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The mechanism of oxidation of NADH analogues
4. Photooxidation of *N*-acetyl-substituted 1,4-dihydropyridine in the presence of quinones

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Abstract

Mechanism of photoinitiated oxidation of *N*-acetyl-3,5-dicarbomethoxy-4-phenyl-1,4-dihydropyridine (**I**) in the presence of quinones has been studied by means of CIDNP method in polar solvents. 3,5-Dicarbomethoxy-4-phenyl-pyridine (**II**) has been identified to be the main reaction product. It has been found that the process involves the radical ions as well as neutral radicals of dinydropyridine and quinone. Sigmatropic rearrangement (1-3 shift) has been suggested to occur in N-centered dihydropyridine radicals. © 1997 Elsevier Science S.A.

Keywords: 1,4-Dihydropyridine; Quinone; CIDNP; Photooxidation; Deacetylation

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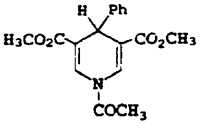
1. Introduction

^{1}H and ^{15}N chemically induced dynamic nuclear polarization (CIDNP) techniques have been successfully employed to study the elementary stages of the photooxidation of natural NADH coenzymes [1] and their synthetic analogs, 1,4-dihydropyridines (DHP) [2–5]. The participation of neutral radicals and radical ions in photooxidation of 1,4-dihydropyridines by various electron acceptors has been proved by these methods [3–5]. The dependence of the sequence of elementary stage on the acceptor structure and properties has been demonstrated. It has been also shown [3] that the reactive substituents in the dihydropyridine molecule ensures its polyfunctionality. For example, DHP containing acetyl groups in 3,5 positions could undergo autooxidation. Taking into account the abovesaid, CIDNP method seems to be very informative in the investigation of the photolysis of *N*-acetyl-3,5-dicarbomethoxy-4-phenyl-1,4-dihydropyridine (**I**), because this compound is known to eliminate the acetyl group under irradiation [6].



I

The aim of the present paper is to use ^{1}H CIDNP to study the mechanism of the oxidation process of **I**.

2. Experimental

2.1. *Chemicals*

N-acetyl-substituted 1,4-DHP **I** was synthesized by alkylation of the N-unsubstituted compound synthesized according to the classic scheme of the Hantzsch reaction. A number of various quinones was used as electron acceptors: chloranil (CA), 2,5-dichlorobenzoquinone (DBQ) and 2,3-dichloro-5,6-dicyano-benzoquinone (DDQ). All quinones were purified by sublimation. Deuterated solvents (Isotop") were used as supplied without preliminary purification. Solutions of **I** in CD_3CN or acetone-D_6 (concentrations in the range from 10^{-3} to 3.10^{-2} M) in the presence of the electron acceptors ($10^{-3}-10^{-1}$ M) were deaerated by Ar bubbling.

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2.2. Experimental setup

Samples in the standard 5 mm Pyrex NMR tubes were irradiated directly in the probe of NMR spectrometers at room temperature. Steady state (SS) experiments were performed using JEOL FX 90Q NMR spectrometer (90 MHz ^{1}H operating frequency). The light source employed was high-pressure mercury lamp (1 kW) with thermal filter and a light band pass filter. Two types of filters were used. In the case of the first filter ($280 < \lambda_{trans} < 380$ nm) the transmission band covers the absorption wavelengths of quinones and **I**. The transmission band of another filter ($\lambda > 380$ nm) corresponds to the shoulder of the absorption wavelength of quinones: $\varepsilon > 100$, and **I** has no absorption in this region.

Note, that when the light filter with $\lambda > 380$ nm was used, the light is absorbed only by quinones, whereas in the range $280 < \lambda < 380$ nm the extinction coefficients of **I** and quinones are of the same order of magnitude. The conditions for predominant light absorption by either quinone or dihydropyridine can be attained by varying the concentrations.

Time resolved (TR) and quasi steady state (QSS) experiments were performed using Lambda Physik EMG 101 MSC excimer laser as a light source ($\lambda = 308$ nm, 15 ns, 100 mJ). Photo-CIDNP spectra were detected using AM-250 Bruker NMR spectrometer (250 MHz ^{1}H operating frequency). Standard presaturation technique was employed to suppress the equilibrium signals.

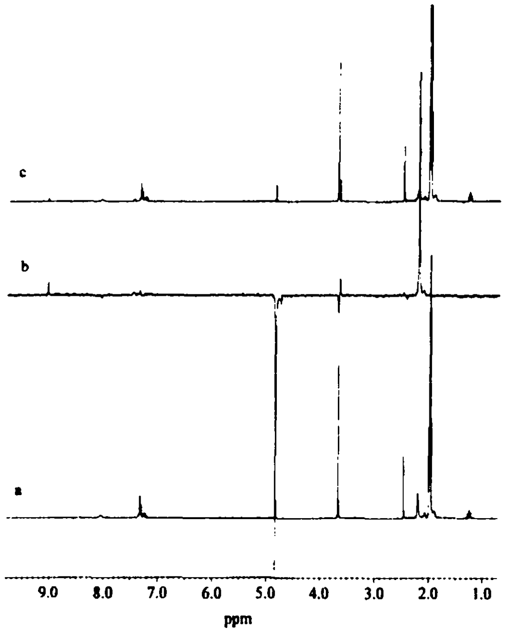


Fig. 1. ^{1}H CIDNP effects during the quasi steady state laser irradiation of DHP **I** in the presence of chloranil in acetonitrile-d_3: (a) initial spectrum; (b) CIDNP spectrum under irradiation; (c) dark spectrum after photolysis. See Table 1 for line assignment.

3. Results

The direct irradiation of the deairated solution of **I** in polar media (acetonitrile and acetone) with full light of high-pressure mercury lamp in 10 min doesn't results in products formation. Laser irradiation of the same solution allows us to detect a weak CIDNP effects on the protons of compound **I** and the main product, which was identified as 3,5-dicarbomethoxy-4-phenyl-pyridine (**II**). In the absence of acceptors only a step amount of **II** was detected after long laser irradiation (5000 pulses).

In the presence of quinones (see Section 2) 20 s lamp irradiation of 1 mM solution of **I** with CA results in complete transformation of **I** to **II**. No dark reaction was observed even for the strongest acceptor—DDQ.

CIDNP effects were observed in all kinds of experiments. As an example, Fig. 1 shows CIDNP effects as well as NMR spectra of the initial compound (a) and the final products (c) after QSS laser irradiation of **I** in the presence of CA in acetonitrile. The same effects were observed in acetone solution. The line assignment of the spectra is shown in Table 1. NMR signals of **II** were identified by means of addition of the independently prepared compounds to the solution after photolysis. It is suggested the other lines in the region 2–3 ppm and 7–7.5 ppm (in the case of DBQ) belong to acetylated quinones and hydroquinones.

In all cases the signs of CIDNP effects are independent of the irradiation wavelength, i.e., are identical both for the irradiation in the absorption region of DHP ($280 < \lambda < 380$ nm, $[DHP] \gg [Q]$) and quinone ($\lambda > 380$ nm).

Table 1
CIDNP effects observed in QSS photolysis of **I** in CD_3CN

Acceptor	**I** δ (ppm)					Pyridine-**II**		Other products
	1-H (2.45)	2,6-H (8.04)	3,5-H (3.67)	4-H (4.84)	Ph (7.30)	2,6-H (9.04)	3,5-H (3.64)	
No	–	–	–	*A*	–	*A*	–	*E*-H_2O, (2.17, broad)
CA	–	*E*	–	*E*	*A*	*A*	*A*	*A*-H_2O, *A*(2.70), *E*(2.30, 2.4, 2.44)
DBQ	–	–	*E*	*E*	*A*	*A*	*A*	*A*-H_2O, *E*(2.30)
DDQ	–	–	–	*E*	*A*	–	–	*A*-H_2O

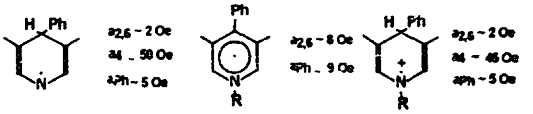
4. Discussion

As it was said above, the QSS photolysis of **I** in the absence of acceptors results in the formation only a step amount of **II**. On the other side, the photolysis of **I** in the presence of strong acceptors—quinones results in pyridine **II** formations with high yield. From this fact and CIDNP observation on the initial DHP we have suggested, that the primary act of the reaction is single electron transfer (SET). Note, that early SET had been registrated in the reaction of quinones with N-unsubstituted DHP [3]. The comparison of the redox potentials of quinones [7] and **I** (approximately, $E_{1/2}{}^{+}=2$ eV) shows the possibility of electron transfer and the formation of radical ion pair (RIP) which comprised of quinone radical anion and radical cation of **I**. The CIDNP analysis by Kaptein's rules [8] leads us to conclusion, that CIDNP was formed in triplet RIP. Really, CIDNP intensities and signs of different protons of the initial DHP correlate with spin density distribution in its radical cation (V) [5] (Fig. 1). Thus, the maximum polarization of the initial DHP was detected for the protons in 4th position. Evidently, in time-resolved experiments DHP is polarized as a cage product of RIP. It means that CIDNP effects result from the back electron transfer in the radical ion pair of the DHP radical cation and quinone radical anion.

In the previous studies of photoinduced electron transfer between various 1,4-DHP and acceptors [3] we supposed the triplet reactive state arises from charge transfer complex or exciplex formation. However, in our case, the analysis of CIDNP effects detected under direct irradiation of **I** without quinones also points to the triplet reactive state of the initial DHP. Actually, the enhanced adsorption on 4-H of **I** (cage recombination, $g(\mathrm{DHP})>g(\mathrm{COCH_3})$, $a>0$) correspond to the triplet radical pair of N-centered DHP radical (**III**) and acetyl radical ($\mu\cdot\varepsilon\cdot\Delta g\cdot a++ + =A$, [8]).

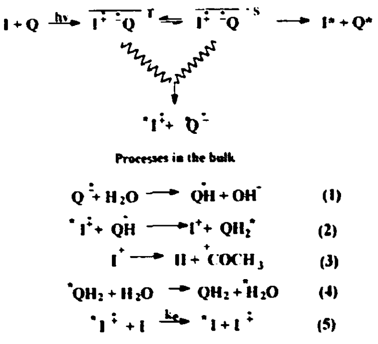
In the reaction in the presence of quinones the CIDNP effects were also detected on the pyridine **II** protons and water (present in CD_3CN, see Fig. 1). CIDNP intensity of water protons is comparable with that of 4-H of DHP, but has an opposite sign. According CIDNP theory [8,9], it corresponds to the escape product of the same RIP and means that almost all protons from 4th position of radical cation escaped from the cage were transferred to the water. Analogous to Ref. [4], one might suggest the processes in Scheme 1 to occur in the bulk. Polarized nuclei are denoted by asterisk (*). Note, however, that Scheme 1 does not include reactions of acetyl fragment in volume.

CIDNP of the protons of pyridine **II** has a certain peculiarities. CIDNP intensity of 2,6 protons is much greater than that of phenyl group. Note, that all paramagnetic species resulting from **I** (radical cation, N- and C-centered neutral radicals) have minor hfi constants in 2,6 positions, their magnitudes do not exceeding several Oe [1,5,9].



Assuming that similar to starting DHP nuclear polarization of **II** is formed in the initial RIP, in accordance with CIDNP theory [9], one might conclude that pyridine is an escape product. Another escape product, as it was said above, is water which polarization is resulted from the 4th position of radical cation (see Scheme 1). In this case, in S–T$_0$ approximation [8], the polarization of the identical protons for cage and escape products in time resolved experiments should have equal intensities and opposite signs. Actually, as we can see from Fig. 1, the balance is observed for ether and phenyl protons of **I** and **II**. However, integral intensity 2,6-H of pyridine is approximately 3 times more than for DHP.

We suppose the source of this CIDNP could be only the CIDNP of 4th position of radical cation **V**. It is most probable, that polarized pyridine results not only from the fragmentation of pyridinium cation (stage (3) in Scheme 1, doesn't observed in the spectrum after photolysis), but also from radical cation via the formation of N-centered radical **III**.



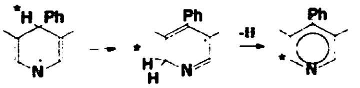
Scheme 1.

$$\mathbf{I}^{\mp}\rightarrow\mathbf{III}+\mathbf{COCH}_3^{+} \qquad (6)$$

Than, one might explain the large enhancement coefficient of 2,6-protons of pyridine observed in combination with a very small effect of 2,6-H of the initial DHP, assuming the polarization transfer from the 4th position. This transfer might occur via 1–3 sigmatropic rearrangement of the N-centered DHP radical. We have not found the examples of sigmatropic 1–3 rearrangement in N-centered DHP radicals, although there are several examples of sigmatropic rearrangements in some N-containing radicals in the literature [10,11].

To estimate the possibility of such rearrangement we have performed MNDO UHF calculation of model N-centered 3,5-$COCH_3$-4-Me-1,4-DHP radical. By our opinion, 4-Ph is perpendicular to pyridine plane and out of conjugation, therefore the substitution of Ph group to Me group and $COOCH_3$ to $COCH_3$ doesn't change principally the results of calculations. AO coefficients of HOMO (single occupied) have opposite sign on C4 (−) and both C2 and C6 (+). It means that sigmatropic shift has to proceed in antra-facial manner. According to orbital selection rules, only 1–3 antra-facial shift is allowed in radical ground state.

It is just the case, when strongly polarized 4th proton is transferred to the 2,6-positions.



VI

(7)

In this case, one can imagine the formation of weak polarized in 2,6 position pyridine **II** via reaction (3) (Scheme 1) and the strong polarized pyridine via reactions (6–7).

5. Conclusion

Photooxidation of *N*-acetyl-3,5-dicarbomethoxy-4-phenyl-1,4-dihydropyridine by quinones results in 3,5-dicarbomethoxy-4-phenyl-pyridine **II**, rather than the pyridinium cation as it is the case for *N*-methyl-substituted DHP. CIDNP study shows, that pyridine precursor in polar media is DHP radical cation. An assumption has been made about two possible pathways of pyridine **II** formation. Namely, the fragmentation of pyridinium cation and DHP radical cation mediated the formation of N-centered neutral radical. N-centered radical **III** undergoes sigmatropic 1–3 shift in the bulk from position 4 to position 2.

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