ELECTROCHEMICAL OXIDATION OF FERROCENYLSUBSTITUTED 1,4-DIHYDROPYRIDINES

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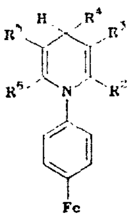
1-p-Ferrocenylphenyl- and 4-ferrocenylsubstituted Hantzsch esters were subjected to electrochemical oxidation using a graphite cyclic rotating disk electrode in acetonitrile medium; in each case the initial response was one-electron oxidation of the ferrocenyl substituent to give a ferrocenium cation, which was followed by a two-electron electrochemical oxidation of the dihydropyridine ring involving intermediate deprotonation of the latter and formation of a ferroceniumpyridinium dication. We have also detected for the first time at room temperature relatively stable cation radicals of 2,6-dimethyl-3,5-diethoxycarbonyl-1,4-dihydropyridine containing a cationic ferrocenium substituent in the 4-position; these proved to be more stable than cation radicals of dihydropyridines containing ferrocenyl substituents attached to the nitrogen atom.

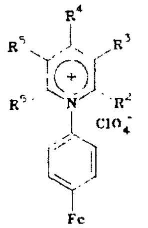
The aromatization of ferrocene-containing Hantzsch esters upon treatment with 1-oxo-2,2,6,6-tetramethylpiperidinium perchlorate occurs via a stage involving oxidation of the ferrocenyl substituent to a ferrocenium cation, although the final reaction products are pyridinium salts containing a reduced ferrocenyl substituent [1]. One possible mechanism for this process would involve successive one-electron oxidations of the ferrocenyl residue and dihydropyridine nucleus, respectively, to give a ferrocenium-substituted dihydropyridine dication radical, which could then undergo either intra- or intermolecular oxidation of the dihydropyridine cation radical to a cation stage via reduction of the ferrocenium substituent to ferrocene; the final product formed in this manner would be a pyridinium salt with a neutral ferrocenyl substituent.

However, it is not possible to exclude a possible mechanism involving reduction of a ferroceniumpyridinium dication intermediate, formed during the course of the reaction, by means of unreacted dihydropyridine precursor. The literature does contain evidence [2] for the feasibility of this type of a reduction reaction of ferrocenium-containing compounds by this pathway.

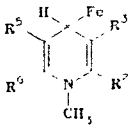
In order to elucidate the mechanism of oxidation of ferrocenylsubstituted Hantzsch esters, as well as the properties of the intermediate and final products of this reaction process, we have investigated the following compounds:



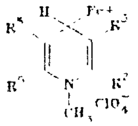
Ia-e



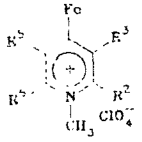
IIa-c



III



IV



V

I—V $R^2=R^6=CH_3$; $R^3=R^5=COOC_2H_5$; I—V **a** $R^4=C_6H_4OCH_3$-*p*, b $R^4=C_6H_4NO_2$-*p*, **c** $R^4=C_6H_4NO_2$-*m*, **d** $R^4=C_6H_4NO_2$-*o*, **e** $R^4=$2-furyl

As the electrochemical oxidation method, we used a graphite cyclic rotating disk electrode (CRDE) in acetonitrile medium; this method was deemed most suitable for studying the

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intermediate and final products of electrochemical reactions, including any intermediate stages involving homogeneous chemical reactions.

Compounds II, IV, and V were synthesized as model compounds of the assumed final oxidation products of I and III [1]. As can be seen, the starting materials Ia-e and III contain two electroactive centers which are reactive toward electrooxidation: the ferrocenyl and dihydropyridine fragments. Compounds Ib-d also contain nitro groups, which are additionally reactive with respect to electroreduction. Similar 4-nitroaryl-1-dihydropyridines which do not contain ferrocenyl substituents have been studied previously using electrochemical methods [3].

It was found that the first stage of the electrochemical oxidation of compounds I and III on a disk electrode at potentials of 0.13-0.14 and 0.03 V, respectively, involves reversible one-electron oxidation of the ferrocenyl fragment to give a ferrocenium cation attached as a substituent to a dihydropyridine ring. We have also found, using the methods of CRDE and cyclic voltammetry, that the lifetimes of these electrooxidatively-generated cations IV and VI are greater than 1 sec. The chemical oxidation of compound I was studied by UV spectroscopy [1], which established that ferrocenium cations of the type VI have only short intermediate lifetimes in acetonitrile, but that corresponding oxidation of compound III permitted the isolation of the corresponding salt IV in crystalline form. The disappearance of the ferrocenium cation VI could be due, in accordance with previous work [4], to its participation in a relatively slow oxidation reaction of starting material I, i.e., reduction of the ferrocenium cation by means of the starting material. The stability of the ferrocenium cation IV, which appears during the oxidation of compound III, can be explained in terms of its lower oxidative reactivity (the electrooxidation potential of the ferrocenyl fragment in compound III is on average 100 mV lower than that of compound I). It is also possible that steric factors play an important role here; the ferrocenium cation formed from compound III is sterically more hindered than that from compound I (due to the substituents attached to positions 3 and 5). The electrooxidation potential of the ferrocenyl fragment in compounds Ia-e is on the average 80 mV higher than that measured by us under identical experimental conditions for unsubstituted ferrocene, $E_{1/2}$ = 0.046 V (the $E_{1/2}$ value has been reported previously [5] as 0.092 V relative to $Ag/AgClO_4$ reference electrode). These results indicate that the dihydropyridine fragments in the compounds under investigation exhibit electron-withdrawing properties relative to the ferrocenyl fragment. The electrooxidation potential of the ferrocene fragment in compound III does not differ significantly (it is 15 mV lower) from the potential of unsubstituted ferrocene.

According to the volt-ampere (current) curves which were recorded, at higher potentials ($E_{1/2}$ = 0.86-0.95 V) a second irreversible electrooxidative step takes place, namely, that of the dihydropyridine fragment in compounds Ia-e and III via transfer of two electrons. The electrooxidative process for the dihydropyridine fragment is identical to that described previously for the electrooxidation of 1,4-dihydropyridines [3], with the exception that all the steps occur in the presence of a ferrocenium cation substituent on the pyridine ring.

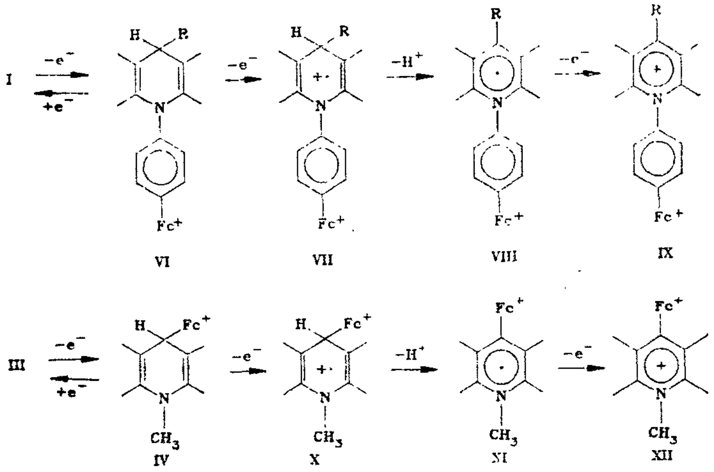
Electrochemical oxidation of the dihydropyridine fragment in compounds I and III (see Scheme outlined below) proceeds via initial removal of an electron from the unshared electron pair on nitrogen, forming the dihydropyridine cation radicals VII and X, which undergo deprotonation to give the radicals VIII and XI; this is followed by removal of a second electron from the pyridine ring to give dications IX and XII, which are the final electrooxidation products of the starting materials. Both electron transfer steps occur at the same potential value, since only one coalesced two electron oxidation wave is recorded on the disk electrode for the dihydropyridine fragment.

The course of the electrooxidations of compounds Ia-e and III is illustrated in the Scheme at top of next page.

Several significant differences in the distinct electrooxidation stages of compounds Ia-e and III should be pointed out.

In the first place, the dihydropyridine cation radical X formed from compound III is relatively stable at room temperature, as evidenced by the presence of an anodic-cathodic wave for reversible electroreduction of the latter on the cyclic electrode. The half-life for decomposition of this cation radical was estimated to be $\tau_{1/2} \leq 0.01$ sec. In the case of the electrooxidation of compounds Ia-e, the corresponding cation radicals VII have life-

Scheme



times of less than 10^{-6} sec, just as was observed in an earlier study of 1,4-dihydropyridines; as a consequence, these cation radicals could not be detected by CRDE.

A second significant difference is seen in the electroreduction potential of the ferrocenium cation in the final product of the electrooxidation process of compounds Ia-e, namely, the dications IXa-e, which is up to 200 mV lower than the corresponding potential for dication XII. The corresponding potential for electrooxidation of the ferrocenyl fragment in the model compound II is 200 mV lower than that of compound V. Comparison of these potential values indicates that the pyridinium cation fragment exerts a very strong influence on the ferrocenium cation when the latter is located in the 4-position of the pyridinyl ring. As a result of this influence, the ferrocenium cation exhibits greater oxidative reactivity in the final product of the electrooxidation sequence of compound III, namely, dication XII, than in the dications IX, which are formed as the final products in the electrooxidation of compounds Ia-e. Apparently, in the case of XII, the oxidizing ability of the ferrocenium cation is sufficient to oxidize approaching molecules of the neutral starting material III, resulting in the conversion of dication XII to the monocation V. This observation would explain why we were unable to obtain dication XII as a stable substance during the chemical oxidation of compound III.

It should also be noted that dications IX and XII are relatively stable as the final products of the electrooxidation of the starting materials I and III (their lifetimes are greater than 1 sec). This latter fact is confirmed by the observation of two electroreduction waves using the cyclic electrode, with a current yield of Q = 100% [6], at the lowest rates of rotation of the electrode (300 rpm). The first wave corresponds to reduction of the ferrocenium cation (for compounds IX, this is observed at a potential of 0.11-0.14 V, for compound XII at a potential of 0.38 V); the second wave corresponds to electroreduction of the pyridinium cation fragment (at a potential of −1.18 to −1.36 V for compounds IX and at −1.43 V for compound XII). Comparison of the electroreduction potentials for the final products of the electrooxidation process of compounds Ia-e with the electroreduction potentials of the model compounds II reveals that they are identical. At more negative potential values (−1.5 V), the electroreduction wave for the nitro group in compounds Ib-d and IIb,c is observed (the details of this process have been examined earlier [3]).

The experimentally determined potential values for the electrooxidation of the dihydropyridine fragment in compounds I (see Table 1) (in the presence of a ferrocenium cation) proved to be 110 mV higher than the potentials measured previously for N-phenyl-1,4-dihydropyridines [7], which do not contain ferrocenyl substituents. The potential value for electrooxidation of compound I can be placed in the σ^*–ρ correlation sequence prepared previously by us [8] for the $E_{1/2}$ values of N-substituted 2,6-dimethyl-3,5-diethoxycarbonyl-1,4-dihydropyridines; using this method, a σ^* constant of 1.2 is obtained for the ferrocenyl substituent (taking into account the bridging effect of the phenyl ring).

In conclusion, electrochemical methods (CRDE and cyclic voltammetry) have allowed us to examine in depth the mechanism of the oxidation process of ferrocene-containing 1,4-dihydropyridines; this is made possible by the ability to discern the structures of the intermediate products in the oxidation sequence, which cannot be isolated by chemical means.

TABLE 1. Half-wave Potential* Values for Electrooxidation of the Ferrocenium (EO Fc) and Dihydropyridine (EO DHP) Fragments, as well as for Electroreduction of the Final Products, Pyridinium Cations (ER K_{pyr})

Compound	$E_{1/2}$ EO, V		$E_{1/2}$ ER K_{pyr}, V
	Fc	DHP	
Ia	0,14	0,86	1,36
IIa	0,18	—	1,36
Ib	0,13	0,90	1,13
IIb	0,17	—	1,12
Ic	0,13	0,92	1,22
IIc	0,18	—	1,22
III	0,03	0,95	1,42
IV	—	0,95	1,43
V	0,38	—	

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*Potential values were measured using a graphite disk electrode in acetonitrile solution relative to a Ag/AgNO₃ electrode (0.1 M), at a depolarizer concentration of $5 \cdot 10^{-4}$ mole/liter and a temperature of 20°C.

EXPERIMENTAL

Electrochemical studies were carried out using a rotating disk electrode under cyclic conditions [6] at room temperature. The disk electrode was made of graphite, the cycling electrode of platinum, and the rate of rotation of the electrode was 2000 rpm. All potential values were measured relative to a $Ag/AgNO_3$ reference electrode (0.1 M in acetonitrile). The number of electrons discharged from the oxidized substrate during the course of electrochemical oxidation was calculated using the equation for diffusion limited current [9]. The diffusion coefficients for the compounds under investigation were calculated using coefficients measured previously for corresponding isomers [8], based on the assumption that they were inversely proportional to the molecular weights of the compounds by an order of 1/2. The concentration of depolarizer was $5 \cdot 10^{-4}$ mole/liter in all cases; background potentials were measured using a solution of tetrabutylammonium perchlorate (0.1 mole/liter), which was prepared as described previously [10]. The syntheses and physical chemical properties of the compounds under investigation have been reported earlier [1].

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