. 6).

It might have been expected that the addition of gelatin would also bring about displacement of I from the electrode surface. However, it was found that when 0.01% gelatin is present, the reduction of I in KCl solution is not inhibited as the ionic strength increases, and there is an apparent shift of the $E_{1/2}$ value to positive potentials ($\Delta E_{1/2}/\Delta \log C_{KCl} = 14$ mV) as a result of a decrease in the slope of the wave. The addition of gelatin leads to the disappearance of the wave of reduction of III simultaneously at all of the investigated KCl concentrations (from 0.01 to 1.8 M). These same phenomena are observed during polarography of I with the addition of excess acid, and in the case of gelatin the experimental facts are apparently associated with the proton-donor properties of this surface-active substance [14].

Our study makes it possible to assume the following refined scheme for the polarographic reduction of the sydnoneimmonium cation:





The sydnoneimine cation in the adsorbed state is reduced with the participation of two electrons* to dihydro compounds IV, which can be considered to be the cation of the cyclic imino ether. In moderately acidic media, IV, by taking on four electrons, is reduced to the amide of an N-substituted aminoacetic acid (V) and the ammonium ion. In strongly acidic media the rate of reduction proved to be comparable to the rate of acid hydrolysis of the imino ether (IV) to hydroxylamine derivative VI. As one might have expected, the latter does not undergo reduction to substituted hydrazine VII (the products of reduction in strongly acidic media do not give anode waves) but is apparently hydrolyzed further to the amide of an amino acid (V) and HN(OH)₂. In neutral and weakly acidic media cation IV dissociates by splitting out a proton, and the corresponding base (VIII) is reduced with the participation of two electrons to hydrazine derivative VII, which also gives the anode waves mentioned above.

The reduction of both cation IV and the corresponding base VIII occurs at more positive potentials than the reduction of starting sydnoneimmonium cation I. As a result, one overall wave is observed in buffered solutions over all of the investigated pH ranges, a six-electron wave is observed in acidic media, and a four-electron wave is observed in neutral media. The acid hydrolysis of IV leads to an understatement in strongly acidic media of the real consumption of electrons measured by means of a microcoulometer.

As we have already stated above, the dissociation of cation I becomes appreciable in neutral media — the slope of the wave increases, and the wave is branched at low proton concentrations in a nonbuffered medium. This is the first direct evidence for the existence of the unstable sydnoneimine base II.

As was demonstrated in [12], nitrositrile III is reduced in alkaline media to aminoacetonitrile IX — the second wave that appears at more negative potentials in unbuffered media corresponds to this process. The opening of cyclic imino ether VIII should be catalyzed not only by acids (through cation IV) but also by alkalis. In this case reversible opening to nitrile X, which is capable of conversion to aminonitrile IX, may apparently occur. As a result, a decrease in the height of the wave of reduction of I to the current corresponding to transfer of two electrons might be observed in alkaline media, but this cannot be recorded because of the instability of sydnoneimines at pH > 7.

EXPERIMENTAL METHOD

The polarographic investigations were carried out in a thermostatted cell at 25 ± 0.1°. The polarograms were recorded with a Radiometer PO-4 polarograph. A dropping mercury electrode with forced detachment of the drops was used (m = 0.75 mg/sec and t = 0.26 sec), and a saturated calomel electrode served as the anode.

The cyclic voltamperograms were recorded on a hanging mercury drop, and the measurements were made at 25 ± 0.1° by means of a PAR-170 electrochemical system (the rate of imposition of the potential was 0.1-1.0 V/sec).

A cell with separation of the anode and cathode spaces was used for electrolysis at a controllable potential. A mercury electrode with an area of 4.9 cm² was used as the cathode. Platinum gauze served as the anode. A 1 N K₂SO₄ solution was poured into the anode chamber. The comparison electrode was a saturated calomel electrode. A constant potential was maintained by means of a PAR-170 electrochemical system. Nitrogen was passed through the catholyte during the electrolysis. The periodic circuit of the electrolyzer was closed, and the polarograms of the solution in the cathode space were recorded by means of a dropping mercury electrode placed in the same electrolyzer. The solutions of the background electrolyte were subjected to prior electrolysis at the same potential in order to determine the amount of electricity expended in the reduction of sydnophen (see Fig. 4).

* In [4] it was erroneously indicated that four electrons are consumed in the reduction of sydnoneimines to IV.

LITERATURE CITED

1. P. Zuman, Coll. Czech. Chem. Commun., 25, 3245 (1960).
2. P. Zuman, Coll. Czech. Chem. Commun., 25, 3252 (1960).
3. P. Zuman, Coll. Czech. Chem. Commun., 25, 3265 (1960).
4. S. G. Mairanovskii, L. E. Kholodov, and V. G. Yashunskii, Zh. Obshch. Khim., 33, 347 (1963).
5. R. A. Al'tshuler, O. N. Volzhina, F. Ya. Leibel'man, M. D. Mashkovskii, I. S. Slyusarenko, and V. G. Yashunskii, Khim.-Farmats. Zh., No. 4, 59 (1971).
6. L. E. Kholodov, V. G. Yashunskii, R. A. Al'tshuler, M. D. Mashkovskii, L. F. Roshchina, S. I. Shershneva, F. Ya. Leibel'man, O. N. Volzhina, L. Sh. Gorodetskii, and N. A. Petrova, Khim.-Farmats. Zh., No. 1, 50 (1973).
7. V. G. Yashunskii, L. E. Kholodov, and E. M. Peresleni, Zh. Obshch. Khim., 33, 3699 (1963).
8. L. E. Kholodov, E. V. Borisov, and V. G. Yashunskii, Khim. Geterotsikl. Soedin., 702 (1968).
9. S. G. Mairanovskii and V. P. Gul'tyai, Élektrokimiya, 1, 76 (1965).
10. L. E. Kholodov, A. M. Khelem, and V. G. Yashunskii, Zh. Organ. Khim., 3, 1870 (1967).
11. S. G. Mairanovskii, Catalytic and Kinetic Waves in Polarography [in Russian], Nauka, Moscow (1966).
12. L. E. Kholodov and V. V. Alekseev, Zh. Fiz. Khim., 39, 1566 (1965).
13. L. G. Feoktistov and S. I. Zhdanov, Izv. Akad. Nauk SSSR, Otd. Khim. Nauk, 45 (1963).
14. S. G. Mairanovskii and V. P. Gul'tyai, Zavod. Lab., 1070 (1972).