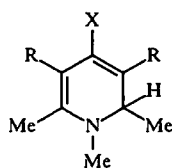


CATION-RADICALS IN THE ELECTROCHEMICAL OXIDATION OF 1,2,6-TRIMETHYL-3,5-DIACETYL-1,2-DIHYDROPYRIDINES

Ya. Stradyn', R. Gavars, L. Baumane,
and G. Duburs

The ESR spectra of the cation-radicals of 4-substituted 3,5-diacetyl-1,2,6-trimethyl-1,2-dihydropyridines were generated electrochemically by oxidation in acetonitrile at -40°C . The unpaired electron distribution in the cation-radicals was established by analysis of the hyperfine structure of the ESR spectra. It was found that the size of the electrochemical oxidation potential of the compounds and the unpaired electron distribution in the cation-radical were subject to the inductive effect of the substituents in positions 3 and 5 of the heterocycle.

The biochemical conversions of compounds containing a dihydropyridine fragment, which are promising in drug research, may be caused in part by their reduction or oxidation properties. Electrochemical modeling of the conversions of these compounds is effected successfully on studying reduction processes. The character of the intermediate particles formed in these processes are also clarified in this way. An electrochemical investigation of the mechanism of conversion of compounds containing a dihydropyridine fragment has been carried out with a combination of electrochemical generation of free radicals and simultaneous recording of them by ESR [1, 2]. The free radical intermediates in the reduction were also obtained and studied. These included primary ion-radicals which are the products of one-electron reduction of the molecules being investigated. Primary anion-radicals (secondary free radicals also in certain cases) studied in this way were of nitrophenyl substituted derivatives of 1,4- and 1,2-dihydropyridines [3-8] and anion-radicals of 3-nitro-1,4- [9], 3-nitro-1,2- [10], 3,5-dinitro-1,4- [11], and 3,5-dinitro-1,2-dihydropyridines [12]. The primary electrochemical process when generating these radicals is the one-electron reduction of the nitro group substituent and not the atoms of the dihydropyridine ring.



I, II a-c

I R = COMe; II R = COOEt;

a X = *p*-MeC₆H₄, b X = C₆H₅, c X = *p*-MeOC₆H₄

The method of generating free radicals electrochemically is significantly more difficult when applied to the study of cation-radicals formed during the electrochemical oxidation of dihydropyridines, the primary stage of which is the one-electron oxidation of the nitrogen atom of the dihydropyridine ring [13-15].

Results are given in the present work of the electrooxidation on a rotating ring-disc electrode, the electrochemical generation of cation-radicals during the electrochemical oxidation of 4-substituted 1,2,6-trimethyl-3,5-diacetyl-1,2-dihydropyridines (Ia-c), and the study of them by ESR. The characteristics of the cation-radicals (IIa-c) [15] are given for comparison.

TABLE 1. Values of the Polarographic Potential of the Electrochemical Oxidation on a Rotating Disc Electrode ($E_{1/2}$, V relative to 0.1 M Ag/AgNO₃), Number of Electrons (n) Consumed by One Molecule, Values of Electrochemical Generation Potentials (E , V relative to a Pt electrode), Hyperfine Structure Character, Values of Constants (a , G) and Line Widths (ΔH , G) of ESR Spectra of Cation-Radicals of Compounds (I) and (II) in Acetonitrile

Compound	X	Hyperfine structure character	$E_{1/2}$	n	E	a_N	a_{3H}	a_H	ΔH
Ia	<i>p</i> -H ₃ CC ₆ H ₄	2 _H × 4 _H × 3 _N	0,35	1,0	1,4	5,25	5,00	20,79	1,8
IIa	<i>p</i> -H ₃ CC ₆ H ₄	2 _H × 4 _H × 3 _N	0,41	1,3	1,3	5,04*	5,51*	24,36*	1,0
Ib	C ₆ H ₅	2 _H × 4 _H × 3 _N	0,39	1,0	1,5	4,99	4,83	21,00	1,8
IIb	C ₆ H ₅	2 _H × 4 _H × 3 _N	0,42	1,2	1,0	4,93	5,20	24,05	1,0
Ic	<i>p</i> -H ₃ COC ₆ H ₄	2 _H × 4 _H × 3 _N	0,37	1,3	1,3	4,93	4,88	19,95	1,8
IIc	<i>p</i> -H ₃ COC ₆ H ₄	2 _H × 4 _H × 3 _N	0,44	1,3	1,4	4,72	4,99	23,31	1,0

*Values of the hyperfine structure constants were refined by simulating the hyperfine structure of the ESR spectrum.

One irreversible wave was recorded during the electrochemical oxidation of compounds (I) on the disc electrode in the potential interval +0.35 to +0.39 V relative to Ag/AgNO₃. The limiting current of this wave corresponded to the one-electron level or somewhat greater which indicates the possible formation of primary cation-radicals in the oxidation process. However during electrochemical generation at room temperature it was impossible to record free radicals by ESR. Only by reducing the temperature of the solution being investigated to -40°C at potentials of the limiting current plateau were ESR spectra of free radicals adequate for interpretation recorded successfully. On increasing the temperature the ESR signal intensity was reduced and disappeared completely at -10°C.

The resolved hyperfine structure of the ESR spectra of electrochemically generated free cation-radicals of compounds (Ia-c) had a single character, viz. 2_H × 3_N × 4_H. For example, the hyperfine structure of the ESR spectrum of the cation-radical of compound (Ia) is caused by the interaction of the unpaired electron with a single proton ($a_N = 21.00$ G), with the nucleus of the nitrogen atom of the heterocycle ($a_N = 4.99$ G), and with three equivalent protons ($a_N = 4.83$ G) of the methyl group substituent at the nitrogen atom of the 1,2-dihydropyridine ring. The latter is proved by the ESR spectra of cation-radicals similar to (IIa-c) [15] in which the hyperfine structure caused by the three equivalent protons is absent when there was no methyl substituent on the heterocyclic nitrogen atom. The hyperfine structure constants of the ESR spectra of the electrochemically generated free radicals of compounds (Ia-c) are given in Table 1.

The display of a single proton in the hyperfine structure of the ESR spectra in the absence of an interaction of the unpaired electron with the 2-methyl substituent protons indicates that the radicals recorded are formed by fission of a single electron from the heterocyclic nitrogen atom by cation-radicals of the investigated 1,2-dihydropyridines. The values of the doublet splitting constants caused by a single proton ($a_H \sim 21$ G) negate the possibility that the ESR spectrum is caused by a radical of pyridinyl structure, since such high values for the hyperfine structure constants of an ESR spectrum are characteristic of the interaction of an unpaired electron with a proton located out of the plane of the π -electron system of an sp³ hybridized carbon atom, and are caused by the overlap of the 1s-orbital of a hydrogen atom and the orbitals of 2(p) π -electrons of the C₍₃₎ and N₍₁₎ atoms [16]. As a result of fission of one electron from the nitrogen atom and delocalization of the second (unpaired) electron a significant positive charge is concentrated on the nitrogen atom. The comparatively low value of the hyperfine constant for the interaction of the unpaired electron with the nucleus of the heterocyclic nitrogen atom ($a_N \sim 5$ G) indicates delocalization of the unpaired electron through the π -system of the heterocycle. It follows from the relationship $a_N = 28.6\rho_N$ that the unpaired electron density on the nitrogen atom (ρ_N) of the studied cation-radicals is less than one fifth of an electron, i.e. the unpaired electron is delocalized to a significant extent through the π -electron system of the heterocycle. However the hyperfine structure of the ESR spectra indicates an insignificant ($\rho < 0.01$ electron) unpaired electron density at the C₍₆₎ atom, since no interaction of the unpaired electron with the protons of the C₍₆₎ substituent is clearly displayed, although a weak interaction may be hidden in the width of the EPR signals ($\Delta H \sim 1.8$ G). The unpaired π^1 -electron of the nitrogen atom of electronic state $1s^2 2s^2 \pi^1$ has four-fifths of its density delocalized through the π -electron

system of the $C_{(3)}$, $C_{(4)}$, and $C_{(5)}$ atoms of the ring. This is indicated not only by the deficit of unpaired electron at the nitrogen atom but also by the significant width of the ESR spectral lines probably caused by hidden hyperfine structure determined by the protons of substituents in positions 3 and 5 of the heterocycle. Such delocalization of the unpaired electron is determined by the higher overall electrophilicity of the position 3, 4, and 5 substituents compared with those at positions 1 and 6, and also with the nitrogen atom in the $1s^2 2s^2 \pi^1$ state. In a comparison of the change of the a_N constant value as a function of the electrophilic properties of substituents characterized by various constants (reflecting the display of electrophilic effects of various types), it turned out that the change in electrophilic effect of substituents at positions 3 and 5 on the redistribution of the unpaired electron in the investigated cation-radicals did not correspond with the expected direction of changes of the Hammett σ -constants. However it complied with the change of values of the modified Swain–Lapton F constants [18], characterizing the inductive effect of a substituent's field. Thus on replacing acetyl substituents (compounds of type I) ($\sigma_m = 0.38$, $\sigma_p = 0.50$, $F = 0.33$, $R = 0.17$) by ethoxycarbonyl (compounds of type II) ($\sigma_m = 0.37$, $\sigma_p = 0.46$, $F = 0.34$, $R = 0.11$) the size of the a_N constant is reduced, which indicates an increase in the electrophilic properties of the substituent and agrees only with the change in the size of F. At first sight the unexpectedly more difficult oxidation of the ethoxycarbonyl derivatives (II) compared with the acetyl analogs (I) (see Table 1) is probably explained by this inductive effect. It was impossible to determine the nature of the effect of substituents at position 4 on the oxidation potential of the investigated compounds and also on the distribution of the unpaired electron in the cation-radicals in a similar way, since the changes of the experimental values obtained on going from compound to compound did not correlate either with the Hammett constants or with the Swain–Lapton constants.

EXPERIMENTAL

Polarograms of the compounds (I) ($C = 5 \cdot 10^{-4}$ M) being investigated were recorded on a rotating ring-disk electrode (graphite/graphite) on Bruker 350C electrochemical equipment. The auxiliary electrode was a platinum wire in acetonitrile with a base electrolyte of tetrabutylammonium hexafluorophosphate ($C = 10^{-1}$ M). The reference electrode was 10^{-1} M Ag/AgNO₃ in acetonitrile. The number of electrons was determined by comparing the height of the wave of a compound with the height of the one-electron wave on reducing 3,5-diethoxycarbonyl-1,2,6-trimethyl-4-(m-nitrophenyl)-1,4-dihydropyridine [8].

Free radicals were generated by the procedure proposed in [1] in stationary mode on the surface of a flat platinum electrode placed in a type H₁₀₂ rectilinear resonator of an ER-9 ESR spectrometer (Karl Zeiss, Jena) fitted with a temperature controller. Sample temperature was measured with a precision of 1°C. Electrochemical generation potentials were determined relative to a Pt electrode. Solutions of compounds (I) ($5 \cdot 10^{-3}$ M) in acetonitrile were used for the electrochemical generation of free radicals. The solutions contained tetrabutylammonium hexafluorophosphate (10^{-1} M). The method of synthesis of compounds (I) is given in [19].

The work was carried out with a grant from the Latvian Soviet for Science No. 700.

REFERENCES

1. B. Kastening, *Progress of Polarography*, Vol. 3, p. 195 (1972).
2. Ya. Stradyn', R. Gavars, and L. Baumanė, *Elektrokhimiya*, 31, No. 10, 1100 (1995).
3. Ya. V. Ogle, L. Kh. Baumanė, Ya. P. Stradyn', G. Ya. Dubur, V. P. Kadysh, R. A. Gavar, and V. K. Lusiš, *Khim. Geterotsikl. Soedin.*, No. 8, 1099 (1985).
4. L. Kh. Baumanė, Ya. P. Stradyn', R. A. Gavar, A. P. Gaukhman, and G. Ya. Dubur, *Khim. Geterotsikl. Soedin.*, No. 11, 1494 (1988).
5. L. Kh. Baumanė, Ya. P. Stradyn', R. A. Gavar, B. S. Chekavichus, and G. Ya. Dubur, *Khim. Geterotsikl. Soedin.*, No. 4, 481 (1991).
6. L. Baumanė, J. Stradins, R. Gavars, and G. Duburs, *Electrochimica Acta*, 37, No. 14, 2599 (1992).
7. Ya. Stradyn', L. Baumanė, R. Gavars, B. Chekavichus, and G. Dubur, *Khim. Geterotsikl. Soedin.*, No. 11, 1498 (1992).
8. L. Baumanė, R. Gavars, Ya. Stradyn', and G. Duburs, *Khim. Geterotsikl. Soedin.*, No. 2, 219 (1997).

9. Ya. Stradyn', L. Baumane, R. Gavars, B. Vigante, and G. Duburs, *Khim. Geterotsikl. Soedin.*, No. 3, 355 (1995).
10. Ya. Stradyn', R. Gavars, L. Baumane, B. Vigante, and G. Duburs, *Khim. Geterotsikl. Soedin.*, No. 9, 1222 (1996).
11. Ya. Stradyn', L. Baumane, R. Gavars, B. Vigante, and G. Duburs, *Khim. Geterotsikl. Soedin.*, No. 6, 936 (1996).
12. Ya. Stradyn', R. Gavars, L. Baumane, B. Vigante, and G. Duburs, *Khim. Geterotsikl. Soedin.*, No. 2, 212 (1997).
13. J. Ludvik, J. Klima, J. Volke, A. Kurfürst, and J. Kuthan, *J. Electroanalyt. Chem.*, **138**, 131 (1982).
14. L. Kh. Baumane, Ya. V. Ogle, R. A. Gavar, Ya. P. Stradyn', and G. Ya. Dubur, *Khim. Geterotsikl. Soedin.*, No. 10, 1422 (1983).
15. J. Stradins, J. Ogle, V. Kadysh, L. Baumane, R. Gavars, and G. Duburs, *J. Electroanalyt. Chem.*, **226**, 103 (1987).
16. A. L. Buchachenko and A. M. Vasserman, *Stable Radicals [in Russian]*, Khimiya, Moscow (1973), p. 51.
17. E. W. Stone and A. H. Maki, *J. Chem. Phys.*, **39**, 1635 (1963).
18. C. Hansch, A. Leo, and R. W. Taft, *Chem. Rev.*, **91**, 165 (1991).
19. V. K. Lasis, A. Z. Zandersons, D. Kh. Mutsenietse, and G. Ya. Dubur, *Khim. Geterotsikl. Soedin.*, No. 4, 508 (1993).