POLAROGRAPHIC REDUCTION OF BENZAZOLYL-SUBSTITUTED PYRIDINIUM SALTS

V. P. Kadysh, Ya. P. Stradyn',
É. S. Lavrinovich, and P. P. Zarin

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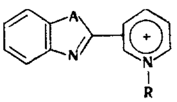
N-Methyl- and N-benzyl-substituted 2-, 3-, and 4-benzazolypyridinium (BAP) salts are reduced on a dropping mercury electrode (DME) to give a free radical in the first step and the corresponding dihydropyridine derivative in the second step. The free radicals of 2- and 4-BAP salts are distinguished by high stability as compared with other radicals with a pyridine structure owing to delocalization of the unpaired electron over the conjugated system and can be recorded by ESR spectroscopy. A peculiarity of the BAP salts is their facile reduction on the electrode; this is particularly true of the 2- and 4-benzoxazolyl- and benzothiazolyl-substituted salts.

It is well known that N-methyl- and N-phenyl-substituted quaternary pyridinium salts are redueed on a dropping mercury electrode (DME) in two one-electron steps via a radical mechanism with the formation of N-alkyldihydropyridine derivatives, and the free radicals formed in the first step in the electroreduction are partially dimerized [1-4].

Inasmuch as the polarographic reduction of N-methyl- and N-benzyl-substituted 2-, 3-, and 4-benzazolylpyridinium (BAP) salts with structures I-XVI, which have physiological activity, is sui generis a model of hydride reduction [5], it seemed of value to clear up the problem of the peculiarities of the mechanism of the electrochemical reduction of these compounds. In particular, it seemed of interest to determine whether the BAP salts differ from simple N-substituted pyridinium salts with respect to the mechanism of their electroreduction, whether only the pyridinium ring or the conjugated system as a whole is involved in the electroreduction process, and to what extent the presence and position of a benzazole substituent in the pyridine ring affect the ease and mechanism of the electroreduction.



I-XVI

A = O, S, NH. R = $-CH_3$, $-CH_2C_6H_5$

A comparison of the experimental data presented in Table 1 enabled us to isolate some characteristic pecularities of the polarographic reduction of the investigated compounds and to link them with the peculiarities of the structures of the particles reduced on the electrode.

Three reduction waves are observed on the polarograms of N-methyl- and N-benzyl-2- and 3-benzoxazolyl- and benzothiazdyl-substituted pyridinium salts (I, II, IV, V, IX, and XII), whereas two reduction waves are observed on the polarograms of the corresponding 4-substituted compounds (III, VI, X, XI, XIII, and XIV). Moreover, the $E_{1/2}$ values of the 4-isomers are close to the $E_{1/2}$ values of the 2-isomers but are more positive as compared with the $E_{1/2}$ values of the 3-isomers. The N-methyl- and N-benzyl-3- and 4-benzimidazolylpyridinium salts (VII, VIII, XV, and XVI) each give three reduction waves.

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TABLE 1. Half-Wave Potentials ($E_{1/2}$) and Limiting Currents (i_{lim}) for N-Substituted Benzazolylpyridinium Salts in Dimethylformamide with a 0.1 N Tetrabutylammonium Iodide Background Electrolyte

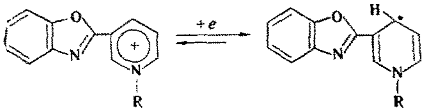
Compound	R	A	Substituent position	Anion	I wave		II wave		III wave	
					i_{lim}, μA	$-E_{1/2}$, V	i_{lim}, μA	$-E_{1/2}$, V	i_{lim}, μA	$-E_{1/2}$, V
I	CH_3	O	2	I^-	1,17	0,27	0,58	0,97	0,78	1,62
II	CH_3	O	3	I^-	1,04	0,41	0,24	1,51	1,28	1,86
III	CH_3	O	4	I^-	1,37	0,27	1,54	1,00		
IV	CH_3	S	2	I^-	1,21	0,36	0,74	0,97	0,52	1,60
V	CH_3	S	3	I^-	1,18	0,45	0,46	1,31	1,23	1,75
VI	CH_3	S	4	I^-	1,31	0,30	1,37	0,95		
VII	CH_3	NH	3	I^-	0,73	0,59	0,76	1,56	1,29	2,28
VIII	CH_3	NH	4	I^-	1,06	0,52	0,80	1,21	0,22	1,91
IX	$CH_2C_6H_5$	O	3	Br^-	1,20	0,38	0,46	1,35	1,07	1,87
X	$CH_2C_6H_5$	O	4	Br^-	1,42	0,21	1,33	0,98		
XI	$CH_2C_6H_5$	O	4	I^-	1,25	0,22	1,36	0,97		
XII	$CH_2C_6H_5$	S	3	Br^-	1,09	0,38	0,46	1,34	1,13	1,75
XIII	$CH_2C_6H_5$	S	4	Br^-	1,20	0,23	1,14	0,92		
XIV	$CH_2C_6H_5$	S	4	I^-	1,40	0,23	1,25	0,93		
XV	$CH_2C_6H_5$	NH	3	Br^-	0,74	0,52	0,42	1,66	0,68	2,23
XVI	$CH_2C_6H_5$	NH	4	Br^-	1,00	0,42	0,86	1,15	1,53	2,10

It was shown by a millicoulometric method and also by calculations from the Il'kovich equation that the first wave of all of the investigated N-substituted BAP salts corresponds to a one-electron process. Partial reversibility of the electrochemical process corresponding to the first wave was confirmed by the presence of an anode peak on the oscillopolarogram at a scanning rate of 1 V/sec and by recording of Breyer ac polarograms (Fig. 1).

The ESR spectra recorded under conditions of electrochemical generation of radicals at potentials of the plateau of the limiting current of the first wave (−1.4 V) prove the formation of free radicals during the electroreduction of 2- and 4-substituted BAP salts. Consequently, free radicals that are sufficiently stable for experimental detection are formed during the electroreduction of the latter, while the radicals formed during the electroreduction of most of the simple pyridinium salts have low stabilities and their development is only postulated on the basis of indirect data [1-4]. This peculiarity of the BAP salts is explained by substantial stabilization of their radicals due to delocalization of the unpaired electron over the entire conjugated system. However, in the case of the 3-isomers, in which conjugation of the pyridinium system with the benzazolyl ring is disrupted, the radicals lose their unusually high stability and cannot be recorded by ESR spectroscopy.

A comparison of the experimental data with the literature data on the reduction of other pyridinium salts enabled us to represent the electroreduction of the investigated compounds by a combination of a series of reactions.

The first wave in the electroreduction of BAP salts corresponds to partially reversible transfer of one electron:



(1)

The radicals thus formed are either further reduced in subsequent steps or (in the case of the 3-isomers) are also dimerized in the near-electrode space. We were unable to preparatively isolate dimers from the solution after controllable potential electrolysis (CPE), but the polarographic criteria for II – the rectilinear character of the graph of the dependence of log $[i^{2/3}/(i_d - i)]$ on E (correlation coefficient 0.996) (Fig. 2) and the shift in the $E_{1/2}$ value to more positive values by 20 mV as the depolarizer concentration increases by one order of magnitude (Fig. 3) in conformity with the Koutecký–Hanuš equation [6] – constitute evidence in favor of the fact that dimerization of the free radicals formed as a result of the first step in the electroreduction proceeds in parallel to transfer of a second electron. It should be noted that because of the incomplete reversibility of the first step in the electrochemical reduction, the reciprocal of the slope of the line for the 3-isomers in coordinates of log $[i^{2/3}/(i_d - i)]$ and E is higher than the theoretical value (59 mV). In the case of the 2- and 4-isomers, the Koutecký–Hanuš equation is not observed, and the shift in $E_{1/2}$ as the depolarizer concentration increases has the opposite sign (Fig. 3).

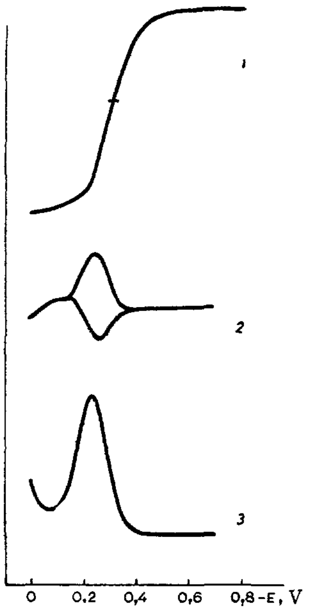


Fig. 1

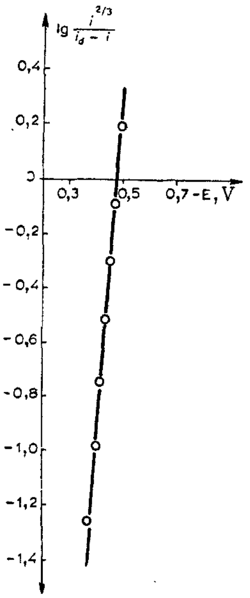


Fig. 2

Fig. 1. First step in the electrochemical reduction of N-methyl-4-(2-benzoxazolyl)pyridinium iodide in dimethylformamide at a depolarizer concentration of $2.5 \cdot 10^{-3}$ mole/liter: 1) dc polarogram (sensitivity 5 μA); 2) oscillopolarogram (scanning rate 1 V/sec); 3) Breyer ac polarogram (frequency 50 Hz, peak amplitude 20 mV).

Fig. 2. Dependence of log $[i^{2/3}/(i_d - i)]$ on E for the first wave of N-methyl-3-(2-benzoxazolyl)pyridinium iodide in DMF.

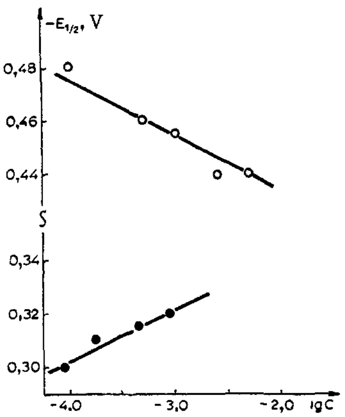


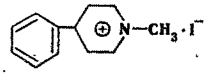
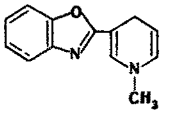
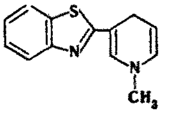
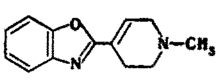
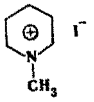
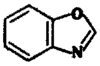
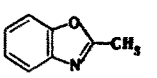
Fig. 3. Dependence of $E_{1/2}$ on the concentration for the first wave of N-methyl-3-(2-benzoxazolyl)pyridinium iodide (—○—) and N-methyl-2-(2-benzoxazolyl)-pyridinium iodide (—●—) (for an interval of concentration change of $1 \cdot 10^{-4}$-$1 \cdot 10^{-2}$ mole/liter).

The coincidence of the UV spectra of solutions of II and XVIII after CPE at −1.4 V constitutes evidence that a 1,4-dihydro derivative is formed as a result of the second step in the electrochemical reduction of 3-substituted BAP salts. We were unable to accomplish this sort of comparison of the UV spectra for the 2- and 4-substituted BAP salts because of the impossibility of the synthesis of the appropriate dihydropyridines. We note that 1,4-dihydropyridines are also products of hydride reduction of 3-benzazolylpyridinium salts [7].

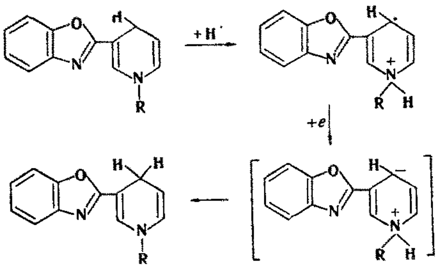
As a result of the parallel occurrence of a rather rapid dimerization reaction, the concentration of free radicals in solution is low, and the second wave of the one-electron level is not reached in the case of the 3-isomers (Table 1). However, it follows from the results of CPE for II that the height of the second wave increases approaching the level of the one-electron wave during prolonged electrolysis. A similar increase in the second wave during prolonged electrolysis was observed by Mairanovskii [8] during the reduction of quaternary pyridinium salts, and this fact was explained by buildup in solution of the catalytically active electrolysis product. In our case the second wave is not a catalytic wave. This is confirmed by the increase in its height as the depolarizer concentration and the height of the mercury column are increased.

A confirmation of the fact that the second wave in the electrochemical reduction takes place with the consumption of protons is the fact that the second wave also reaches the one-electron level as the concentration of the proton donor (water) in dimethylformamide (DMF) solutuion increases, and the $E_{1/2}$ values

TABLE 2. Half-Wave Potentials ($E_{1/2}$) and Limiting Currents (i_{lim}) for Compounds Modeling Two Heterocyclic Systems Entering into the Composition of the Benzazolylpyridinium Salt for Dimethylformamide Solutions with a 0.1 N Tetrabutylammonium Iodide Background Electrolyte

Compound	Compound formula	Name	I wave		II wave		III wave	
			i_{lim}, μA	$-E_{1/2}$, V	i_{lim}, μA	$-E_{1/2}$, V	i_{lim}, μA	$-E_{1/2}$, V
XVII		N-Methyl-4-phenylpyridinium iodide	1,44	0,75	0,52	1,50	1,16	2,03
XVIII		N-Methyl-3-(2-benzoxazolyl)-1,4-dihydropyridine	1,20	1,87	—	—	—	—
XIX		N-Methyl-3-(2-benzothiazolyl)-1,4-dihydropyridine	1,01	1,68	—	—	—	—
XX		N-Methyl-4-(2-benzoxazolyl)-1,2,5,6-tetrahydropyridine	1,97	1,71	—	—	—	—
XXI		N-Methylpyridinium iodide	1,55	0,76	—	—	—	—
XXII		Benzoxazole	2,00	2,14	—	—	—	—
XXIII		2-Methylbenzoxazole	2,24	2,29	—	—	—	—

of the increased second wave are shifted in both cases to the positive side by 120 mV, i.e., the reaction is facilitated.* On the basis of what was stated above, the formation of the second wave can be represented by the following scheme:



(2)

In contrast to the 2- and 3-isomeric BAP salts the second wave of the 4-isomers, judging from its height, is a one-electron wave. This difference in the character of the second wave should be explained by the different rates of dimerization of the free radicals of these compounds. The construction of Stuart–Briegleb models showed that the formation of dimers in the 2, 2'-position is sterically hindered for the 4-substituted compounds, whereas the formation of dimers in the 4,4'-position is completely impossible. Consequently, the rate of dimerization in this case is the minimum rate, and almost all of the free radicals formed in the first step are subsequently reduced via scheme (2). The fact that those BAP salts that give exclusively monomeric compounds during chemical reduction [10] have first and second waves on the polaro-

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*The reason for the overstated second wave during prolonged electrolysis of II may be reaction of the dimers, which are strong oxidizing agents, with the pyridinium salts, as a result of which viologenic salts, which are capable of reduction [9], are formed.

grams that are close in height may also serve as an indirect confirmation of the fact that the height of the second wave is limited by the ability of the intermediately formed free radicals to undergo dimerization.

The inhibited dimerization of the radicals of the 4-substituted salts is a consequence of the above-noted stabilization of these radicals by delocalization of the unpaired electron over the conjugated system.

Finally, the nonprotonated radicals can apparently also be reduced at more negative potentials (−1.8 V), and this is responsible for the appearance of a third wave on the polarograms. However, the fact that the $E_{1/2}$ value of the third wave of II corresponds with the $E_{1/2}$ value of XVIII (Table 2) may also constitute evidence for a different origin of this wave – namely, subsequent electroreduction of the dihydro product to the tetrahydro derivative. Thus the nature of the third wave cannot be considered to be definitely explained.

A confirmation of the fact that the first step in the reduction ultimately involves the pyridine ring is the polarographic behavior of XVII and XXII. Compound XXII is reduced at more negative potentials and the observance of electroreduction processes involving this fragment of the molecule is difficult in the investigation of I-XVI. An analysis of the data on the first polarographic wave enabled us to isolate some characteristic peculiarities of the electroreduction of the investigated compounds. The addition of the first electron to the 3-substituted salts is realized in all cases (see Table 1) at potentials that are 70-150 mV more negative than in the case of addition to the corresponding 2- and 4-isomers, and this is explained by the difficulty involved in drawing off of electrons from the 3 position of the pyridinium ring by the benzazole ring. The lesser effect of a substituent in the 3 position on the electroreduction of the pyridinium ring as compared with the effect of substituents in the 2 and 4 positions has already been repeatedly noted in the literature for other compounds [8, 11-13].

As a rule, N-benzylpyridinium salts (IX-XVI) are reduced at more positive potentials than the corresponding N-methyl derivatives (I-VIII). This is explained by the negative inductive effect of the benzyl substituent, which facilitates electroreduction [11].

The nature of the anion (Br^-, I^-) does not affect the reduction potentials, inasmuch as the same substituted pyridinium ion is reduced in all cases.

The most interesting feature of the investigated compounds is the ease of addition of the first electron. It is well known that the potentials of transfer of the first electron to the lower vacant MO of the pyridinium ring to give a free radical – a π septet – can be used as a characteristic of the electrophilicity of the corresponding pyridinium salts or as an estimate of the electrophilicity of a given substituent in the corresponding position.

Whereas unsubstituted N-methylpyridinium salts are reduced at −1.0 V in DMF and the corresponding 4-phenyl-substituted salts are reduced at −0.75 V, the reduction potentials of benzazolyl-substituted pyridinium salts are shifted from −0.3 to −0.6 V. Moreover, 2- and 4-benzoxazolyl-substituted compounds (I and III) are reduced most readily (−0.27 V), benzothiazolyl-substituted salts (IV and VI) are reduced with greater difficulty (−0.30 and −0.36 V, respectively), and benzimidazolyl-substituted salts (VIII) are reduced with the greatest difficulty (−0.52 V). This sort of relationship between the reduction potentials may constitute evidence for the manifestation of two competitive effects: withdrawal of electrons from the pyridinium system by the benzazolyl substituent as a whole and transfer of electrons from the unshared pair of electrons of the heteroatom of the benzazole ring, during which negativization of the reduction potentials is observed in the order $0 \leq S < NH$. The effects of a benzazolyl substituent in the 2 and 4 positions on the electroreduction of the pyridinium system are approximately equal, whereas the effect in the 3 position is considerably smaller.

The approximate Hammett σ constants in the 4 position that we calculated are as follows, respectively: +0.6 for the benzoxazole and benzothiazole substituents, +0.3 for the benzimidazole substituents, whereas the values are +0.3 in the 3 position for the benzoxazole and benzothiazole substitutents and +0.2 for the benzimidazole substituent, i.e., all of the indicated substituents are electron acceptors of medium strength.

EXPERIMENTAL METHOD

The polarographic investigation of I-XXIII was carried out with recrystallized samples.

In order to exlude the effect of protonation on the electrochemical reaction and to separate the electrochemical reduction into individual steps, polarography was carried out with a short-period electrode in anhydrous DMF purified by the method in [14]. Specially purified tetrabutylammonium iodide was used as the inert electrolyte. The depolarizer concentration in all cases was $2.5 \cdot 10^{-3}$ mole/liter, and the ionic strength was 0.125.

The polarographic investigations were carried out with a Radiometer RO-4 polarograph at 25° with a thermostatted cell [15]. A dropping mercury electrode with forced detachment and m = 0.31 mg/sec and t = 0.25 sec (during open circuit) was used as the indicator electrode (the cathode). Mercury poured into the bottom of the cell served as the anode. A correction for the internal resistance of the cell was introduced.

The number of electrons (n) consumed in the electroreduction of one particle of the depolarizer was calculated from the Il'kovich equation, and the diffusion coefficients were determined from pycnometric data from the Stokes–Einstein equation [16]. Inasmuch as the latter equation is applicable for uncharged molecules, the diffusion coefficients were determined for model compounds [3-benzoxazolylpyridine ($D = 5.56 \cdot 10^{-6}$ cm^2/sec) and 4-benzothiazolylpyridine ($D = 4.38 \cdot 10^{-6}$ cm^2/sec)], and the values obtained were used for the calculation of the n values of the investigated compounds existing in the form of ions. The n values obtained for the first wave of all of the investigated BAP salts were 1.0.

In the case of II, the n value for the first wave was also determined by an independent millicoulometric method [17] and was found to be 0.92, i.e., the wave was a one-electron wave.

In order to establish the character of the electroreduction we carried out CPE [17] with subsequent identification of the electrolysis products by independent methods (UV spectroscopy and ESR spectrometry). In order to detect the free radicals we carried out the electrolysis in a special cell placed directly in the resonator of a ESR spectrometer by the method in [18].

In order to ascertain the character of the successive steps in the electroreduction at more negative potentials we made a polarographic investigation of some compounds that model both heterocyclic systems that include BAP salts and the supposed products of their electrochemical reduction (Table 2), which were synthesized by the methods in [5, 7, 19]. In addition we carried out the CPE of II at the potentials of the plateau of the limiting current of the first (−1.4 V) and third (−2.7 V) waves.

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