# MECHANISM OF HYDRIDE TRANSFER IN DIHYDROPYRIDINES AND THEIR ANALOGS (REVIEW)

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The literature data of the last 5-7 years from studies of the mechanism of hydride transfer by various chemical and physical methods have been systematized. It has been noted that in the current literature there is no unanimous opinion regarding the nature of hydride transfer, although the data in favor of the stepwise mechanism predominate.

Many reactions which are used in organic chemistry and technology, viz., reduction and dehydrogenation, disproportionation, and various rearrangements, are related to hydride transfers† [1-6]. The hydride-equivalent transfer of hydrogen underlies very important metabolic processes with the participation of the coenzymes NAD, NADP, and FAD [7-9].

The debate on the exact mechanism for the transfer of $H^-$, which began about 30 years ago, has not subsided even today [10-20]. The increased interest in the problem is explicable, since, in the words of E. M. Kosower, "the selection of the method of hydride transfer is of practical importance in establishing the mechanism of the reactions of pyridine nucleotides" [11]. Two principal types of transfer have been discussed: one-step (synchronous) and stepwise, (the one-electron SET redox mechanism). The following processes are distinguished in the latter case: a) transfer of an electron and an atom; b) transfer of two electrons and a proton.‡ In the present review we have made an attempt to examine the current state of the question on the basis of the literature data from the last 5-7 years.

The bulk of the investigations on hydride transfer have been carried out on derivatives of dihydropyridine. This is due to their structural similarity to the pyridine-dependent dehydrogenases, as well as the possibility to widely vary the structure, as well as the electronic and steric factors, and to thereby influence the hydride mobility. A significant role is also played by the accessibility and relative stability of dihydropyridines.

Even the first investigations of the mechanism of hydrogen transfer from dihydropyridine derivatives gave contradictory results. For example, the acceleration of reactions with a whole series of acceptors as the polarity of the solvent is increased, the absence of hydrogen exchange between dihydropyridine and the solvent [21-23], the symbatic variation of the rate constants of hydrogen transfer from donors to acceptors with the equilibrium constants for the nucleophilic addition of $CN^-$ to pyridinium salts, and the absence of deuterium exchange [24] were cited as evidence of the one-step nature of dehydrogenation. At the same time, there were examples which demonstrated the possibility of the radical nature of this process [25-27], viz., the influence of inhibitors of radical reactions, photolytic and thermal initiation, the isolation of compounds formed as a result of the recombination of radical particles, and, finally, the direct detection of radicals and radical ions by ESR [28, 29] and by electrochemical methods [30]. In the last few years the debate on the mechanism of hydride transfer has been regenerated as a result of improvements in the possibilities of physicochemical experiments.

*Deceased.

†Here and in the following the term hydride transfer refers to the transfer of a proton and two electrons (or $H^-$ taken together) regardless of the mechanism.

‡In the reactions of dihydropyridine and its analogs, the elimination of a substituent from a geminal fragment bearing a hydrogen atom is often oberved. This is a special question, which will not be considered in the present review.

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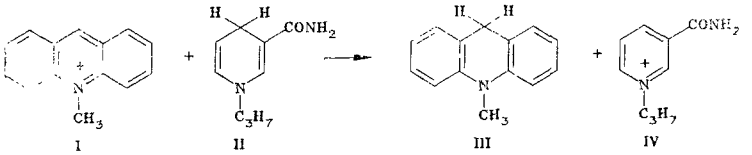
For example, there has been extensive use of isotope effects, viz., kinetic, both primary and second, and the distribution of a label in the reaction products (the "product" isotope effect), which provide information on the rate-determining step for the cleavage of a C–H bond and make it possible to draw conclusions regarding the existence of intermediates [31-36]. The maximum primary kinetic isotope effect reflecting the synchronous transfer of a hydride ion and calculated for C–H bonds amounts to $K_H/K_D \approx 7$ [36-38]. The normal secondary kinetic isotope effects characterizing a change in the transition hybridization state from $sp^3$ to $sp^2$ for a carbon atom to which an H(D) atom is bonded have values on the order of $K_H/K_D \approx 1$ [35, 36].

The discovery of anomalous isotope effects indicates that the process does not follow the simple scheme of a three-center linear transition state (A–H + B → A...H⁻...B → A + H–B), but includes the formation of at least one intermediate, which influences the overall rate and in which the cleavage of the C–H bond is hindered in comparison to the original dihydropyridine. The interpretation of primary and secondary kinetic isotope effects can also be aided by an analysis of the reaction products.

For example, significant secondary isotope effects (1.7) together with large "product" isotope effects (5.4) were discovered in the case of the reduction of the N-methylacridinium cation [39-41].

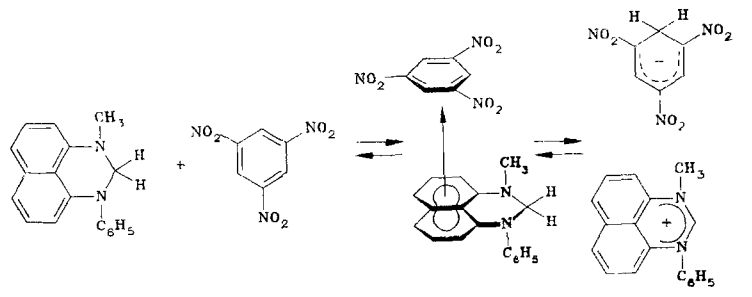



When the reaction was carried out in $D_2O$, in incorporation of deuterium in acridan III was not observed, and, in addition, hydroquinone and tert-butylcatechol did not inhibit the process. All these facts supported the one-step transfer of $H^-$. However, as Hajdu et al. suggested, the high kinetic isotope effects and the analysis of the reaction products are indications of the possibility of the existence along the reaction path of a kinetically important intermediate V, whose rate of formation limits the overall process:

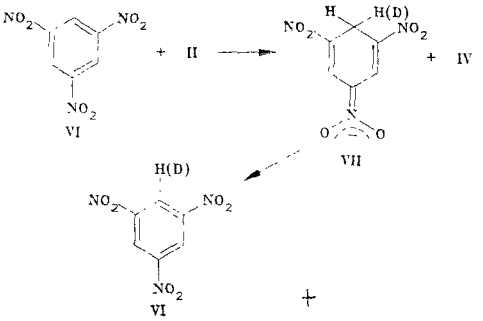
$$I + II \rightleftarrows V \rightarrow III + IV.$$

It was postulated that the intermediate may be a charge-transfer (CT) complex.

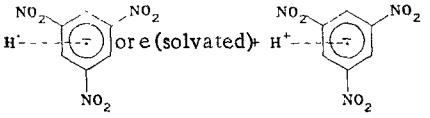
A conclusion that the formation of a CT complex should precede hydride transfer was drawn in [42]. It was shown with the use of IR and NMR spectroscopy that the deeply colored CT complexes of 1-phenyl-3-methyl-2,3-dihydroperimidine and 10-methylacridan with trinitrobenzene are converted with time into the final reaction products:




The kinetics of the reaction of the trinitrobenzene–dihydropyridine system were studied in [43], in which the reoxidation of anionic σ complex VII to trinitrobenzene was successfully observed:

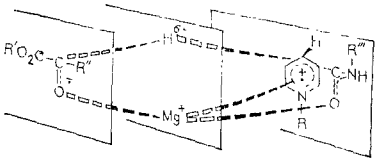


Reduction with the aid of II-$D_4$ showed that 11.4% deterium was incorporated into the final compound VI. While the overall reaction is second-order, it is first-order both with respect to the acceptor and with respect to the donor. On the basis of the values found for the second-order constant, the kinetic isotope effect of the reaction is equal to 7.02. The kinetic isotope effect for the oxidation of anionic complex VII is equal to 10.0. The "product" isotope effect determined mass-sepctrometrically $Y_H/Y_D$ = 7.8. The existence of extraordinarily large isotope effects is an indication, in the opinion of Ohno, Yamamoto, and Oka, that the hydride hydrogen is relatively free in the transitions state. However, since the hydride ion is very unstable, the system consisting of a free hydride ion must be stabilized by an interaction associated with charge transfer:



Similar investigations and conclusions have also been presented for the reactions of dihydropyridines with the ferricyanide ion [44, 45] and the N-methylphenazinium cation [46].

The objects of investigations are often dihydropyridine—acceptor reaction mixtures, in which the transfer of $H^-$ occurs in the presence of a metal ion. Such systems are more complex, but just these systems are closest to the models of biochemical processes catalyzed by pyridine-dependent dehydrogenases. The zinc ion is known to accelerate hydrogen transfer between coenzymes and substrates [47-49]. The reduction of benzoyl formate with the aid of dihydronicotinamide in the presence of magnesium ions is accompanied by the appearance of anomalous kinetic and "product" effects, which, according to [50], are attributable to the ability of the metal ion to stabilize the transition state in which the transfer of an electron from the dihydro compound to the acceptor takes place. However, the reduction of the N-methylacridinium ion [51] in the presence of divalent magnesium takes place with the isotope effect expected for the heterolytic cleavage of a C—H bond, in contradiction to the experiments without the metal, in which the appearance of an intermediate was postulated. It is still unclear whether the magnesium ion promotes the ability of dihydropyridines to donate an electron [52] to α-keto esters [53], trifluoroacetophenone [54], α,β-diketones, etc. [55, 56], or whether it retards this ability, as is seen from the example of the reaction of dihydropyridine with thiopivalophenone [57]. An attempt to explain the role of the metal ion was undertaken in [58]. It was postulated that magnesium is coordinated in the intermediate complex to the dihydropyridine molecule and the acceptor:



As a result of such coordination, a positive charge localized on the $C_{(4)}$ carbon atom is induced, as is evinced by the downfield shift of the signal of the 4-H proton in the PMR spectrum. Therefore, the elimination of a hydride ion is less preferable than the elimination of a proton.

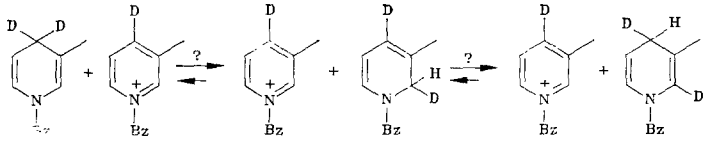
The observed differences between the influences of metal ions on the rate of hydrogen

TABLE 1. Isotope Effects in Reactions of Dihydropyridines

| Dihydropyridine | Quaternary salt | Isotope effect | Change in the hybridization of $C_{(4)}$ |
|---|---|---|---|
| N-Benzyl-4-$^3$H- | N-Benzyl | 0,79 | $sp^3 \rightarrow sp^2$ secondary tritium |
| N-Benzyl-4-$^1$H- | N-Benzyl-4-$^3$H- | 1,30 | $sp^2 \rightarrow sp^3$ secondary tritium |
| N-Benzyl-$^3$H-4-$^2$H- | N-Benzyl | 6,20 | $sp^3 \rightarrow sp^2$ primary deuterium |

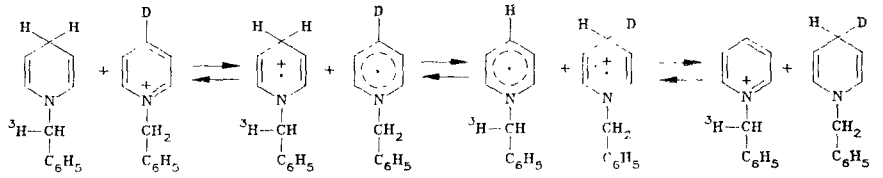
transfer and the indefiniteness of the nature of the bond of the metal to the hydride-hydrogen donor both in the initial state and in the transition state presently perclude the drawing of any substantiated conclusions regarding the mechanism of these complex reactions. The systems should apparently be simplified by separately revealing the nature of the interaction of the metal cation with the dihydro compound, the hydride acceptor, and the radical-ion intermediates, i.e., the possibility of their stabilization, their departure from the solvation cage, etc.

A detailed investigation of the mechanism of hydride transfer was carried out in [59] in the case of deuterium- and tritium-labeled N-benzyldihydronicotinamides and their quaternary salts. The course of the reaction was monitored according to the changes in the radioactivity of the initial and final reaction products. When a deuterium label was used, it was shown that the 1,2- and 1,6-dihydro derivatives do not form. The study of the NMR spectra confirmed that 97% of the deuterium is retained in position 4 of the dihydropyridine:



The secondary tritium effects of hydrogen transfer were anomalous, while the primary deuterium effect coincided with the expected (Table 1).

The normal tritium secondary isotope effects corresponding to hydride transfer should be equal to approximately 1.2 when the hybridization changes from $sp^3$ to $sp^2$ and about 0.83 for an $sp^2 \rightarrow sp^3$ transition. The anomalies in the secondary isotope effects are attributed to the large contribution of the induction effect of the isotope to the stability of the radical cation which can appear as a result of electron transfer. The equilibrium constant of the one-electron step increases in this case, promoting the appearance of anomalies. With the reaction products the profile of the free energy should also be symmetric: The first step should also be identical to the last. On this basis, the only possibility for hydrogen transfer which is consistent with the symmetry of the reaction included primary transfer of an electron, then a proton, and again an electron:



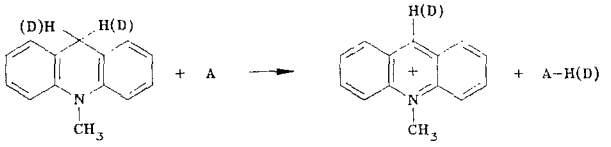
Precisely the same symmetric dihydropyridine—acceptor system was used in [59], in which van Eikeren and Grier also observed anomalies in the measurements of the secondary kinetic isotope effects.

In these studies it was shown that the existence of isotope effects in hydride transfer does not provide an unequivocal answer to the question of the form (as a proton, atom, or hydride ion) in which hydrogen is eliminated in the rate-determining step. The investigation of the secondary isotope effects, especially the tritium effects, can provide information on the changes in the transition state. However, Colter and Saito [61, 62] expressed some doubt

TABLE 2. Kinetic and "Product" Isotope Effects of the Reaction of Acridan III with Acceptors

| Acceptor | Solvent | $p$ | $s$ | $Y$ |
|---|---|---|---|---|
| Benzoquinone | $CH_3CN—H_2O$, 3 : 1 | 11,0 | 1,04 | 9,1 |
| | $CH_3CN—H_2O$, 9 : 1 | 11,8 | 1,02 | 9,4 |
| | $CH_3CN$ | 13,3 | 1,06 | — |
| Tetracyanoquinodimethane | $CH_3CN$ | 6,2 | 1,16 | — |
| Chloranil | $CH_3CN$ | 7,6 | 1,14 | 6,2 |
| Tetracyanoethylene | $CH_3CN$ | 4,8 | 1,10 | 4,5 |

regarding this claim. N-methylacridan, which produces comparatively stable radical particles, whose stability is increased as a result of the annelation of the pyridine ring by benzene rings, was studied as a model of NADH.




III I

A: benzoquinone, tetracyanoquinodimethane, chloranil, tetracyanoethylene

A CT complex, which precedes the formation of the final compounds, was detected in the reaction. Investigating the influence of the replacement of the 9-H hydrogen by deuterium on the kinetics, Colter and Saito showed that a mechanism in which hydrogen is transferred in a rate-determining step involving the reactants of intermediates in equilibrium with the reactants affords the relations summarized in (1):

$$\begin{aligned} &\text{III(HH)} \xrightarrow{2K_H} \text{I(H)} && K_{HH}=2K_H;\\ &\text{III(HD)} \begin{cases} \xrightarrow{K_{H'}} \text{I(D)} \\ \xrightarrow{K_D} \text{I(H)} \end{cases} && K_{HD}=K_{H'}+K_D; \\ &\text{III(DD)} \xrightarrow{2K_{D'}} \text{I(D)} && K_{DD}=2K_{D'}. \end{aligned} \qquad (1)$$

The rate constants $K_{HH}$, $K_{HD}$, and $K_{DD}$ are the experimental constants for III (HH), III (HD), and III (DD), respectively; $K_H$, $K_H'$, $K_D$, and $K_D'$, are the rate constants for the transfer of each of the hydrogens and deuteriums; Y is the "product" isotope effect. The primary isotope effect (p) and the secondary isotope effect (s) determined from Eqs. (2) and (3) are related to the experimental constants by relations (4) and (5):

$$p=\frac{K_H}{K_D}=\frac{K_{H'}}{K_{D'}}; \qquad (2)$$

$$s=\frac{K_H}{K_{H'}}=\frac{K_D}{K_{D'}}; \qquad (3)$$

$$\frac{K_{HH}}{K_{DD}}=\frac{2K_H}{2K_{D'}}=p\times s; \qquad (4)$$

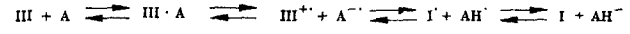
$$\frac{K_{HD}}{K_{DD}}=\frac{K_{H'}+K_{D'}}{2K_{D'}}=\frac{p+s}{2}. \qquad (5)$$

Analyzing the experimental data (Table 2), these investigators considered two mechanisms: the one-step transfer of a hydride ion, and the transfer of an electron and an atom.

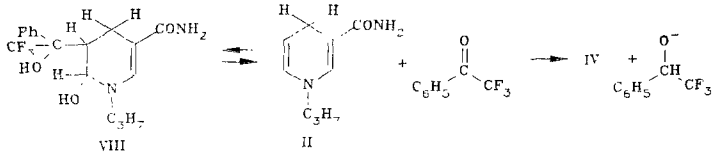
$$\text{III}+\text{A} \underset{}{\overset{\text{fast}}{\rightleftharpoons}} \underbrace{\text{III}\cdot\text{A}}_{\text{CT complex}} \xrightarrow{\text{slow}} \text{I}+\text{AH}^-;$$

$$\text{III}+\text{A} \overset{\text{fast}}{\rightleftharpoons} \text{III}\cdot\text{A} \overset{\text{fast}}{\rightleftharpoons} \text{III}^+\cdot\text{A}^- \xrightarrow{\text{slow}} \text{I}+\text{AH}^-.$$

The increase in the reaction rate with increasing polarity of the solvent and the tendency for an increase in the primary isotope effects are completely consistent, in their opinion, with the one-step mechanism. It is not clear why these investigators did not consider another possibility for the occurrence of the reaction:

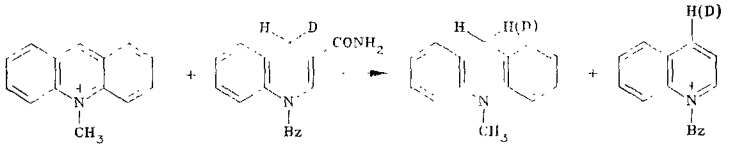


No explanation was given for the anomalous isotope effects detected, only a suggestion of the possibility of tunneling being offered. The large values of the primary isotope effect and their coincidence with the "product" effect support a stepwise mechanism rather than a synchronous mechanism (see, for example, [39-46]). The need for a thorough and cautious interpretation of measurements of isotope effects, in which the results of a detailed study of the reaction mixtures and the possibility of the occurrence of secondary reactions, as well as parallel and equilibrium processes, must be taken into account, should be underlined. All these data can radically alter the conclusions. For example, in one of the most frequently quoted papers of Steffens and Chipman in recent years [63] anomalously high primary isotope effects were observed in reactions of various dihydropyridines with trifluoro-acetophenone. In addition, the "product" isotope effect was distinguished from the reaction kinetics determined. The existence of radical-ion hydride-transfer intermediates was postulated on this basis. However, 9 years later, Chipman rejected the earlier conclusions and reported that the inconsistency in the isotope effects is due to the reversible formation of a covalent adduct (VIII), which does not appear along the path of the redox reaction [64]:



VIII II IV

The reaction kinetics and the "product" isotope effect may also be influenced by the isotope mixing occurring between the components of the reaction mixture [65]. For example, the following substances form in the reaction of the N-methylacridinium cation with dihydroquinoline:



I IX III X

In this case, processes associated with the following isotope transitions can occur:

This is the reason why the "product" isotope effect is greater than the kinetic isotope effect. As a result of an investigation of the previously described reactions of N-methylacridinium with N-benzyl-1,4-dihydronicotinamide [66], N-benzyl-3-carbamoyl-1,4-dihydroquinoline [67], and N-aryl-1,4-dihydronicotinamide [68] it was shown that one-step transfer, rather than the presumed stepwise hydride-equivalent hydrogen transfer, is characteristic of these systems. At the same time, van Eikeren et al., [69, 70] presented evidence in support of a scheme involving the transfer of an electron from a dihydropyridine to a pyridinium salt through an intermediate radical—radical-cation pair with consideration not only of the redox process, but also of the hydration reaction and the hydrogen-exchange reaction of the dihydropyridine with the medium described in [64, 65].

The contradictory nature of the results presented confirms Melander's statement that "isotope effects should be used in conjunction with as large a number of other characteristics of the reaction as is possible: the final products, the kinetics, salt effects, the influence of the solvent, the stereochemistry, etc. Isotope effects by themselves are no substitute for a

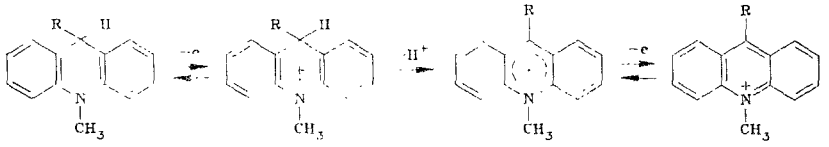
TABLE 3. Results of the Reduction of Compounds XVIIIa-d with the Aid of Compounds XVI and XVII

| Substrate | Solvent | Deuterium content in XIXa-d, %, in reaction | |
|---|---|---|---|
| | | with XVI | with XVII |
| XVIIIa | DMSO $-CD_3OD$ | 84 | 89 |
| XVIIIb | DMSO $-CD_3OD$ | 38 | 92 |
| | DMSO $-CH_3OH$ | 43* | |
| | $CD_3CN$ | 0 | |
| XVIIIc | DMSO $-CD_3OD$ | 15 | 43 |
| | DMSO $-CH_3OH$ | 36* | |
| XVIIId | DMSO $-CD_3OD$ | 0 | 34 |
| | DMSO $-CH_3OH$ | 100* | |

*Reaction with XVI-4, 4-$d_2$.

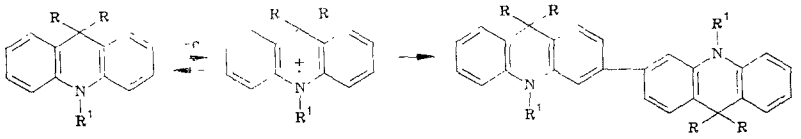
complete investigation and are only a valuable supplement to the remaining data" [36]. Methods which make it possible to detect fast reversible interactions are often utilized to obtain information on dehydrogenation processes. One of these methods, which has become widely used, is an electrochemical method.

In the case of the oxidation of acridans by salts of divalent copper, it was discovered that 2 moles of $Cu^{2+}$, which is reduced to $Cu^{+}$, are consumed per mole of the dihydro compound [71]. The electrochemical oxidation of acridans carried out in that work made it possible to establish that, as in the case of other dihydroazines [72-76], it takes place with the successive transfer of an electron, a proton, and and electron:



R=$CH_3$, $C_6H_5NH_2$, $C_6H_5N(CH_3)_2$

The results in [71] were subsequently confirmed in [77, 78] in studies of the oxidation of the same and other acridans. Data from cyclic voltammetry, electrolysis at a controlled potential, and independent syntheses [78] showed that 9,9-disubstituted compounds (9,9-dimethylacridan, 9,9,10-trimethylacridan, 9,9-diphenylacridan, and 10-methyl-9,9-diphenylacridan) are oxidized to a radical monocation (reversible one-electron transfer) and dimerization to readily oxidized 2,2-bisacridan systems occurs after the elimination of a proton.



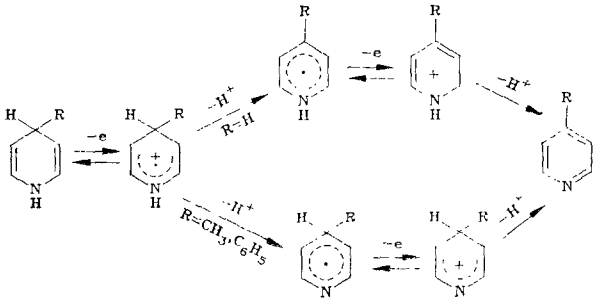
At the same time, the oxidation of 9-H-acridans takes place according to an EPE mechanism (E denotes an electron and P denotes a proton) and yields an acridinium cation. The cyclic voltammogram showed a peak belonging to the reduction of protons, which is additional evidence in support of the proposed oxidation scheme.

In evaluating these results, we should still admit that electrochemical reactions are a fairly approximate model for any chemical reaction, including hydride transfer. The data from electrochemical investigations of a mechanism can be used only in conjunction with other chemical and physical methods.

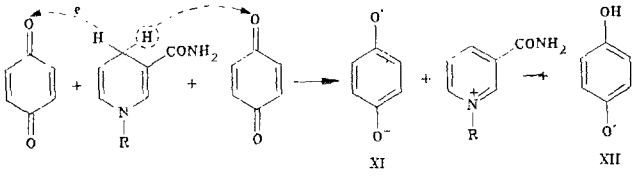
Perhaps one of the first attempts to compare electrochemical oxidation data with the results of kinetic measurements was undertaken in the work of the Latvian chemists Dubur et al. in the case of the reactions of a large series of dihydropyridines, viz., Hantzsch esters [79-81]. The influence of the structure on the reactivity of dihydropyridines in chemical, enzymatic, and electrochemical reactions was investigated. While noting some agreement in a number of cases, these investigators reveals the shortcomings of the electrochemical method, which does not take into account the influence of the partner in the redox process, its structure, and its orientation, as well as the influence of the solvent etc.

A comparison of the rates of the enzymatic oxidation of pyridine-containing dinucleotides with the standard potentials does not make it possible to choose between the transfer of a hydride ion and a hydrogen atom [82].

In [83] it was noted that some 3,5-bifunctional derivatives of 1,4-dihydropyridines are irreversibly oxidized on a rotating platinum electrode to the corresponding pyridines with the expenditure of two electrons and two products and that proton elimination does not limit the overall reaction rate. Conversely, in [84] it was reported that a potential-determining influence of proton elimination on the step involving the deprotonation of the radical cation formed after the elimination of an electron from the dihydropyridine molecule is observed. The experimental data obtained support the mechanism of the sucessive elimination of electrons and protons from the reacting molecule, for which the following scheme was given in [85].

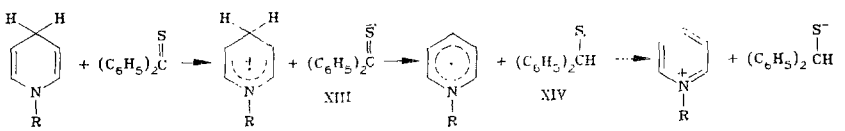


The possibility of the direct detection of one-electron acts during hydride transfer may also be allowed by ESR spectroscopy [86-88]. For example, the oxidation of N-benzyl-1,4-dihydronicotinamide by quinone in a solution of tert-butanol is accompanied by the appearance semiquinone XI in the form of an anion, which is detected by ESR [89]. The fact that semiquinone XI and its protonated form XII appear is an indication, in the opinion of Yasnikov et al., of the separate transfer of a hydrogen atom and an electron to two different quinone molecules:



Unfortunately, for some reason the other possibility of the formation of semiquinone XII as a result of the successive transfer of an electron and a proton was not considered. The separate transfer of an electron and a hydrogen atom was previously [90] demonstrated in the case of the combined oxidation of N-benzyl-1,4-dihydronicotinamide and phenylglyoxal by hydrogen peroxide in the presence of molecular oxygen. The hydroxyl radical formed during the reaction eliminates a hydrogen atom from the dihydropyridine only if there is a possibility for the transfer of an electron to molecular oxygen. A hypothesis of similar transfer of a hydrogen atom from the reduced coenzyme NADH to a substrate in biochemical processes was advanced.

The direct formation of radicals in the reactions of dihydropyridines and thiobenzophenone was observed in [29]. The ESR spectra of the radical anion of thiobenzophenone (XIII) was recorded when a 2-methyltetrahydrofuran solution was frozen. At room temperature this radical anion was converted into free radical XIV:

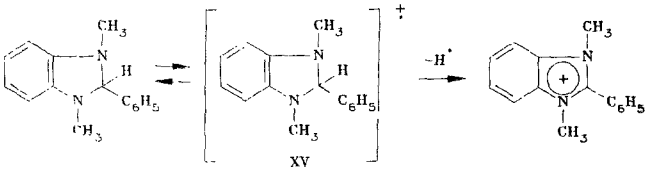


Kill and Widdouson [91] succeeded in detecting a pyridinyl radical during the interaction of 1-benzyldihydronicotinamide with bromonitromethane. In this case, the addition of p-dinitrobenzene slowed the reaction, while benzoyl peroxide significantly increased the rate of

oxidation of the dihydro compound. However, in the case of oxidation by m-chlorobenzaldehyde [92], the presence of oxygen or p-dinitrobenzene does not influence the reaction. Indirect confirmation of the possibility of the formation of radical particles from dihydro derivatives may be provided by the reactions of dihydropyridines and their analogs with free radicals [93, 94], their use as antioxidants and inhibitors of radical processes [95, 96], and the photo- and radioactivation of reduction with the aid of dihydropyridines [97-99].

An attempt was made to use chemically induced dynamic nuclear polarization (CIDNP) to detect radical particles in reactions of dihydronicotanimide with phenyldiazonium fluoborates [100] and triphenylchloromethane [101]. The absence of CIDNP supports the transfer of a hydride ion, although latent radical processes, which are not accompanied by the formation of long-lived radical pairs, are possible.

An unusual phenomenon, viz., the irreversible elimination of a hydrogen atom from a radical cation, was discovered in the case of the oxidation of benzimidazoline [102], which, according to the kinetic data in [103], is characterized by the elimination of $H^-$:



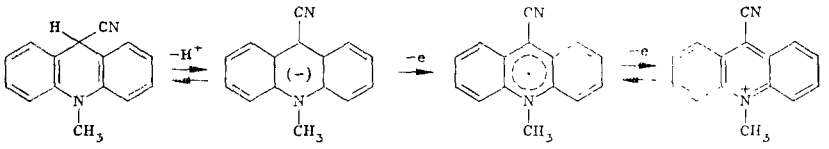

Radical cation XV is easily dehydrogenated. The hydrogen released in the reaction reduces palladium black. This is possibly the first case of a path for the dehydrogenation of a radical cation for which the deprotonation process is more characteristic [104], although in general there is a fairly large number of examples of the elimination of hydrogen atoms from dihydropyridines [105-111].

Despite the abundance of cases of the detection of radical-ion particles during the oxidation of dihydroazines, as well as the appearance of a whole series of investigations devoted to the direct study of the properties of dihydropyridine radicals [11, 104, 112-114], the ESR method still does not provide sufficiently convincing evidence for the SET mechanism of hydride transfer, since, as Borg noted, "the presence of an ESR signal in chemical and biochemical reactions is not sufficient proof that an important radical component or reaction path has been discovered or confirmed. Further correlations, for example, the quantitative treatment of ESR spectra and a kinetic analysis of the reaction are needed. Unfortunately, studies of stoichiometric relations or kinetics in the case of reactive and short-lived radical products are carried out much too rarely" [88].

An analysis of the influence of substituent is often used in the study of reactivity and mechanisms. The term "hydride mobility" is used to compare the reducing ability of dihydropyridines, although the concept itself does not have a strict definition. While the proton mobility can easily be characterized by the $pK_a$, the hydride activity can apparently be estimated only indirectly from the values of the $pK_R+$. There are a few studies in which the relationship between the structure of a dihydro compound and its ability to undergo oxidation was investigated. In [115] it was shown in the example of Hantzsch esters that α electron-donor substituents facilitate dehydrogenation, but it was noted that special effects are superimposed on the electronic effects. For example, an electron-donor methyl group introduced into a α position should increase the hydride mobility, but inhibition of the oxidation process is observed [116]. Spatial factors probably also cause the stereospecificity of hydride-transfer reactions, which has been observed for a number of optically active NADH models in reactions with various acceptors [117-123]. If a geminal fragment of an N-alkyldihydropyridine contains an electron-acceptor grouping, which hinders hydride elimination, the elimination of the substituent is noted, as, for example, in the case of a nitrile [124] or carboxyl group [125]. In the latter case, the benzoannelation of the dihydropyridine makes it an $H^-$ donor. The influence of benzoannelation is not entirely clear, since it usually results in lowering of the hydride mobility, as is seen, say, when dihydropyridines and dihydroquinolines are compared [126-128]. In the case of N-acyl dihydro compounds of the quinoline series, the elimination of other groupings is observed [129-131]

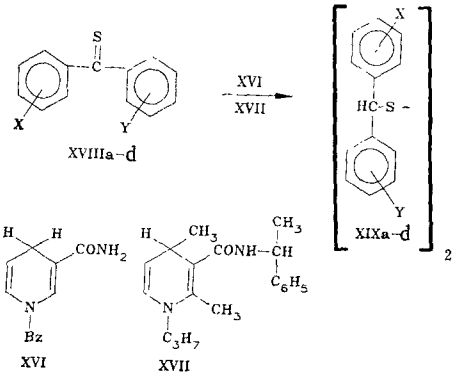
Substituents have the strongest influence on a hydrogen atom attached to a tetragonal carbon atom, whose hybridization changes upon $H^-$ transfer. Here, the substituent, including

deuterium, has a direct influence not only in the initial step of the dehydrogenation process, but also in the transition state. As has already been mentioned [29, 30, 39-46, 52-60, 67-84], the transition state may be associated with radical-ion intermediates. On this basis we can explain why donor substituents, which should promote hydride transfer, sometimes slow the process, possibly due to the stabilization of radical-cation particles owing to the inductive or steric effects. The effects of a geminally bonded grouping can be traced especially well with the aid of methods which permit the detection of fast steps. For example, the introduction of a nitrile residue into positions 9 of acridan results in the oxidation of the dihydro compound not only by means of an EPE mechanism [71, 77, 78], but also by means of an EEP mechanism [132]. In addition, under certain conditions such a dihydro derivative may display proton acitivity. For example, when 9-cyanoacridan is oxidized in the presence of sodium nitrite as a base, the elimination of a proton followed by the successive transfer of two electrons (PEE) is observed [133]:



The realization of this reaction in a cell placed in the resonator of an ESR spectrometer made it possible to record a stable, well resolved spectrum belonging to the cyanoacridinyl radical. Precisely the same spectrum was also obtained in the case of chemical oxidation by atmospheric oxygen under the conditions of base catalysis.

Variation of the substituents in dihydro compounds aids the detection of kinetic steps which are too fast to be detected by experimental methods. One of the latest reports of Ohno's research team [134], which has been intensely studying hydride transfer, is fundamental in this respect. They oxidized derivatives of thiobenzophenone by the dihydropyridines 1-benzyl-1,4-dihydronicotinamide (XVI) and N-(α-phenylethyl)-1-propyl-2,4-dimethyl-1,4-dihydronicotinamide (XVII):

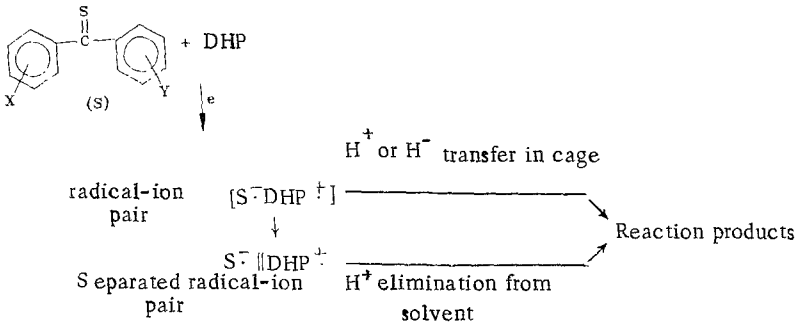


XVIII [a] X=*p*-Cl, Y=H; [b] X=Y=H; [c] X=Y=*p*-MeO; [d] X=*o*-OH, Y=H

Each of the acceptors XVIIIa-d reacted with the NADH models in a DMSO–methanol mixture at room temperature in a nitrogen atmosphere with the formation of the corresponding dibenzhydryl disulfides XIXa-d. In DMSO-$CD_3CN$ did not contain deuterium. Ohno et al. justifiably postulated the possibility of the transfer of labeled hydrogen from the solvent. The reduction of compounds XVIIIa-d with the aid of dihydropyridine XVI-4,4-$d_2$ gives completely deuterated methine groupings. The solvent had the strongest hydrogen-donor influence on the compounds reduced with the aid of XVII in DMSO–$CD_3OD$ or DMSO–$C_2H_5OD$ media. Deuterated XIXd could be obtained even in the reaction with XVIIId. The results of the experiments are given in Table 3. It should be mentioned that the hydrogen atoms in the methine positions in compounds XIXa-d are not exchanged with hydrogen from the medium even under alkaline conditions. As we know, hydrogen exchange is not observed for dihydro compounds. Therefore, in cases of the incorporation of hydrogen from the solvent, it is necessary to allow for the existence of at least one intermediate. It is also clear that hydrogen is eliminated from the solvent in the form of a proton, as demonstrated by a comparison of the reduction of XVIIIb in $CD_3CN$ and

in a DMSO—$CD_3OD$ medium. Thus, the intermediates leaving the reaction cage must have an anionic character. Even before this work there were sufficient examples that radical anions might be such intermediates in the reactions just described.

The difference between the donor—acceptor properties of compounds XVI and XVII (the latter is a stronger reducing agent), as well as the presence of a methyl group in position 4 of compound XVII, are the reasons why it is more difficult to eliminate a proton from dihydropyridine XVII than from XVI. Consequently, the intermediates appearing from compounds XVIIIa-d in the reactions with XVII are more inclined to undergo exchange with the solvent than in the case of the reactions with XVI. Therefore, even the molecule of XIXd contains deuterium in the methine position. The anomalous behavior of XVIIId in the reaction with XVI is attributable to the appearance of a hydrogen bond between the hydroxyl and thiocarbonyl groups, which enhances the energy barrier to proton transfer. As a result, compound XVIIId has a great possibility for reacting in the reaction cage. In this case, the radical-ion pair appearing during the interaction of compounds XVIIId and XVI does not leave the reaction cage, whereas such departure occurs in the case of the reaction with XVII. The following general scheme was proposed on the basis of the results obtained:




The establishment of deuterium exchange with the solvent is the most important finding. The absence of such exchange was previously [21-24] one of the main arguments in support of the one-step mechanism of hydride transfer.

Summing up the discussion of the data on hydride transfer for dihydropyridines and their analogs, it should be stated that the data supporting the stepwise transfer of $H^-$ in this series, as well as in other classes of compounds, predominate in the current literature. Arguments in support of a one-electron mechanism of hydride transfer are generally provided by numerous studies from the past 2-3 years, in which radical-ion intermediates were discovered in redox reactions of even such classical hydride donors as alkylsilanes [135, 136] and metal hydrides [137-145 and editorial 146].

At the same time, arguments in support of a one-step process have been presented in a number of very recent investigations [64, 65, 128, 147-150].

This question, which is still [151] open to debate, can clearly be resolved for many reactions after strict criteria for the residence of short-lived radical particles on the reaction coordinate will be obtained. This requires the measurement of rate constants according to the changes in the concentrations not only of the initial and final products, but also of the intermediates, with the use of flow and relaxation methods.

Apparently, there are also reactions in which the step-wise nature of the transfer process cannot be detected at the present level of technology.

With regard to such cases, Bridgman [152] wrote more than 50 years ago that "if no practical method which would make it possible to choose between alternative theories can be found, one should ponder whether these theories are, in fact, alternatives."

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