VOLT-AMPEROMETRY OF 1,4-DIHYDROPYRIDINE DERIVATIVES

I. ELECTROCHEMICAL OXIDATION POTENTIALS OF 3,5-DIACYL- AND 3,5-DI(ALKOXYCARBONYL)-1,4-DIHYDROPYRIDINES IN ACETONITRILE

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It was found that compounds of the 3,5-dicarbonyl-1,4-dihydropyridine series are oxidized on a rotating platinum microelectrode in acetonitrile at potentials that are accessible for electrochemical investigation (from 0.8 to 1.4 V relative to a saturated calomel electrode). The electrochemical oxidation potentials of 41 compounds were determined, and the influence of electronic effects of substituents introduced into various positions of the dihydropyridine ring on E_p and $E_{1/2}$ was revealed. The potentials obtained were compared with the peculiarities of the chemical and enzymatic oxidation of the corresponding compounds.

3,5-Dicarbonyl-1,4-dihydropyridines (DHP) are derivatives and analogs of extremely important biologically active compounds (dihydronicotinamide, NADN, and NADPN). The DHP have clearly expressed electron-donor and hydrogen-donor properties in chemical reactions [1-4], undergo reactions with free radicals [5], and are biologically active [6-9]. While the literature does not contain information regarding the electrochemical behavior of DHP, while the electrooxidation (EO) potentials of various representatives of the DHP class may serve as a qualitative characteristic of the reactivities of these derivatives as electrons donors. The present investigation was undertaken to ascertain the numerical values of the anode potentials and to establish their interrelationship with the molecular structures.

Distinct volt–ampere curves, caused by electrooxidation of the DHP molecules on an anode-polarized platinum electrode, were obtained for most of the investigated compounds.

An examination of the E_p values (Tables 1 and 2) revealed a number of principles that touch upon the sequence of the position of the EO potentials of individual representatives of the DHP as a function of the introduction of various substituents into different positions of the molecule (α-, β-, and γ-substitution in the DHP ring).

Thus the introduction of methyl groups into the α position in the 3,5-diacetyl-1,4-dihydropyridine molecule (compound 2) causes a pronounced shift (of ~200 mV) in E_p for oxidation to less positive potentials.

For β-substitution in systems of the I-IV type, the EO potentials are arranged in the following order of increase in the E_p anode values:

$$COC_6H_5 \leqslant COCH_3,\ COOR < COC_6H_4(\alpha) < COCH_2C(CH_3)_2CH_2(\alpha) \leqslant CN.$$

Lengthening the carbon chain in the β-carbalkoxy group or the introduction of alkoxy or aryl substituents into the β-carbalkoxy group does not induce substantial changes in the E_p values.

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TABLE 1. Potentials of the Peaks and Half Waves of the Electro-oxidation of Mononuclear DHP of the I Type

Compound	R^2	R^3	R^4	R	Synthetic method	E_p, V	$E_{1/2}$, V
1	CH_3	COC_6H_5	H	H	*	0,87	0,83
2	H	$COCH_3$	H	H	14	1,11	1,03
3	CH_3	$COCH_3$	H	H	15	0,90	0,86
4	CH_3	$COOCH_3$	H	H	16	0,93	0,84
5	CH_3	$COOC_2H_5$	H	H	17	0,93	0,90
6	CH_3	$COOC_5H_{11}$-*n*	H	H	*	0,91	0,82
7	CH_3	$COOC_5H_{11}$-*i*	H	H	*	0,90	0,84
8	CH_3	$COOC_9H_{19}$	H	H	*	0,93	0,86
9	CH_3	$COOC_{12}H_{25}$	H	H	*	0,94	0,83
10	CH_3	$COO(CH_2)_2OC_2H_5$	H	H	*	0,94	0,86
11	CH_3	$COOCH_2C_6H_5$	H	H	*	0,92	0,85
12	CH_3	CN	H	H	18	1,16	1,08
13	CH_3	COC_6H_5	CH_3	H	19	0,91	0,85
14	CH_3	$COCH_3$	CH_3	H	20	0,97	0,90
15	CH_3	$COOC_2H_5$	CH_3	H	21	1,00	0,92
16	CH_3	CN	CH_3	CH_3	22	1,27	1,20
17	CH_3	$COCH_3$	C_6H_5	H	23	1,13	1,06
18	CH_3	$COOC_2H_5$	C_6H_5	H	24	1,07	1,02
19	CH_3	$COOC_5H_{11}$-*n*	C_6H_5	H	*	1,11	1,03
20	CH_3	$COOC_2H_5$	$C_6H_4CH_3$-*p*	H	25	1,09	1,07
21	CH_3	$COOC_2H_5$	$C_6H_4OCH_3$-*p*	H	26	1,08	1,00
22	CH_3	$COOC_2H_5$	$C_6H_2(OCH_3)_3$-3,4,5	H	*	1,10	1,02
23	CH_3	$COOC_2H_5$	C_6H_4Cl-*p*	H	26	1,12	1,06
24	CH_3	$COOC_2H_5$	$C_6H_4N(CH_3)_2$-*p*	H	27	0,68 1,20	0,63
25	CH_3	$COOC_2H_5$	$C_6H_4NO_2$-*p*	H	25	1,30	1,24
26	CH_3	$COOC_2H_5$	2-Furyl	H	24	1,18	1,09
27	CH_3	$COOC_2H_5$	$CON(CH_2CH_2)_2O$	H	28	1,11	1,04
28	CH_3	$COOC_2H_5$	COOH	H	29	1,24	1,16
29	CH_3	$COOC_2H_5$	$COOCH_3$	H	28	1,28	1,16
30	CH_3	CN	C_6H_5	H	30	1,38	1,31

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*The synthesis will be published separately.

TABLE 2. Potentials of the Peaks and Half Waves of the Electro-oxidation of Polynuclear DHP of the II-IV Type

Compound	R^3	R^4	Synthetic method	E_p, V	$E_{1/2}$, V
31	$COOC_2H_5$	H	31	0,98	0,91
32	COC_6H_5	C_6H_5	32	1,11	0,98
33	$COCH_3$	C_6H_5	32	1,16	1,08
34	$COOC_2H_5$	C_6H_5	32	1,15	1,07
35	$COOC_9H_{19}$	C_6H_5	*	1,13	1,06
36	$COCH_2C(CH_3)_2CH_2(\alpha)$	C_6H_5	33	1,23	1,14
37	CN	C_6H_5	*	1,26	1,16
38	$COCH_3$	$C_6H_4NO_2$-*p*	32	1,23	1,15
39	$COOC_2H_5$	$C_6H_4NO_2$-*p*	32	1,26	1,19
40†			34	1,13	1,10
41‡			35	1,20	1,16

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*The synthesis will be published separately.

†Compound III.

‡Compound IV.

The introduction of methyl, phenyl, 2-furyl, and carboxyl groups into the γ position induces a shift in E_p to more anodic potentials by 60, 200, 250, and 300 mV, respectively. This sort of directed effect of the functional groups (except for the methyl group) is in good agreement with the previously established effect of these substituents on the EO potentials of aniline derivatives [10]. We note that the unexpected effect of the CH_3 substituent was also observed in a study of the UV spectra of DHP [12], which is possibly due to the steric effect of the substituent.

The introduction of substituents into the γ-carboxyl and γ-phenyl groups also affects the oxidation potentials: the EO potential of the morpholide is shifted to less positive potentials, while the EO potential of the methyl ester, on the other hand, is shifted to more positive E_p values as compared with the potential of a compound that contains a carboxyl group (compound XXVIII). Except for the p-NO_2 group, substituents in the phenyl ring (compound XX-XXV) do not have a considerable effect on the E_p values of the derivatives studied in this research. In this case, the first of the two oxidation waves on the volt–ampere curve of compound XXIV can apparently be ascribed to the oxidation of the dimethylaniline residue.

It should be noted that the effect of the examined functional groups on the EO potentials of DHP substituted in various positions is, in most cases, in qualitative agreement with the effect of the same groups on chemical and enzymatic oxidation. In particular, the decrease in the E_p values is in good agreement with the increase in the ease of oxidation of α,β-unsaturated carbonyl compounds [4] and the increase in the rate of enzymatic oxidation of the peroxidase–H_2O_2 system [13]. The first of these reactions probably proceeds by way of a hydride shift, while the second probably proceeds through one-electron oxidation. The characteristic electron-donor effect of the α-methyl group shows up distinctly in all cases. In the case of the chemical oxidation of β-substituted DHP by chloranil [4], the same sequence of the position of substituents in the series with respect to their electronic effect is retained. However, when other oxidizing agents are used, the above-established sequence of the effect of the substituents is disrupted; in this case, the introduction of a benzoylene group usually increases the reactivity of DHP very markedly. The introduction of a methyl group in the γ position of the DHP ring has a substantially greater effect in the case of chemical and enzymatic oxidation than during electrooxidation [4, 13].

All of the compounds examined above also have electron-donor properties in aqueous alcohol media, and their EO potentials in these media are less positive (by ~ 200-300 mV) than in acetonitrile.*

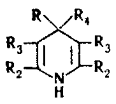
The mechanism of the electrooxidation of compounds of the I-IV type is currently being studied, and the results will be published in subsequent communications.

EXPERIMENTAL

The EO potentials were determined by the method described in [10]. The volt–ampere curves were recorded with an LP-60 recording polarograph under integral (polarograph sensitivity of 1/50) and differential (sensitivity of 1/2) recording conditions. The experimentally found E_p and $E_{1/2}$ values, measured relative to a saturated calomel electrode (SCE) with an accuracy of ±20-40 mV, are presented in Tables 1 and 2. The peak potentials (E_p) were used as the more reliable values for the comparison of the various representatives of the series during the discussion of the results.

The polarizing electrode was a rotating platinum microanode (the diameter was 1 mm, the angular rate of rotation was 1400 rpm, and the rate of polarization was 400 mV/min), which was cleaned thoroughly with a fine emory cloth after each experiment. An aqueous SCE connected to the solution to be polarographed through an agar–agar bridge in $LiClO_4$ was used as the comparison electrode. The medium for carrying out the polarographic experiments was acetonitrile, purified by the method in [11], on a 1 M $LiClO_4$ background, the decomposition potential of which was 1.9-2.1 V.

We investigated DHP with structures I-IV. All of the compounds were studied under the same experimental conditions [at the same depolarizing concentrations (10^{-4} M) on the same platinum electrode at constant electrode parameters]. The compounds were synthesized by the methods indicated in Tables 1 and 2.



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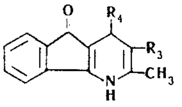

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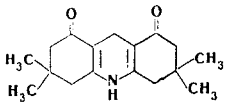

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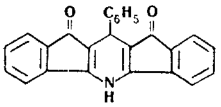

IV

Acetonitrile was selected as the medium for the volt-amperometric measurements because of the possibility of the study of all of the DHP in their nonionized form, since neither protonation nor deprotonation of the nitrogen atom in the DHP ring are possible under these conditions (except for compound XXVIII).

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*The EO potentials in aqueous alcohol were determined by A. Yu. Karklin' for several DHP derivatives.

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