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Progress in the studies of oxidation of dihydropyridines and their analogues

A I Matern, V N Charushin, O N Chupakhin

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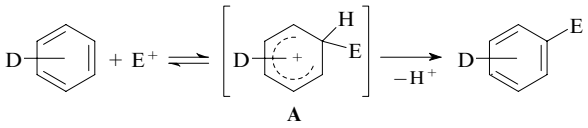
Abstract. Published data on oxidation of dihydropyridines and on the mechanisms and the role of hydride shifts in bioorganic chemistry, enantioselective synthesis and supramolecular chemistry are generalised. The bibliography includes 218 references.

I. Introduction

Almost two hundred years ago, the German chemist Schorlemmer defined organic chemistry as the chemistry of hydrocarbons and their derivatives, from which it follows that the nature of C – H bonds and the conditions of their formation and cleavage are important subjects of chemical investigation.

Actually, many processes associated with the formation of new chemical bonds involve the attack of various reagents, such as electrophiles, nucleophiles, radicals, carbenes and other active species, on the C – H fragment. Radical reagents cause C(sp^3) – H bond homolysis, carbenes are inserted into C(sp^3 or sp^2) – H bonds, whereas the attack of electrophilic or nucleophilic species, which generally occurs on the carbon atoms of C(sp^2) – H, ends in the transformation of the substrate molecule into σ^H adducts containing the C(sp^3) fragment (a geminal unit). It should be noted that the hydrogen atom elimination is preceded by the formation of σ^H adducts and the latter process radically changes the C – H bond character.

Electrophilic aromatic substitution of hydrogen is a typical example of this transformation. This is a well-developed approach to structural modifications of arenes, which has come into common use as an industrial method for the synthesis of various aromatic compounds.

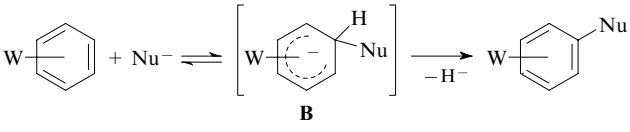


A

D is an electron-donating group and E is an electrophile.

Electrophilic aromatic substitution reactions are based on the ease of C(sp^3) – H bond cleavage in cationic arene onium σ^H complexes **A** with restoration of aromaticity of the system, which is the driving force for the process.

The nucleophilic attack on aromatic carbon atoms gives rise to anionic σ^H adducts **B**. For many years, the difficulties associated with elimination of the hydride ion from these adducts have limited the development of studies on nucleophilic aromatic substitution of hydrogen (S_N^H). However, investigations performed in the last decades substantially extended knowledge of the synthetic potential of this important approach, which is nowadays used in both oxidative and elimination (*ipso* substitution) modifications.[1 – 20]



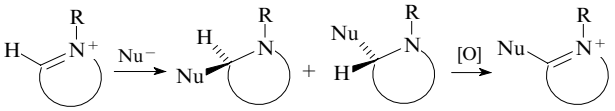
B

W is an electron-withdrawing group and Nu is a nucleophile.

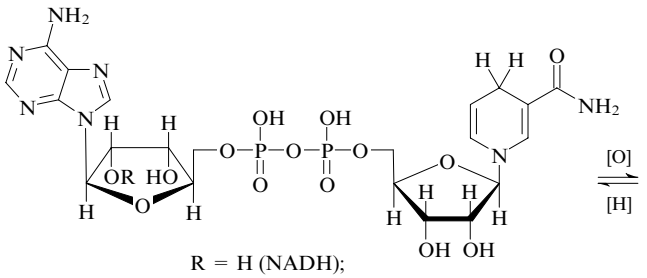
Since the publication of the first review on S_N^H reactions in 1976,[9] extensive data on amination, arylation, alkylation, cyanation, hetarylation and other analogous reactions, which enable the direct introduction of fragments of various nucleophiles into activated aromatic compounds of carbo- or heterocyclic series, have been accumulated in the literature. The conditions of the formation of anionic σ^H adducts (as the first step of S_N^H reactions) [1 – 3, 10 – 19] and the characteristic features of their spatial structures, dissociation and isomerisation were revealed. The asymmetric induction in the new bond formation in nucleophiles containing the unsubstituted carbon atom was examined for a series of azinium salts.[20]

A I Matern Urals State Technical University, ul. Mira 19, 620002 Ekaterinburg, Russian Federation. Fax (7-343) 374 04 58, tel. (7-343) 374 39 05, e-mail decan@htf.ustu.ru
V N Charushin, O N Chupakhin I Ya Postovky Institute of Organic Synthesis, Urals Branch of the Russian Academy of Sciences, ul. S Kovalevskoi 22, 620219 Ekaterinburg, Russian Federation. Fax/tel. (7-343) 374 11 89, e-mail: charushin@ios.uran.ru (V N Charushin), tel. (7-343) 375 45 01, e-mail: chupakhin@ios.uran.ru (O N Chupakhin)

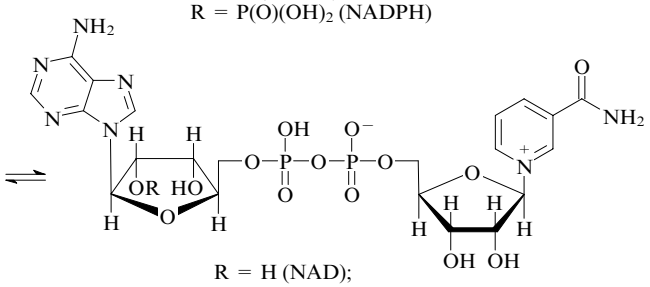
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The mechanism of abstraction of 'hydride-labile hydrogen'† (the second step of S_N^H reactions) from dihydropyridines is of fundamental importance for organic and bioorganic chemistry and has been the subject of numerous studies and discussions for almost three decades.[21–28] The importance of knowledge of this mechanism is not only of theoretical interest. The characteristic features of transformations of dihydropyridines and the hydride transfer mechanism are at the basis of important processes in living nature involving nicotinamide adenine dinucleotides and their phosphates (NADH ⇄ NAD, NADPH ⇄ NADP), which are the main components of metabolism and cell energy supply.[21–23,28–32]



R = H (NADH);
R = P(O)(OH)$_2$ (NADPH)

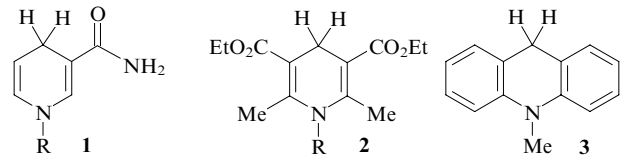


R = H (NAD);
R = P(O)(OH)$_2$ (NADP)

The mechanism of hydride-labile hydrogen transfer has come under discussion almost immediately after the publication of pioneering studies on oxidation of compounds containing such hydrogen atoms. Kosower[21] explained an increased attention to this problem by the fact that the choice between the electron transfer and hydride ion transfer is critical to establishing the oxidation mechanism of pyridine nucleotides. Two fundamentally different mechanisms are considered: the one-step (concerted) and stepwise (redox, single-electron transfer, SET) mechanisms. In the latter case, the electron and hydrogen transfer or the two-electron–proton transfer are distinguished. Biochemists have long considered NADH as a source and a component in the electron transport chain, while organic chemists engaged in studies of model chemical compounds are actively debating the nature of hydride transfer.

In the last two decades, the main approaches to investigation of hydride-labile hydrogen transfer and to the choice of NADH models were developed. 1,4-Dihydropyridine derivatives, such as dihydronicotinamides **1**, Hantzsch esters **2** and *N*-methylacridane (10-methyl-9,10-dihydroacridine, $AcrH_2$, **3**), are most often used as models because these compounds are structurally similar to pyridine-dependent dehydrogenases and their spatial structures and electronic properties can be varied over a wide range, thus influencing the hydride ion mobility.

† The term 'hydride-labile hydrogen' is used to designate H^- that can be eliminated as either a proton and two electrons or a hydrogen atom and an electron, and the hydride shift is used in reference to the transfer of these species.



R = Alk, Ar.

Nowadays, authoritative research groups concerned with the problem of hydride shift in such compounds work in different countries. A considerable contribution to the development of knowledge of the mechanism and characteristic features of oxidation of dihydropyridines was made by the research teams headed by Kosower and Chipman in USA, Stradyn and Duburs in Latvia, Bruice and Moiroux in France, Colter in Canada, Ohno and Fukuzumi in Japan, Cheng and Zhu in China, Hilgeroth in Germany, Beletskaya and Pozharskii in Russia, *etc*. For example, the group headed by Prof. Ohno investigated the characteristic features and stereoselectivity of reduction of various unsaturated systems by dihydronicotinamides, and the results of these studies were published in hundreds of articles. The group headed by Prof. Fukuzumi, who is a recognised expert in the field of investigation of single-electron transfer processes in chemistry and biology and one of the editors of the five-volume encyclopedia *Electron Transfer in Chemistry* published in 2001, has a comparable number of publications on hydride migrations in dihydro derivatives of pyridine and acridine.

The review of the literature demonstrates that the oxidation mechanism of dihydropyridines and the use of these compounds as a 'redox arm' (electron carriers) have attracted considerable interest in the last 5–10 years. This is confirmed by an increase in the number of investigations on the design of qualitatively new materials and processes based on these compounds. The extensive development of biotechnology, nanotechnology and materials sciences and the progress in the field of coordination and supramolecular chemistry facilitated investigations of the hydride shift mechanism. The acquired knowledge of the pathways of redox transformations of nicotinamide adenine dinucleotides was useful in the preparation of antioxidants, free-radical process inhibitors and corrosion inhibitors, in the enantioselective synthesis and asymmetric cleavage, in medicine and biochemistry, in the design of enzyme reactors, bioelectrochemical systems, organic conductors, molecular devices, *etc*.

The present review covers the main directions and trends of the development of knowledge of the hydride transfer mechanism in the series of dihydropyridines and their analogues discussed in the literature in the last two decades. This period of studies of hydride transfer reactions is characterised by development of new methods for initiation and catalysis of oxidation processes, the extension of the range of physicochemical methods and the combined application of various analytical methods.

II. Hydride transfer mechanisms in oxidation of dihydropyridines

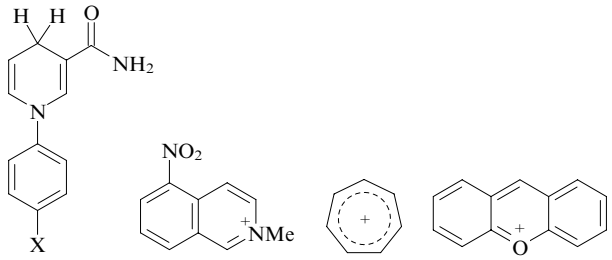
1. Study of the properties of dihydropyridines by theoretical and kinetic methods

A combination of kinetic and calculation methods for studying oxidation of dihydropyridines is a main line of investigation of the hydride transfer mechanism. The development of the single-electron concept in organic chemistry,[32,33] the progress in investigation of redox processes[34–36] and the elaboration of the theory of single-electron transfer‡ (Marcus theory)[36–39] gave impetus to studies, in which experimental results were compared with the calculated energies of hydride transfer reactions and steps of this process.[40–42]

‡ This theory relates the driving force for redox reactions, *i.e*., the energy differences of the reagents and reactions products, to their rates.

Nowadays, various methods are available for quantitative and qualitative estimation of the 'hydride activity' of dihydropyridines taking into account the energy, magnetic, chemical and structural criteria.[1,6,23] For example, a comparison of the energy profiles of the hydride and hydrogen transfer reactions and of the proton and two-electron transfer led to different conclusions about the possible mechanisms of the process.[43–46] It was noted that in the single-electron transfer mechanism, the electron and proton transfer occurs between different reaction centres, which is energetically unfavourable. The solvent effect and reorganisation of the solvent in transition states for both the one-step and stepwise oxidation mechanisms were discussed. A comparison of the calculated and experimental data demonstrated that enzymatic reactions are characterised by the one-step hydride transfer, whereas the proton and two-electron transfer occurs in solutions of model compounds. Analogous conclusions were drawn after calculations by the Marcus equation, which relates the reaction rate constants to the standard free energy changes, for the hydride transfer between NADH and NAD analogues.[47]

The Gibbs free energy changes and the Brønsted and Hammet coefficients were calculated for oxidation of 1-aryl-1,4-dihydronicotinamides **1a–e** by 5-nitroisoquinolinium (**4**), tropylium (**5**) and xanthylium (**6**) cations.[48] It appeared that the one-step hydride transfer is most probable for isoquinolinium cation **4**, whereas the initial electron transfer (the single-electron transfer mechanism) is more probable for the tropylium and xanthylium cations.



1a–e **4** **5** **6**

X = OMe (**a**), Me (**b**), H (**c**), Cl (**d**), Br (**e**).

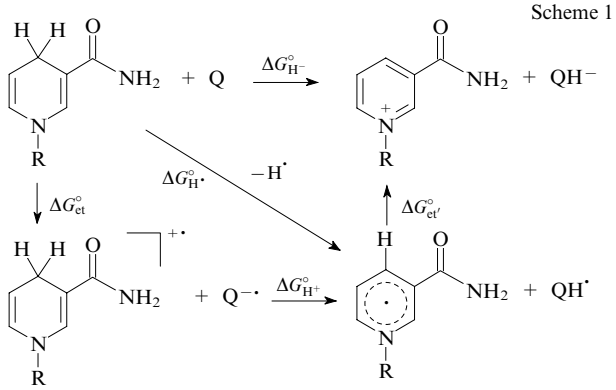
Analysis of the kinetic data, including the isotope effects, and calculations of the activation parameters of oxidation of 1,4-dihydropyridines (Hantzsch esters) and benzylidenemalononitriles suggested the one-step hydride transfer mechanism for these processes.[49] Based on the estimation of the influence of the structural factors of substituents on the hydride mobility and the direct detection of radical species, it was concluded that the hydrogen abstraction in reduction of radicals and radical ions by a series of 4-substituted 1,4-dihydropyridines occurs by the single-electron transfer mechanism.[50]

Lu *et al.*[51] believed that considerable differences between the expected and real kinetic isotope effects, the difference between the energy profiles of the one-step and stepwise hydride transfer reactions and the detection of intermediates in the reaction of 10-methyl-9,10-dihydroacridine (**3**) with the 1-benzyl-3-cyanoquinolinium ion (see below) do not rule out the possibility of hydride tunnelling.

Based on the energy profiles of the hydride transfer from 1-benzyl-1,4-dihydronicotinamide (BNAH, **1f**) to *p*-benzoquinone derivatives calculated thermodynamically, the stepwise mechanism of electron and proton abstraction according to the electron–proton–electron (EPE) scheme was assumed.[52,53] It was noted that the Gibbs free energy changes for the single-electron transfer between dihydro adducts and electron acceptors correlate well with the rate constants and the primary kinetic isotope effects.

For the reactions of quinones (Q) with dihydropyridines PyH_2 (including 1-benzyl-1,4-dihydronicotinamide), the Gibbs free energy changes (ΔG°) for different steps of the mobile hydrogen

Scheme 1



transfer (Scheme 1), such as the transfer of the first (et) and second (et′) electrons and the proton, hydrogen and hydride abstraction, were calculated[54] according to Eqns (1)–(5), respectively.

$$\frac{\Delta G^\circ_{et}}{F} = E^\circ(PyH^{+\bullet}/PyH_2) - E^\circ(Q/Q^{-\bullet}), \quad (1)$$

$$\frac{\Delta G^\circ_{et'}}{F} = E^\circ(PyH^{+}/PyH^{\bullet}) - E^\circ(QH^{\bullet}/QH^{-}), \quad (2)$$

$$\Delta G^\circ_{H^+} = 2.3\,RT[pK_a(PyH^{+\bullet}/PyH^{\bullet}) - pK_a(QH^{\bullet}/Q^{-\bullet})], \quad (3)$$

$$\Delta G^\circ_{H^\bullet} = \Delta G^\circ_{et} + \Delta G^\circ_{H^+}, \quad (4)$$

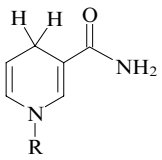
$$\Delta G^\circ_{H^-} = \Delta G^\circ_{et} + \Delta G^\circ_{H^+} + \Delta G^\circ_{et'}, \quad (5)$$

where F is the Faraday constant and E° is the redox potential.

As a result, it was established that the energy barriers of the one-step hydride transfer for dihydronicotinamide are higher than those for the stepwise transfer. A comparison of the calculated and experimental primary kinetic isotope effects and the influence of the magnesium(II) concentration on the hydride transfer rate and the redox potentials of the reactants led to the conclusion that the reaction proceeds by the single-electron transfer mechanism:

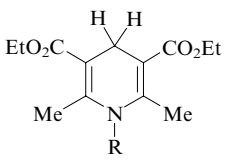
$$PyH_2 \underset{-e}{\rightleftharpoons} PyH_2^{+\bullet} \xrightarrow[-H^+]{} PyH^{\bullet} \underset{-e}{\rightleftharpoons} PyH^{+}$$

The question about the possibility of homolytic and heterolytic C–H bond cleavage in oxidation of the main NADH models, *viz.*, compounds **1a–g**, **2a**,**b** and **3**, by perchlorate of the *N*,*N*,*N*′,*N*′-tetramethyl-*p*-phenylenediamine radical cation ($TMPA^{+\bullet}$) was considered by Chinese researchers[55] with the use of thermodynamic calculations and data from cyclic voltammetry and calorimetric measurements.[55,56]



1a–g

R = 4-XC_6H_4 [X = OMe (**a**), Me (**b**), H (**c**), Cl (**d**), Br (**e**), F_3C (**g**)], $PhCH_2$ (**f**)



2a,**b**

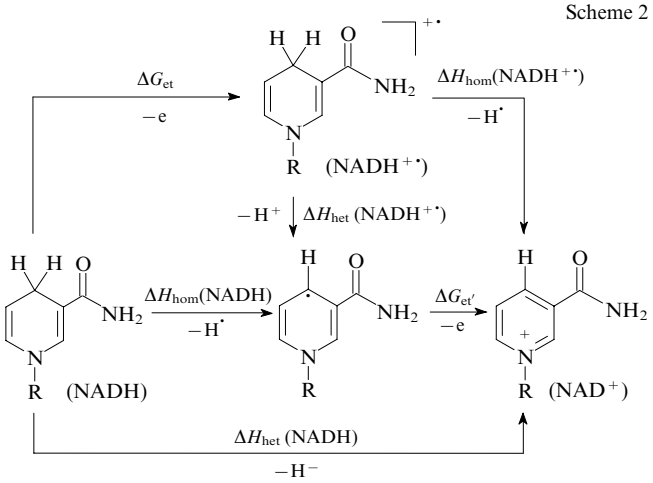
R = H (**a**), Me (**b**)

The heterolytic and homolytic C–H bond dissociation energies in an organic solvent (acetonitrile) are 64.2–81.1 and 67.9–73.7 kcal mol^{-1} (for neutral forms of NADH models) and 4.1–9.7 and 31.4–43.5 kcal mol^{-1} (for radical cations), respectively. The energy differences of the heterolytic C–H bond cleavage for BNAH and $AcrH_2$ are respectively smaller (by 3.62 kcal mol^{-1}) and larger (by 7.4 kcal mol^{-1}) than the corresponding energy of the homolytic process, whereas the analogous values for compound **2a** are similar (69.3 and 69.4 kcal mol^{-1}).

Consequently, the hydride transfer in dihydropyridines **1** should occur more readily than the hydrogen abstraction. An opposite situation is observed for dihydroacridine **3**, whereas both situations are equally probable for Hantzsch esters **2**. The data for the radical cations (for all 10 models, the homolytic C–H bond dissociation energies are 23.3–34.4 kcal mol^{-1} higher than the corresponding energies of heterolytic dissociation) are indicative of the single-electron transfer mechanism and provide evidence that the proton and electron transfer in the final oxidation step is more probable than the hydrogen abstraction.

Analogously, the probability of homolytic and heterolytic cleavage of the neutral and radical cationic forms of NADH in water (Scheme 2) was estimated for the first time:[56]

Scheme 2



R is adenosine diphosphoribosyl.

The following dissociation energies (kcal mol^{-1}) were obtained:

	$NADH^{+\bullet}$	NADH
ΔH_{het}	5.1	53.6
ΔH_{hom}	36.3	79.3

Therefore, the proton transfer from the $NADH^{+\bullet}$ radical cation in aqueous solutions should occur more readily than the hydrogen abstraction, *i.e.*, the EPE sequence is most probable of all possible mechanisms in living systems.

In a series of studies concerned with the hydride transfer mechanism, the possibility of the formation of a charge transfer complex and its position in the reaction coordinate were examined.[57,58] The existence of charge transfer complexes was proved by calculations of changes in the activation enthalpy for the reactions of substituted dihydroacridines with *p*-benzoquinone derivatives and tetracyanoethylene.[26] The reaction rate was found to depend on the temperature. It was also demonstrated that the nature of the solvent influences the reaction enthalpy change. Calculations of the equilibrium constants of the electron and proton transfer steps demonstrated that deprotonation of radical cations is the rate-determining step.

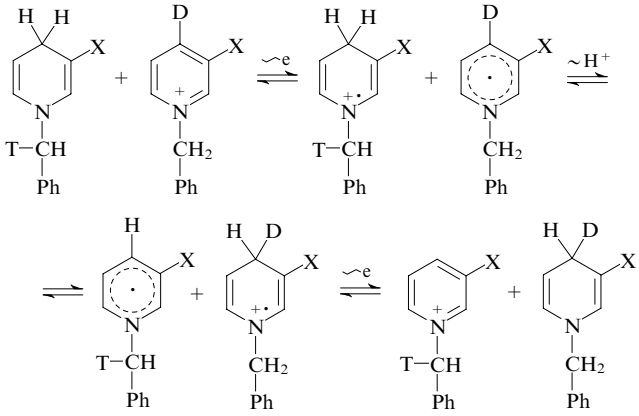
The stepwise hydride transfer mechanism was suggested based on the results of calculations of the free energy changes of elementary reactions involved in the one-step and multistep mechanisms of reduction of metal cations and quinones by NADH models combined with measurements of the kinetic isotope effects.[59–61]

Based on the results of theoretical studies performed for various models of nicotinamide adenine dinucleotides, it is impossible to unambiguously decide whether the hydride-labile hydrogen transfer occurs by the one-step or stepwise mechanism. It should be taken into account that most of calculations were carried out for models in the gas phase without consideration of the solvent effect. However, these calculations can be used for comparing the reactivities of dihydropyridine derivatives.

The influence of such factors as the primary and secondary isotope effects, acid–base catalysis, the nature of the solvent, the steric and electronic effects of substituents in the substrate, the presence of metal complexes or ions and photoinitiation on the hydride transfer rate was examined.[24,62–66] The experimental data can be interpreted in favour of both the one-step hydride transfer and the multistep (single-electron transfer) mechanism.

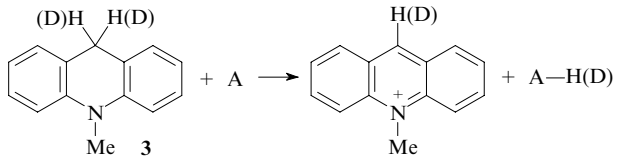
Measurements of the isotope effects, *viz.*, the kinetic effects (primary and secondary) and the label distribution in the reaction products, provide information on the rate-determining step of the C–H bond cleavage and give evidence for the existence of intermediates. The maximum primary kinetic isotope effect K_H/K_D, which is associated with the concerted hydride transfer and was calculated for the C–H bonds, is ~7. The usual secondary kinetic isotope effects characterising the change in hybridisation of the carbon atom ($sp^3 \rightarrow sp^2$) in the transition state are $K_H/K_D \sim 1$.[26,43,44,54]

A detailed study of the hydride transfer mechanism was carried out for deuterium- (D) and tritium- (T) labelled *N*-benzyldihydronicotinamides and their quaternary salts.[67] The course of the reactions was monitored based on the changes in radioactivity of the starting reactants and final reaction products. The secondary tritium isotope effects for the hydrogen transfer were anomalous, whereas the primary deuterium isotope effect was identical to the expected value. The typical secondary tritium isotope effects corresponding to the hydride transfer should be equal to ~1.2 and ~0.83 upon the change in hybridisation from sp^3 to sp^2 and from sp^2 to sp^3, respectively. Anomalies of the secondary effects of the isotope are attributed to the larger contribution of the inductive isotope effect to stability of the radical cation generated as a result of electron transfer. In this case, the equilibrium constant of the single-electron step increases, which is responsible for the appearance of an anomaly. Due to symmetry of the reactants and the reaction products, the free-energy profile should also be symmetrical. Hence, the only mechanism consistent with the symmetry of the reaction involves the successive electron–proton–electron transfer (EPE). For BNAH, this sequence can be represented as follows:



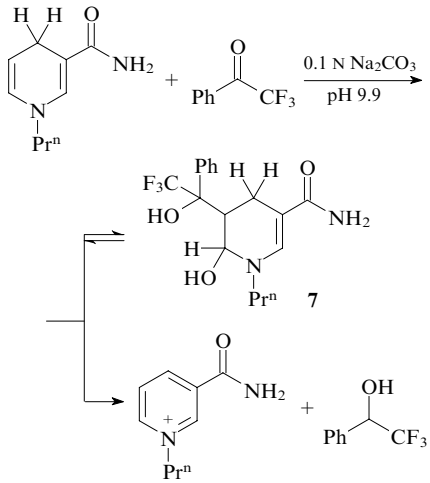
X = $C(O)NH_2$.

The presence of isotope effects in the hydride transfer does not provide an unambiguous answer to the question as to the form in which hydrogen is abstracted (proton, the hydrogen atom or the hydride ion) in the rate-determining step. Studies of the secondary isotope effects, in particular, the tritium isotope effects, can provide information on the changes in the transition state. However, Colter *et al.*[68] were doubtful about this expectation. The authors studied *N*-methylacridane (**3**), which gives rather stable radical species due to annulation of the pyridine ring to the benzene rings, as the NADH model. Oxidation of the latter affords the acridinium cation.



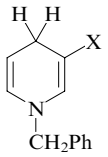
A is benzoquinone, tetracyanoquinodimethane, chloranil or tetracyanoethylene.

The authors [68] considered two reaction mechanisms: the one-step hydride transfer and the electron and hydrogen transfer. No explanation was provided for the anomalous isotope effects, and it was only hypothesised that tunnelling can occur. Large primary isotope effects and the fact that they are in agreement with the isotope label distribution in the products are most likely indicative of the stepwise rather than the concerted mechanism. It should be emphasised that the measured isotope effects should be interpreted with care considering the results of detailed investigation of the reaction mixtures, the possibility of side reactions and concerted and equilibrium processes. All these data can have a substantial effect on the conclusions. For example, in one of the most-cited studies, Steffens and Chipman [69] observed the abnormally high primary isotope effects in reactions of different dihydropyridines with trifluoroacetophenone. The label distribution in the products differs from that determined by the reaction kinetics. Based on this fact, the authors suggested the existence of radical ionic intermediates in the hydride transfer. However, more recently Chipman refuted the earlier conclusions by reporting [70] that the disagreement between the isotope effects is due to the reversible formation of covalent adduct **7**, which does not lie in the redox reaction coordinate.



Unusual condensation of the reaction products of *N*-(α,α-dichlorobenzyl)pyridinium chloride with the chloride ion or pyridines was documented.[71] Presumably, the proton in 4-substituted 1,4-dihydropyridines is transferred from the geminal unit of the dihydropyridine ring to the benzyl dichloromethylene group which is accompanied by the replacement of the chlorine atom to form the corresponding pyridinium cations. Experiments with the use of deuteropyridine confirmed the fact that the redox process involves the transfer of hydrogen (or deuterium) as the cation rather than as the hydride ion or the hydrogen atom.

In the study of oxidation of 3-substituted 1-benzyl-1,4-dihydropyridines **1f** and **8a**–**c** by copper ions, ferricyanide or *N*-methylacridinium iodide, the influence of substituents at position 3 of the heterocyclic moiety on the reaction rate was estimated.[72]



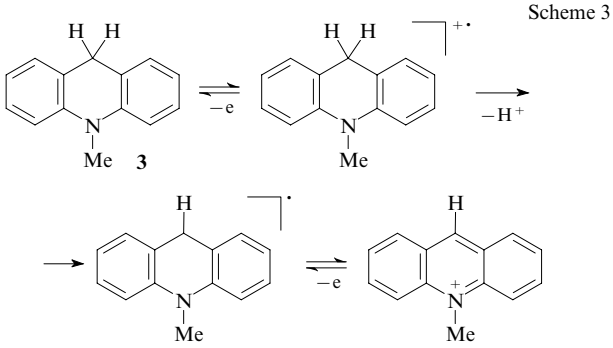
1f, **8a**–**c**

X = C(O)NH$_2$ (**1f**), C(S)NH$_2$ (**8a**), CO$_2$Me (**8b**), Ac (**8c**).

The authors have reached an unexpected (in our opinion) conclusion that oxidation by organic cations is accompanied by the one-step hydride transfer, whereas the reactions with inorganic cations occur by the stepwise single-electron transfer mechanism.

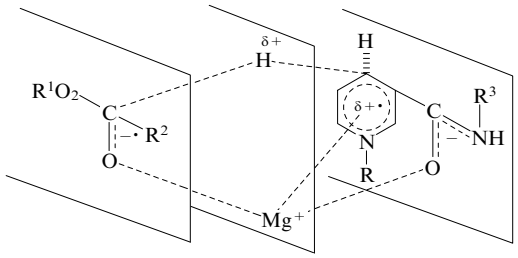
The study of the kinetics and mechanism of oxidation of 10-methyl-9,10-dihydroacridine (**3**) by chromium(VI, V or IV) compounds demonstrated [25] that oxidation of AcrH$_2$ to AcrH$^+$ by chromate ions in a water–acetonitrile mixture occurs by the single-electron transfer mechanism and is inhibited by oxygen. The first step involves the formation of the $AcrH_2^{+\bullet}$ radical cation followed by ionisation to the neutral radical and, finally, the electron transfer to form AcrH$^+$ (Scheme 3).

Scheme 3



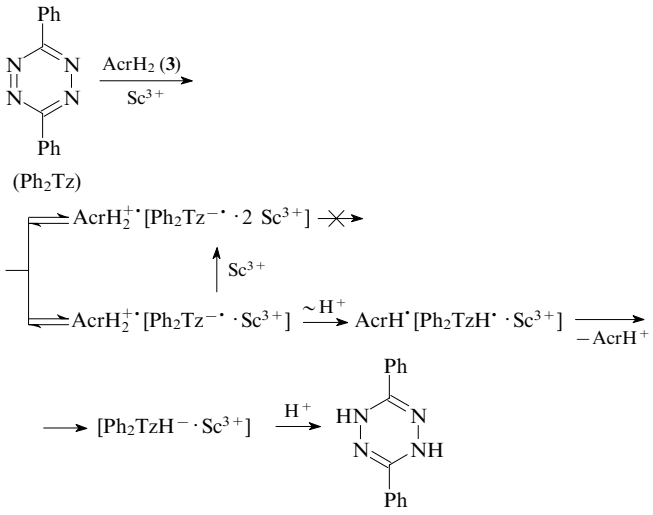
Dihydropyridine–electron acceptor systems, in which the H$^-$ transfer occurs in the presence of metal ions, were extensively studied. These systems are more complex but they are most similar to biochemical processes catalysed by pyridine-dependent dehydrogenases. It is known [66] that zinc ions accelerate the hydrogen transfer between the coenzyme and the substrate. Reduction of methyl benzoyl formate with an analogue of 1-benzyl-1,4-dihydronicotinamide in the presence of magnesium ions is accompanied by the anomalous kinetic and product isotope effects due to the ability of the metal ion to stabilise the transition state in which the electron is transferred from the dihydro compound to the acceptor.[73] The magnesium ion can either enhance the ability of dihydropyridines to donate an electron to α-keto esters, trifluoroacetophenone, diketones and other electron acceptors [74, 75] or decrease this ability, as was exemplified by the reaction of BNAH with thiopivalophenone.[73]

An attempt was made to explain the role of the metal ion in the electron transfer.[76] It was assumed that magnesium in the intermediate complex is coordinated by the dihydropyridine molecule and the acceptor (the parallel planes indicate the spatial orientations of the reagents).



As a result of this coordination, the positive charge is accumulated on the C(4) atom of the pyridine ring [the downfield shift of the signal for the H(4) proton in the ^{1}H NMR spectrum], which is favourable for the proton rather than hydride abstraction. This assumption was confirmed in the study,[54] where the authors observed that the single-electron oxidation potentials of dihydropyridines are changed in the presence of Mg^{2+} ions on the average by 0.2 V, whereas the oxidation potential of *N*-methylacridane in the presence of Mg^{2+} remains unchanged because acridane does not form complexes with metal.

A number of studies were concerned with oxidation of dihydroacridines by metal ions or their complexes. High reactivity of phenoxide radical complexes of alkali metals (Na and K) was documented.[77] The primary kinetic isotope effects provide evidence for the electron and proton transfer mechanism. The cobalt complex of tetraphenylporphyrin and decamethylferrocene catalyse the electron transfer from acridane to *p*-benzoquinones.[78] It was demonstrated[79] that the hydride transfer from 10-methyl-9,10-dihydroacridine (**3**) to 3,6-diphenyl-1,2,4,5-tetrazine (Ph_2Tz) occurs only in the presence of scandium(III) ions, which promote the electron transfer due to the formation of the Ph_2Tz–metal complex.



The mechanism of stepwise oxidation accompanied by the hydrogen abstraction or elimination of the substituent in 9-alkyl-10-methyl-9,10-dihydroacridines catalysed by monomeric or dimeric cobalt complexes in the presence of perchloric acid was suggested in the publication.[80] Acceleration of single-electron oxidation of acridane and 1-benzyl-1,4-dihydronicotinamide (**1f**) in the presence of ruthenium(IV) complexes was documented.[61]

Due to the observed differences in the influence of metal ions on the rate of the hydrogen or hydride transfer and the uncertainty of the nature of the bond between the metal and the hydride donor (with both the starting compound and the transition state), no reliable conclusions can be drawn regarding the mechanism of these complex reactions. Apparently, the systems under study should be simplified by separately elucidating the nature of interactions of the metal cation with dihydro compounds, hydride acceptors and radical ionic intermediates and estimating the possibilities of stabilisation of these species, removal from the solvation cage, *etc*.

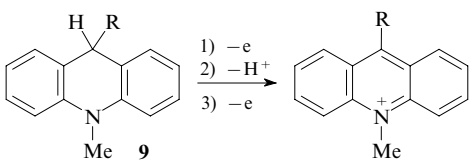
2. Electrochemical simulation

Nicotinamide cofactors are involved in the electron and proton transport, due to which studies of the redox properties of these compounds with the use various model compounds have attracted attention of chemists and biologists.[21,22,24,27] Measurements of the oxidation potentials of NADH at different electrodes, the determination of the conditions of its electrochemical regeneration, biocatalysis and electrocatalytic oxidation of NADH were described in the studies.[81–86] It is commonly accepted[23] that due to the specific features of electrode reactions in solution and the specificity of the electric layer at the electrode–solution interface, the hydride transfer involving dihydropyridines under electrochemical conditions is a very approximate model of real electrochemical reactions in organisms. However, the electrochemical method enables not only the measurements of individual electrochemical characteristics of substances but also the detection of short-lived particles, the electroorganic synthesis, mediated catalysis and transformations of NADH, NAD and their models. In the last decade, the number of publications (see, for example, Refs 85–89) in the field of bioelectrochemistry concerned with regeneration of nicotinamide derivatives, the construction and immobilisation of new electrode systems and the design of electrochemical enzyme reactors has steadily increased, providing evidence that this direction of investigation holds promise.

The electrochemical behaviour of the oxidised and reduced forms of the nicotinamide cofactor was investigated.[84] Mediated electrocatalysis and electrode modifications were found[88,89] to substantially decrease the overvoltage, facilitate oxidation of NADH and enable an increase in the yield of NAD. Organic compounds, which are involved in redox two-electron transfer reactions and simultaneously act as proton donors/acceptors (for example, *ortho*- and *para*-substituted quinones, phenylenediamines, aminophenols), readily oxidise NADPH. NADH-Dependent enzymes existing in contact with an electrode provide high efficiency of bioelectrocatalytic oxidation of NADPH, which was observed, for example, in experiments with the use of diaphorase combined with various quinones, flavins or viologens. The structure–activity relationships of artificial analogues of $NADP^+$ and the possibility of their immobilisation were investigated.[90] The possibility of their use instead of natural $NADP^+$ was examined.[91]

The influence of the structure of dihydropyridines (Hantzsch esters) on their reactivity was studied.[92] The authors mentioned the drawbacks of electrochemical simulation of oxidation of dihydropyridines, which ignores the influence of the nature and structure of the oxidant partner and of the solvent. Based on a comparison of the enzymatic and electrochemical oxidation of dihydropyridines, it is impossible to make an unambiguous choice between the fundamentally different mechanisms of this process involving the hydride and hydrogen transfer.[93] It appeared that 3,5-bifunctional 1,4-dihydropyridine derivatives are irreversibly oxidised at a rotating platinum electrode to the corresponding pyridines with consumption of two electrons and two protons, where the proton abstraction is not the rate-determining step.[94] However, the authors of the publication[95] observed the potential-determining influence of the deprotonation step of the radical cation generated after the electron transfer from the dihydropyridine molecule.

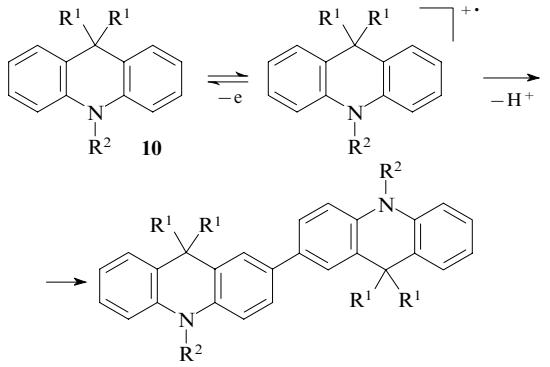
Many studies were concerned with electrochemical oxidation of 9-substituted 9,10-dihydroacridines **9** combined with chemical and spectroscopic methods. Oxidation of these compounds by a divalent copper salt revealed[96] that 2 mol of Cu^{2+} are consumed per mole of acridane. It was also found that electrochemical oxidation of acridanes, like other dihydroazines,[97,98] occurs by the EPE mechanism analogous to that presented in Scheme 3.



R = Me, Ph, NPhMe.

The results of the study[96] were confirmed by more recent investigations[99–101] of oxidation of various 9,10-dihydroacridines. The data from cyclic voltammetry, controlled potential electrolysis and chemical syntheses demonstrated that 9,9-disubstituted 9,10-dihydroacridines **10** are oxidised to radical mono-

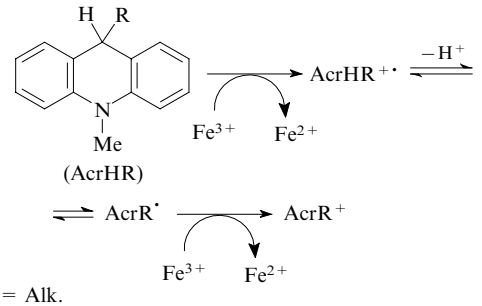
cations (reversible single-electron transfer), and, after the proton abstraction, the resulting radicals undergo dimerisation to readily oxidisable 2,2′-bi(acridane) systems.[100]



R^1 = Me: R^2 = H, Me; R^1 = H, R^2 = Ph.

By contrast, oxidation of 9*H*-acridanes **9** occurs by the EPE mechanism to give the acridinium cation, a peak assigned to reduction of protons being observed in the cyclic voltammogram, which is an additional argument for the proposed oxidation scheme.

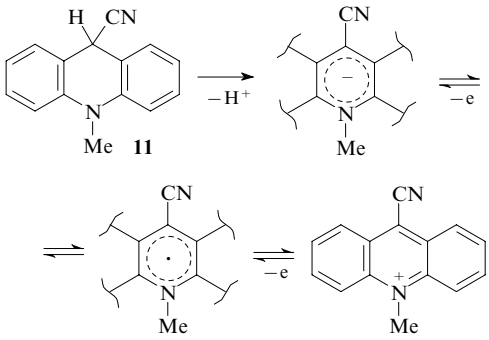
A series of 9-alkylacridanes **9** (AcrHR) were studied by cyclic voltammetry.[102] The reversible formation of radical cations and radicals in the case of oxidation of acridanes and reduction of conjugated cations, respectively, was observed by varying the potential scan rate. The EPE mechanism was confirmed for electrochemical and chemical oxidation (by a trivalent iron salt).



R = Alk.

This example demonstrates that deprotonation of the radical cation is the rate-determining step. A substituent in the geminal unit of acridane favours an increase in the oxidation potential compared to the unsubstituted compound ($AcrH_2$). This increase is insignificant in the case of alkyl electron-donating substituents and is more substantial in the case of electron-withdrawing substituents.

Earlier, the EPE oxidation mechanism has been observed for 1-benzyl-1,4-dihydronicotinamide derivatives containing different substituents in the benzene ring.[54] Electron-donating substituents at position 9 of the acridinium cation favour an increase in the negative potentials of single-electron reduction and the formation of neutral radicals in the reaction pathway of electrochemical oxidation of the corresponding acridane.[26] Electron-withdrawing substituents in the $C(sp^3)-H$ fragment of dihydro compounds substantially decrease their tendency to undergo hydride abstraction and increase the electron affinity of the conjugated azinium cations.[103] For example, the introduction of the cyano group at position 9 of acridane leads to oxidation of the dihydro compound not only by the EPE mechanism but also by the EEP mechanism. Moreover, under certain conditions, hydrogen can be abstracted from dihydro derivatives as a proton.[104, 105] For example, oxidation of 9-cyanoacridane **11** in the presence of sodium nitrite used as a base is accompanied by the proton abstraction followed by the two-electron transfer (the PEE mechanism).[106]



Electrochemical oxidation of unsubstituted *N*-methylacridane (**3**) to the *N*-methylacridinium cation in the presence of pyridinium bases also occurs by the single-electron transfer mechanism (EPE).[101] The deprotonation rate constants of the $AcrH_2^{+\bullet}$ radical cation were determined depending on the strength of the base with the use of spectorphotometric and electrochemical methods, and the constants pK_a were calculated.

Therefore, electrochemical simulation of oxidation of dihydroazines enables the detection of short-lived intermediates in the hydride transfer, *viz*., radical ions and radicals. The existence of these types of intermediates was confirmed by different physicochemical methods.

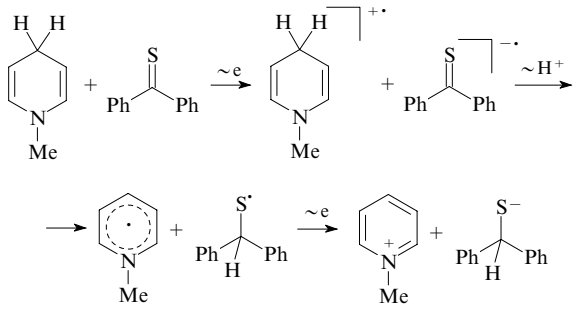
3. Detection of radical products

The radical forms of nicotinamide cofactors ($NAD^{\bullet}$) can be involved in enzyme-catalysed oxidation and reduction reactions. The pyridyl radicals are generated by the addition of one electron to the pyridinium ion or the hydrogen abstraction from dihydropyridine, for example, under irradiation. These radicals are generated also from pyridinium charge-transfer complexes in photochemical reactions, dihydropyridines being able to act as electron donors in charge-transfer complexes. The pyridyl radicals can undergo dimerisation to form unusual π complexes (π-mers).

Single-electron processes in hydride transfer reactions can be directly observed by ESR spectroscopy, which, like electrochemical methods, enables the detection of intermediate radical and radical ionic species.

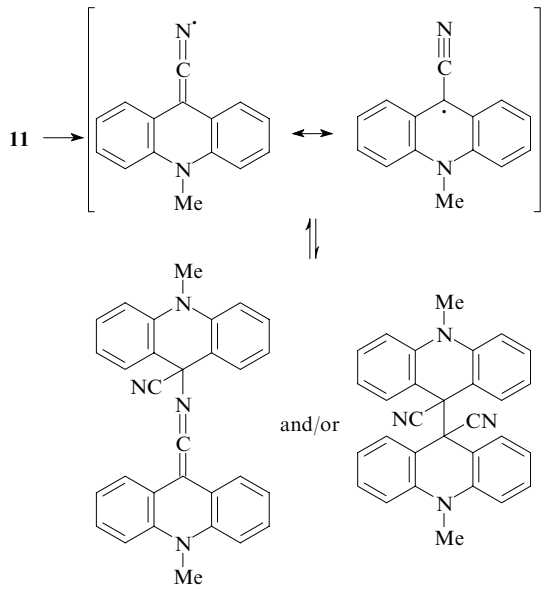
The generation of radicals in chemical oxidation of different dihydro adducts of the pyridine series was confirmed by the formation of dimeric products [107–109] and with the use of radical traps [diphenylpicrylhydrazyl, 2,4,6-tri(*tert*-butyl)phenol, nitroxides, *etc*.].[21, 110] Direct reduction of stable radicals and radical cations by 1,4-dihydropyridines made it possible to observe radical derivatives of pyridines by ESR spectroscopy.[48] The free radical products were detected by UV irradiation of a ternary mixture consisting of bromobenzene, aromatic imine and 1-benzyl-1,4-dihydronicotinamide in acetonitrile.[111] Radicals and radical cations were found also in the study of photoinduced oxidation of 1,4- and 1,2-dihydropyrimidines with quinones.[112]

The direct detection of pyridyl radicals presents difficulties because of their high reactivity toward oxidising agents. Nevertheless, it has been possible to detect radicals generated in oxidation of BNAH with quinones and acids with the use of the ESR method by varying the reaction conditions and the structures of dihydro adducts and using special techniques for observing fast processes.[113–116] The thiobenzophenone radical anion was detected by freezing a solution of dihydropyridine and thiobenzophenone in THF, the radical anion being then transformed into the free radical and anion, whereas dihydropyridine is oxidised to the pyridinium cation through the successive electron–proton–electron transfer.[117]



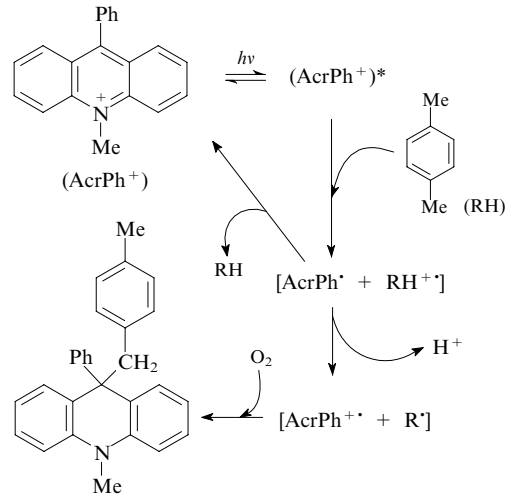
Radicals generated in reduction of the 4-acetyl-1-benzyl-*N*,*N*-diisopropylnicotinamide (ABNA) and 1-benzyl-4-phenylnicotinamide (PhBNA) cations in the presence of trivalent scandium cations, which form complexes with the corresponding pyridines, were detected by ESR spectroscopy.[118]

Benzannulation of the pyridine ring and the introduction of an electron-withdrawing substituent into the geminal unit stabilise the radical intermediates generated in oxidation of dihydro compounds. The generation of the stable 9-cyanoacridinyl radical in oxidation of acridane **11** by atmospheric oxygen in the presence of cyanide ions and potassium *tert*-butoxide used as bases was documented.[104] The acridine radical stable for several hours was prepared by oxidation of 9-cyano-10-methyl-9,10-dihydroacridine (**11**) in the presence of nitrite ions under an inert atmosphere in an electrochemical cell, which was placed in a resonator of an ESR spectrometer.[106] This radical can undergo reversible dimerisation in the temperature range from −30 to 20 °C.[119]

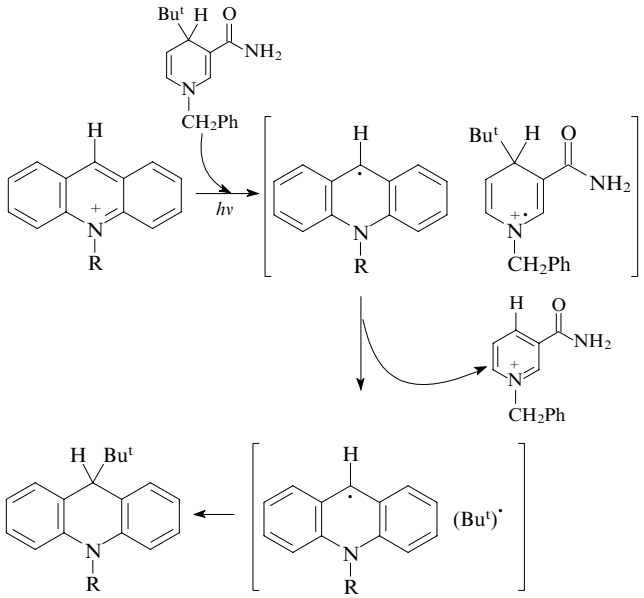


Chemical oxidation of acridane **11** in DMF by *p*-benzoquinone and atmospheric oxygen in the presence of lithium nitrite also enabled the detection of the cyanoacrydinyl radical by ESR. Such spectra were recorded in the case of reduction of the *N*-methylacridinium cation with the cyanide ion and of the 9-cyano-*N*-methylacridinium cation with sodium borohydride,[120] which confirms the possibility of the single-electron transfer from these compounds.[121, 122]

The radical ionic and radical products generated in the photoinitiated reaction of 10-methyl-9-phenyl-9,10-dihydroacridine with *p*-xylene were directly detected by Ohkubo and Fukuzumi.[123]



Photoinduced alkylation of the acridinium cation with 1-benzyl-4-*tert*-butyl-1,4-dihydronicotinamide was investigated.[124] Not only the detection of radical species, but also elimination of the *tert*-butyl radical from the radical cationic analogue of NADH due to the influence of the steric factors on the properties of dihydro compounds and intermediates of their oxidation are of interest.

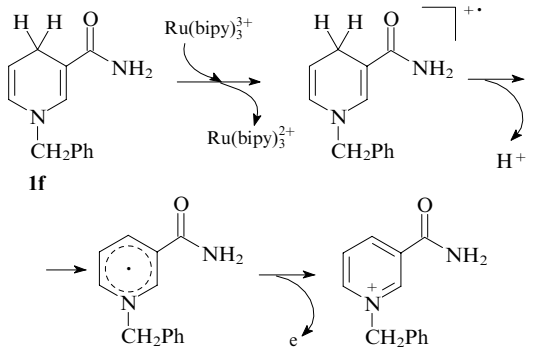


R = Me, n-$C_{10}H_{21}$.

In more recent studies (see, for example, Ref. 125), the acridinium cation was used as a catalyst for photoinduced selective oxidation of aromatic compounds, which occurs through the formation of radical products.

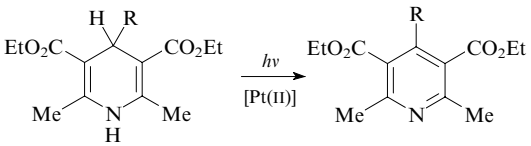
The radical cations of 9-substituted *N*-methylacridanes **9** were observed with the use of the stopped-flow rapid-mixing ESR technique.[102]

Direct evidence for the formation of the 1-benzyl-1,4-dihydronicotinamide radical cation in oxidation of this compound with the iron(III) and rubidium(III) bipyridyl complexes was obtained.[53, 126, 127]



The results of measurements of the deprotonation rate of the 1-benzyl-1,4-dihydronicotinamide radical cation and the observed kinetic isotope effect are indicative of the single-electron transfer mechanism.

The predominant reaction pathway through the formation of radical intermediates was described for photocatalytic oxidation of Hantzsch esters in the presence of the platinum terpyridyl complex.[128]



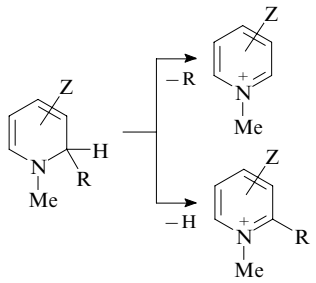
Useful information on the mechanism of processes involving radicals can be obtained by ESR spectroscopy combined with other instrumental methods for monitoring chemical reactions. However, in spite of numerous facts of the detection of radical ionic species in oxidation of dihydroazines and published results of investigation of the properties of pyridinyl radicals, it is still doubtful that ESR spectroscopy provides an unambiguous answer to the question whether the observed radical species lie on the reaction coordinate.

4. Mass spectrometric fragmentation

Ionisation of substrates can be studied by electron-impact mass spectrometry and correlated with the mechanisms of chemical reactions of various nature. In addition, mass spectrometry provides information on the relationship between the molecular structure and the reactivity.[129, 130]

Stability of tetrahydropyrazines with annulated five- and six-membered heterocycles was studied by mass spectrometry.[131] Criteria were proposed for the mass-spectrometric estimation of stability. The validity of estimates of stability of annulated tetrahydropyrazines based on the proposed mass-spectrometric criterion (the ratio of the peaks of the molecular ion or the radical cation and the 1,4-diazinium ion) was confirmed by chemical experiments. Stability of tetrahydropyrazines was demonstrated to depend on the nature and orientation of the heterocycle as well as on the nature and size of the substituent.

In the study,[132] the results of measurements of stability to electron impact and the tendency of dihydroazines to undergo aromatisation were correlated for the first time with the experimental data on chemical oxidation of these compounds. Aromatisation of these compounds is characterised by the formation of conjugated cations from dihydroazines due to elimination of both the substituent and hydride-labile hydrogen.

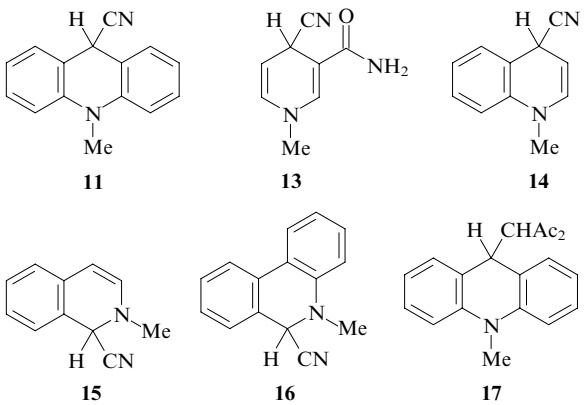


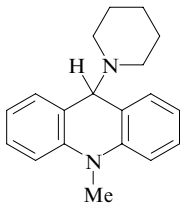
The intensity ratio of the peaks of radical cations generated upon electron impact to the peaks corresponding to the hydrogen abstraction or elimination of a substituent from molecular ions was used as the mass-spectrometric criterion for the pathways of aromatisation of dihydroazines. It should be noted that the single-electron redox mechanism implies the formation of a radical cation identical to the molecular ion (M^+) generated upon electron impact. This indicates that aromatisation of dihydro compounds under electron impact correspond to chemical transformations under the action of dehydrogenating agents. However, it should be remembered that chemical oxidation in solution can differ substantially from the process in the gas phase.

In studies of aromatisation of dihydropyridine derivatives containing electron-donating or electron-withdrawing substituents in the geminal unit (Table 1), a rather good correlation between the products of chemical oxidation and the results of mass-spectrometric experiments was obtained. This can be attributed (with a certain degree of approximation) to the formation of a radical cation as the primary intermediate of the chemical oxidation reaction.[24–27, 102–104]

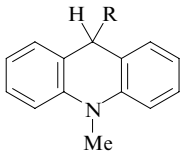
Table 1. Data from mass-spectrometric fragmentation of dihydroazines.[132]

Compound	Characteristic peaks, m/z (intensity, %)			Fragment elimination of which is the most probable in aromatisation
	M^+	$[M-H]^+$	$[M-R]^+$	
11	220 (49)	219 (77)	194 (31)	$-H^{\bullet}$
13	163 (39)	162 (26)	137 (100)	$-CN^{\bullet}$
14	170 (41)	169 (69)	144 (36)	$-H^{\bullet}$
15	170 (99)	169 (99)	144 (100)	$-H^{\bullet}$, $-CN^{\bullet}$
16	220 (36)	219 (34)	194 (100)	$-CN^{\bullet}$
17	293 (39)	292 (4)	194 (100)	$CH(COMe)_2^{\bullet}$
18	278 (12)	–	194 (100)	$-C_5H_8N^{\bullet}$
19a	209 (43)	208 (6)	194 (100)	$-CH_3^{\bullet}$
19b	223 (7)	–	194 (100)	$-C_2H_5^{\bullet}$
19c	271 (100)	270 (39)	194 (14)	$-H^{\bullet}$





18



19a–c

R = Me (**a**), Et (**b**), Ph (**c**)

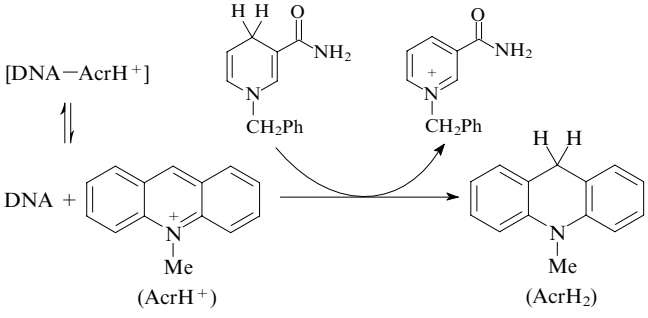
Since the reactions occur in the gas phase at high temperature and radical cations are generated under drastic conditions, the mass spectra give only an approximate model of chemical experiments. Nevertheless, the results of studies demonstrated that mass spectrometry can provide useful information for estimating the influence of the electronic effects of substituents, the steric factors and hetero- and benzannulation on stability of NADH models and the possible pathways of aromatisation.

5. Modelling of biochemical reactions

In recent years, investigations of the hydride transfer mechanism with the use of various models approximating chemical systems to biochemical systems have increased in number. These studies were concerned primarily with catalysis of redox reactions by metal ions and complexes, photoinitiation of processes and the use of mediators and intermediates.[30–32, 133, 134] Quantum-chemical methods are widely used for calculations of the energies of the hydride transfer processes involving enzymes.[40, 135–137]

Japanese chemists [138] studied oxidation of NADH by a system that models the respiratory chain and demonstrated that the ATP synthesis is accompanied by electron transfer. The fact of electron transfer from NADH to the flavin analogue and then to a hemin complex and oxygen was established by spectroscopic studies. Analogous model reactions were performed.[84, 139, 140]

A study of the structure–activity relationships for artificial analogues of $NADP^+$ and examination of the possibility of immobilising these derivatives [90] revealed the conditions for the use of these compounds instead of natural compounds.[91] The influence of DNA on oxidation of BNAH by photoinduced oxygen [141] and acridinium cations and on reduction of the quinolinium cation by a ruthenium bipyridyl complex was investigated.[142] The photoinduced electron transfer from the donor $[Ru(bipy)_3^{2+}]$ to the quinolinium cation (QuH^+) is efficiently accelerated by DNA, as is evidenced by the shift of the single-electron reduction potential of the QuH^+ cation to positive values due to intercalation of QuH^+ with DNA molecules. The $QuH^{\bullet}$ radical generated upon the electron transfer can be stabilised through $\pi-\pi$ intercalation with two bases of the DNA chain. The electronic spectrum of this system was recorded by laser flash photolysis (in the absence of DNA, absorption was not observed). The opposite situation is observed when DNA is involved in the hydride transfer from BNAH to the $AcrH^+$ cation. In the presence of DNA, oxidation of dihydro compounds is inhibited, which is attributed to the intercalation of the bulky $AcrH^+$ ion with bases from the DNA chain.[143]



The isotope effects and their dependence on the temperature for proton transfer reactions involving transhydrogenases were described.[144] Various compact chemical coenzyme reactors were designed based on nicotinamide compounds.[145, 146] An enzyme reactor for enantioselective reduction of pyruvate to L-lactate in high yield can be mentioned as an example.[147]

Arguments in favour of the EPE mechanism of reduction of lipophilic quinones with NADH models were presented by Zlatovic *et al.*[148] The dynamics of the photoinduced electron transfer during oxidation of 1-benzyl-1,4-dihydropyridine by the DNA-intercalated acridinium, quinolinium and phenanthridinium cations in the presence of a ruthenium bipyridyl complex was investigated.[149] The shift of the reduction potentials of cations intercalated into DNA to more positive values and acceleration of the reaction in the presence of metal complexes additionally support the stepwise hydride transfer mechanism. However, the possibility of the single-electron mechanism of reduction of flavins by NADH was not denied.[150] In the study cited, the formation of a charge-transfer complex was detected by stopped-flow electron spectroscopy.

Presumably,[151] insignificant kinetic isotope effects observed in the case of reduction of D-xylose by dihydronicotinamide attest to the one-step hydride transfer mechanism. However, thermodynamic analysis of reduction of quinones by NADPH [152] provided evidence for the stepwise EPE mechanism of hydride-labile hydrogen abstraction.

Photobacterial catalysis of the single-electron transfer from NADPH to ferredoxin or flavodoxin was examined.[153] Kinetic studies by the stopped-flow technique confirmed the stepwise mechanism of reduction of flavodoxin by enzymes. The equilibrium in the NADPH–flavin system was described in the study,[154] where intermediates of the hydride transfer were observed by spectroscopic and electrochemical methods.

The stereoselectivity of reduction of NO-containing cytochromes by dihydropyridines can be considered as evidence for the direct hydride transfer.[155] However, intermediates of hydride transfer were detected in the analogous NADH–cytochrome system,[156] and the oxidation rate was demonstrated to depend on the substituents.

Based on the characteristic features of the reactions involving dihydropyridines in model or real biological systems and understanding of the mechanism of hydride transfer reactions and ways of controlling these reactions, many of the known compounds were recommended as biomimetics and bioprotectors, inhibitors of bacterial processes, neuroprotectors and neuromodulators, radioprotectors, antidiabetic and anti-dermatitis drugs, *etc.* (Refs 157–163).

Therefore, a combination of chemical, electrochemical and enzyme models holds promise for investigation of the hydride transfer reactions.

III. Three-dimensional structures of dihydropyridines and stereospecificity of hydride transfer

In studies of processes that model NADH–NAD transformations, it is necessary to take into account that the dihydropyridine–pyridinium cation system undergoes a substantial rearrangement because hybridisation of the geminal carbon atom changes from sp^3 to sp^2. In this case, not only the aromaticity, chemical, magnetic, electrochemical, physical and energy characteristics of the molecule but also its spatial structure are changed. It is known that biological activity of compounds is related to their structures. Enzymes, for which a dihydronicotinamide derivative is a cofactor, are sensitive to the stereoconfiguration of the substrates involved in the interaction, *i.e.*, the spatial structure of the latter is responsible for stereospecificity of biochemical processes.[29–31]

The development of X-ray spectroscopy enabled the direct examination of the structures of dihydropyridines and estimation of the influence of various substituents on the conformation of NADH analogues.

The presence of sp^3-hybridised carbon atoms in dihydropyridines leads to a distortion of the planarity characteristic of aromatic pyridinium salts. X-Ray diffraction data for 3,5-di-(methoxycarbonyl)-1-methyl-4-phenyl-1,4-dihydropyridine demonstrated that the strain causes bending of the plane of the pyridine ring along the N–C(4) axis (Fig. 1)[164] and a certain degree of shielding of hydride-labile hydrogen in the geminal unit.[165, 166]

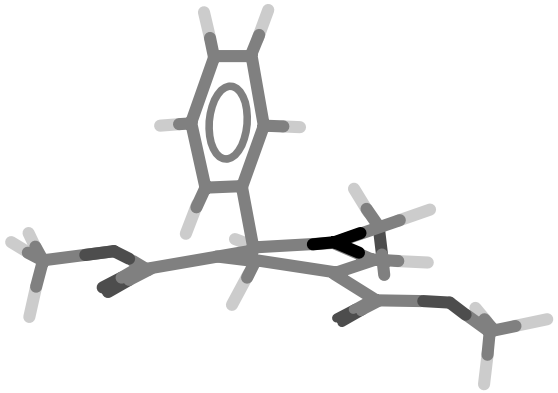
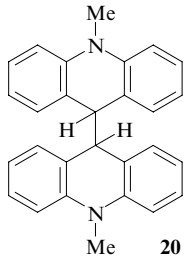


Figure 1. Three-dimensional structure of 3,5-di(methoxycarbonyl)-1-methyl-4-phenyl-1,4-dihydropyridine.[164]

Shielding of the geminal hydrogen atom by bulky substituents decreases the 'hydride activity' of dihydro derivatives, with the result that steric hindrances prevail over the electronic effects.[167] It would be interesting to estimate the $C(sp^3)-H$ bond length and energy in the geminal unit in a series of related compounds. It is the steric factors that are apparently responsible for elimination of substituents, which is sometimes observed in the case of oxidation of dihydropyridines.[54, 102, 132]

For 9-substituted 10-methyl-9,10-dihydroacridines, the pyridine ring is also strongly puckered along the N–C(9) axis, which is characterised by the average dihedral angle of 150°.[168–171] The ease of dissociation of recombination products of acridinyl radicals is attributed to the strained structures of heterocyclic systems,[172] which was exemplified by acridine dimer **20** (Fig. 2).[119, 169]



20

The spatial structures of dihydroacridine radical cations generated in oxidation of 9,10-dihydroacridines by an iron(III) salt were discussed.[102] Radical cations of 9-substituted *N*-methylacridanes **9** were detected with the use of the stopped-flow rapid-mixing ESR technique. The hyperfine splitting constants were calculated by comparing the observed ESR spectra with the results of computer simulation using molecular orbital calculations. The calculations demonstrated that the acridane system adopts a boat conformation with the substituent R in an axial position and the hydrogen atom at C(9) in an equatorial position. It was hypothesised that the steric demands are responsible for the reactivity of the radical cations.

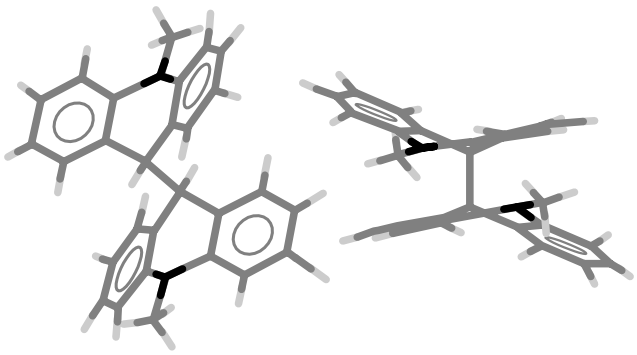
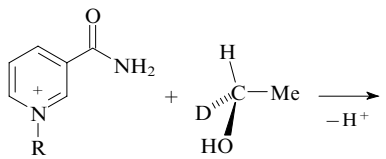


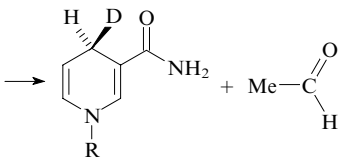
Figure 2. Three-dimensional structure of *N*-methylacridine dimer **20**.

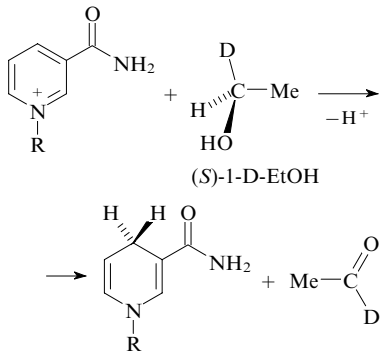
In our opinion, the calculations demonstrating the nonequivalence of the axial and equatorial hydrogen atoms in unsubstituted dihydroacridine are of considerable interest. It is quite probable that the steric effects are not the only factors responsible for differentiation of the geminal hydrogen atoms. Thermodynamic instability of systems that lost aromaticity is also increased by the charge effects, which act together with the structural factors. Presumably, this facilitates stereospecificity of reduction of various substrates by unsubstituted dihydropyridines, which exist in the activated transition state initiated by the single-electron transfer. After the proton abstraction, the sterically hindered active pyridinium radical cation is transformed into the neutral radical structurally similar to the cation, and the secondary electron transfer gives rise to the thermodynamically more favourable planar molecule of the aromatic pyridinium cation or its analogue.[173]

The characteristic feature of the processes in organisms is that only particular stereoisomers are involved in the reactions, resulting in the formation of stereochemically pure products.[30, 174] The stereospecificity is responsible for the fact that only one of enantiomers exhibits biological properties and this lies at the basis of the active principle of many pharmaceuticals. In enzymatic processes in living organisms, the protein chain acts as the chiral recognising fragment. Reduction processes involving NADH are stereoselective. The formation of one of stereoisomers is associated with the fact that enzymes (dehydrogenases) distinguish the enantiotopic hydrogen atoms at the C(4) atom in the 1,4-dihydropyridine ring. The stereospecificity of the transfer of hydride-labile hydrogen was experimentally proved by studying oxidation of deuterium-labelled ethanol. Actually, after oxidation of (*R*)-1-D-ethanol, deuterium was found in the reduced form of NADD at the C(4) atom having the *R* configuration, whereas deuterium completely goes to acetaldehyde in the case of oxidation of (*S*)-1-D-ethanol.[30]



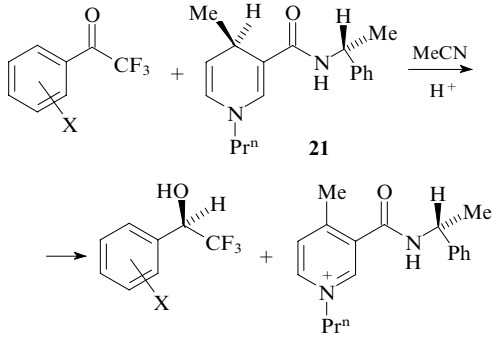
(*R*)-1-D-EtOH





To model natural processes, chiral substituents are deliberately introduced into synthetic dihydropyridines. In the case of formation of reactive chiral complexes, the mutual arrangement of the reactants is determined only by the structural factors. The resulting energy difference of diastereomeric transition states provides an enantiomeric excess of one of the adducts. In recent years, the regiospecific NAD – NADH conversion has been extensively studied because NADH is a necessary component of various bioorganic processes accompanied by the formation of chiral organic compounds.

As an example, let us mention stereoselective reduction of ketones, which was performed by Ohno and co-workers [175] with the use of specially prepared model compounds **21**. The process is characterised by high enantioselectivity.



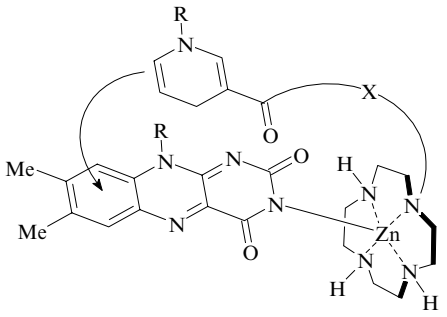
X = H, Me, OMe, Cl, Br.

The chiral recognition is provided by steric interactions along with the electronic effects of the substituents. The stereoselectivity of oxidation of NADH by *p*-quinone derivatives controlled by the electronic effect of the carbonyl group was documented.[63] The structural effects of the substituents at position 4 are responsible also for the reactivity of 1,4-dihydropyridines in reactions with stable radicals.[50]

Quantum-chemical calculations of the potential energy surface for isomers of 2-methyl-4(*R* or *S*)-methyl-1,4-dihydropyridines in the gas phase and in solution were performed by the extended Hartree – Fock method with the 6-311 basis set.[176] The stereoselectivity of reduction with NADH analogues was demonstrated to be controlled by the steric and electronic properties of substituents at position 4 as well as by the solvent polarity.

Enantioselective reactions often proceed through the formation of active prochiral radical species. Numerous examples of such reactions were cited in the review.[177] This is indicative of the single-electron nature of reduction processes based on dihydropyridine derivatives.

Chiral NADH models providing stereoselectivity of the hydride transfer were designed based on benzo[*b*]-1,6-naphthyridines.[178] A system consisting of dihydronicotinamide and a zinc complex was used for reduction of flavin.[179]

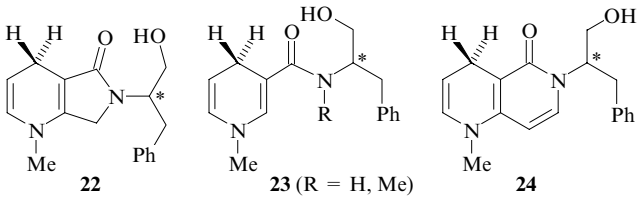


X is a chiral linking group.

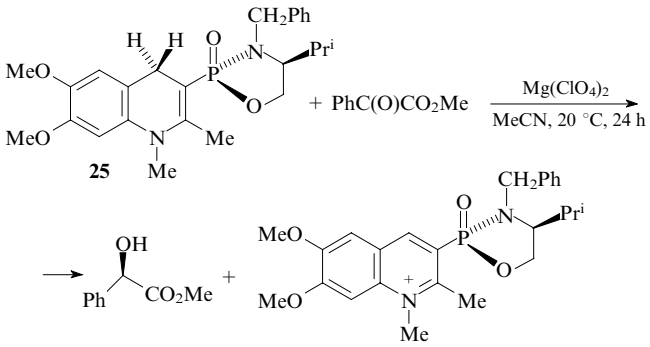
The involvement of bipyridyl complexes of ruthenium and other metals in regioselective reduction of substrates by NADH models was documented.[180, 181]

Data on stereospecificity of the hydride transfer in NAD-dependent synthases in the antibiotic synthesis were published in the literature.[182] The conformational exchange of the carbothioamide group in the hydride transfer between transhydrogenase and the thionicotinamide analogue of NADH was documented.[183] The factors influencing the stereoselectivity of the hydride transfer between the NADH model and the NO-bound cytochrome P450,[155] keto esters [184] and dehydrogenases were reported.[185]

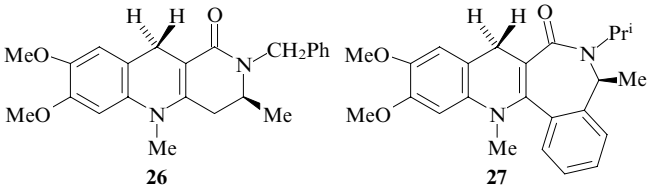
A series of studies on the synthesis and the use of chiral NADH models were performed by French researchers. Detailed NMR studies of asymmetric reduction of methyl benzoylformate by dihydropyridines **22** – **24** were carried out.[186]



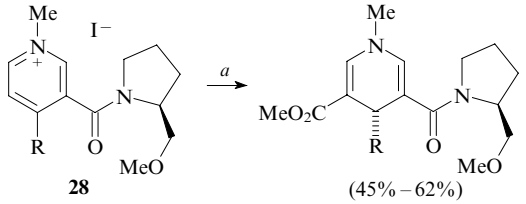
New chiral NADH models were designed based on hydrogenated quinoline.[187 – 189] It appeared that electron-donating groups in the benzene ring of quinoline enhance its ability to eliminate the hydride ion, thus providing a high degree of reduction of methyl benzoylformate with quinoline in the presence of magnesium ions. The enantioselectivity of reduction is determined by the concentration of metal ions. The best results (*ee* 45%) were obtained for dihydroquinoline **25**.[187]



Models favourable for an increase in the stereoselectivity of the hydride transfer were synthesised based on benzo[*b*]-1,6-naphthyridine **26**, its analogue **27** [178] and pyridinium salts **28**.[190]



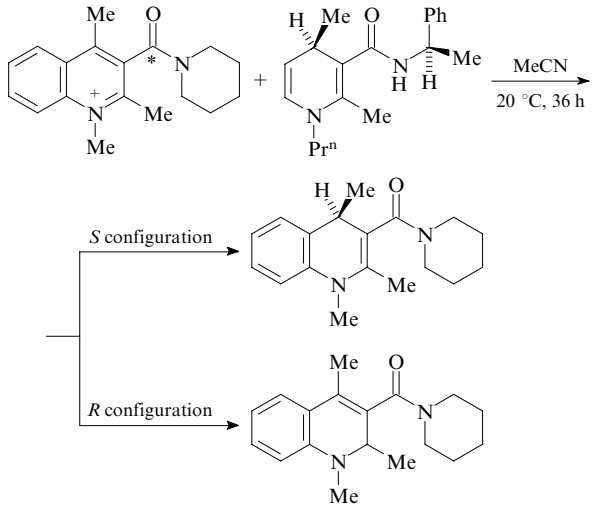
26 **27**



28 (45% – 62%)

R = Me, Bu^n, Ph; (*a*) (1) R_2CuLi, (2) $(Cl_3CCO)_2O$, (3) MeONa.

The optically active model NAD compound based on quinoline was reduced by chiral dihydropyridine [191] to form a mixture of the corresponding 1,2- and 1,4-dihydroquinolines. The orientation of the carbonyl group in quinoline is responsible for regio- and enantioselectivity of the reaction products. Thus, the *S* isomer forms predominantly the chiral 1,4-adduct with *ee* 96%.



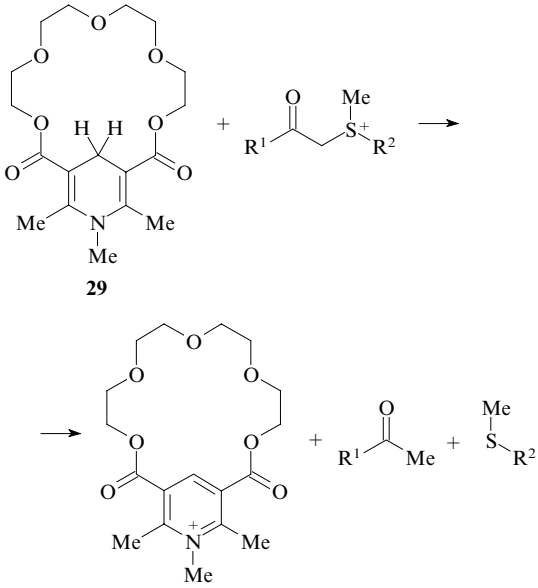
Regioselective reduction of 1-benzylnicotinamide triflate in the presence of a ruthenium bipyridyl complex was documented.[192] Many bridged NADH analogues [147] and 1-benzyl-3-(*p*-toluenesulfonyl)-1,4-dihydropyridine derivatives [193] have high enantioselective reducing ability.

Due to ability of NADH and their synthetic models to be involved in enantioselective reactions along with their tendency to perform the single-electron transfer, dihydropyridines and their analogues are unique compounds, because the optical activity is not generally retained upon the formation of radicals.

IV. Molecular devices based on dihydropyridines

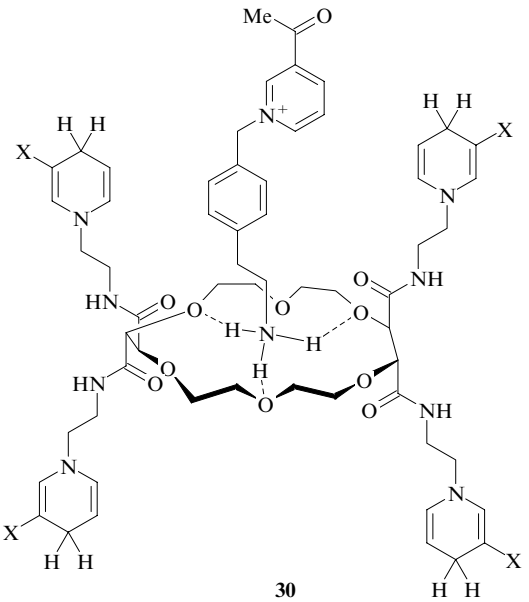
Supramolecular chemistry deals with structures containing non-bonded interactions, such as hydrogen bonds, electrostatic effects, hydrophobic forces, *etc*. These interactions are responsible for fast and reversible changes of biological molecular structures, such as nucleic acids, proteins and enzymes.[194] In the design of supramolecular devices, studies of hydride transfer processes in chemical models of NADH, investigation of the fine mechanism of these reactions and elucidation of the structure – property relationship are of considerable interest.

For example, it was found that macrocycles containing the 1,4-dihydropyridine fragments substantially accelerate the hydrogen transfer. In the studies,[195, 196] crown ether of dihydropyridine **29** was used as the hydride ion donor. The rate of the reaction of ether **29** with acceptors is 2700 times higher than that of the reactions of classical Hantzsch esters or 1-methyl-1,4-dihydropyridine.



29

Efficient reduction of the pyridinium fragments within supramolecular compounds of type **30** through the hydrogen transfer from dihydropyridines in the peripheral positions was documented.[197]

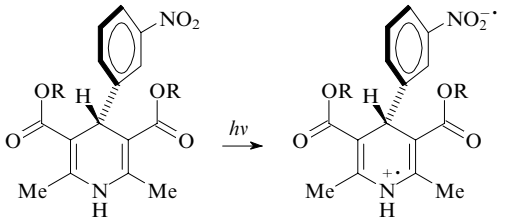


30

X = C(O)NHBu^n.

Such first-order intracomplex reactions are inhibited by cations capable of complex formation.[194] As mentioned above, the influence of metal ions or complexes on the hydrogen transfer is a characteristic feature of oxidation of dihydropyridines.

It was suggested to use 4-(*m*-nitrophenyl)dihydropyridine **31** for the design of new photoinduced intramolecular electron-transfer systems.[198]



31

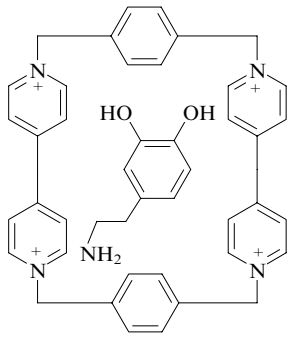
R = Alk.

Molecular magnetism is, in essence, a supramolecular phenomenon, because it is associated with the collective properties of the system components that contain unpaired electrons, and depends on the relative arrangement of these compounds in organised ensembles and crystal structures. A search for high-spin components of the organic (free radicals, carbenes or charge-transfer salts), organometallic (metal complexes) or inorganic (coordination metal centres) nature is presently an important problem.[199–202] This is why the radical ionic salts based on dihydropyridine derivatives have attracted interest. The synthesis and the mechanism of formation of radical anionic salts in the reactions of unsubstituted acridane, *N*-methylacridane or 1-propyl-1,4-dihydropyridine with π-electron acceptors (tetracyanoquinodimethane, dicyanodichloro-*p*-benzoquinone, tetracyanoethylene, *etc*.) were described.[203]

We synthesised analogous compounds by oxidation of 9-cyano-10-methyl-9,10-dihydroacridine (**11**) to the corresponding radical anionic and dianionic salts with the cyanoacridinium cation. These salts have a very narrow electrochemical gap, *i.e*., a small difference between the reversible oxidation and reduction potentials. These systems hold promise for the design of molecular switches, conductors, semiconductors, visible light converters into the electric energy (solar elements) and, on the contrary, nonlinear optical materials, *etc*.

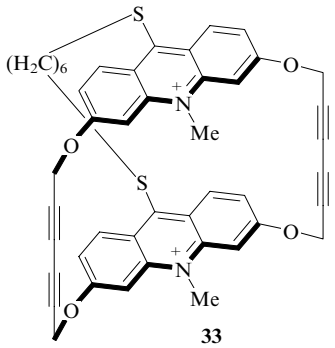
Hydrogen bonding, π–π-stacking interactions or Coulombic interactions can be employed for recognition of amino acids, nucleotides and heterocycles through complementary binding. It was mentioned [142] that such interactions have an effect on the electron and hydride transfer involving DNA in redox reactions of DNA intercalates with NAD and NADH models.

Coulombic interactions and structural factors can be efficiently used for the recognition of systems containing the charged pyridine rings. Supramolecular charge-transfer complexes formed by cyclobis(paraquat-*p*-phenylene) as a model of a molecular receptor and different neuromediators (for example, by dopamine in compound **32**) were studied.[204] Analogous structures were described in the publications.[205–207]



32

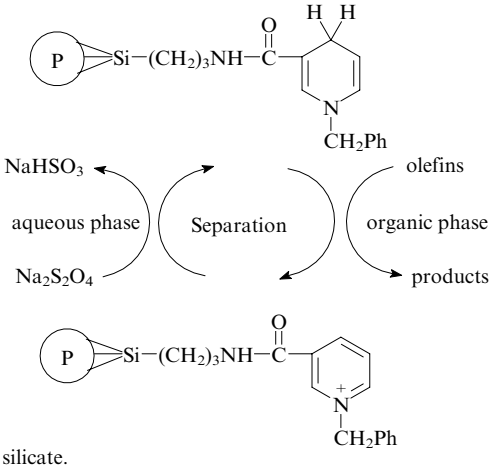
N-Methylacridinium derivatives, which are acceptors of anionic and neutral nucleophiles, can be involved in macrocyclic bis-intercalates (for example, compound **33**) capable of interacting with nucleosides, nucleotides and planar anionic substrates.[208, 209]



33

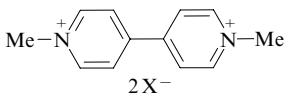
Along with homogeneous processes of molecular recognition in solution, heterogeneous recognition on the surface or in the bulk of organised ordered phases and solid materials is also known. Examples of these reactions are the formation of solid inclusion compounds, *viz*., clathrates, with the use of zeolites or other natural sorbents, as well as intercalation in the formation of hollow clays and the design of hybrid organic–inorganic structures by sol–gel methods.[194] A polysiloxane-immobilised NADH model compound was prepared.[210] This compound provides easy reduction of olefins as well as isolation of the reaction products and recycling of the reducing agent. This environmentally safe process for olefin reduction by immobilised dihydropyridine in a two-phase system is an example of green chemistry (Scheme 4). Catalytic transformations of natural compounds under mild conditions, which are accompanied by the conversion of the reagents, are among such processes.[211]

Scheme 4



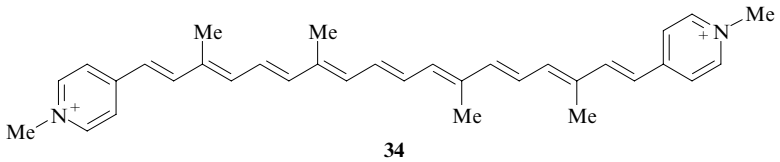
P is silicate.

Redox processes involved in NAD–NADH transformations can be performed in molecular devices which convert molecular recognition events into electronic signals. Quinones and the 1,1′-dimethyl-4,4′-bipyridinium dication were examined as such compounds.[207]

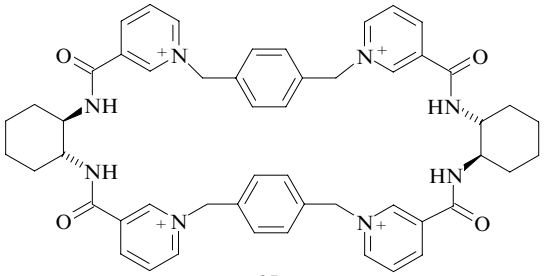


Pyridinium cations **34** linked by a long chain of conjugated C=C bonds are fragments of so-called molecular wires.[194] In such oligomers, pyridinium cations are used as electron acceptors capable of forming stable radicals.

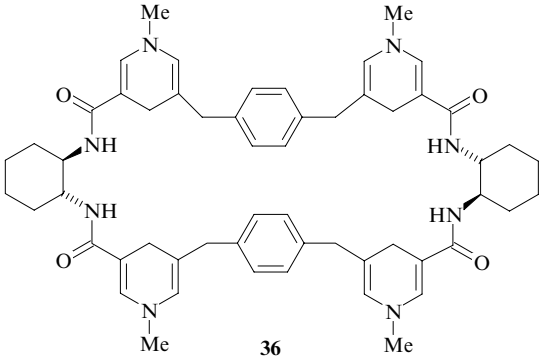
The design of supramolecular ensembles based on the 10-carboxymethyl-9-mesitylacridinium ion and the fullerene cluster with titanium(IV) oxide or tin(IV) oxide for light energy conversion was documented.[212, 213] Systems consisting of donor–acceptor metal complexes, dihydropyridine-based hydride donors and



34



35



36

acceptors and acridinium cations have been designed and found use as photocatalysts.[214]

Macrocyclic NADH models containing two or four nicotinamide fragments were prepared.[215] In the presence of magnesium ion as a catalyst, these macrocyclic dihydropyridines selectively reduce ethyl benzoylformate. Macrocyclic NAD (compound **35**) and NADH models (compound **36**), which can form host–guest complexes were synthesised based on the pyridinium cation and dihydropyridine.[216, 217]

The above data demonstrate that investigations of the hydrogen transfer mechanism NAD ⇄ NADH with the use of model compounds provide a deeper insight into processes in living nature and give possibilities for designing different-purpose devices, receptors and new materials.

* * *

A review of studies on oxidation of dihydropyridines and their analogues leads to the conclusion that, in spite of a continuing discussion regarding the one-step or stepwise mechanism of hydride transfer, evidence in favour of the latter mechanism prevails in the modern literature. It should be noted that the successive electron–proton–electron transfer (EPE mechanism) was accepted by chemists as the most probable pathway of hydride transfer involving coenzymes.

The Nobel laureate Albert Szent-Györgyi stated that electrons drive life. In living systems, electrons move to higher energy levels due to sunlight absorption by the substance and then electrons portionwise release an excess energy. It should be emphasised that electrons perform this cycle one-by-one by being excited and passing through cytochromes, because the central metal atom in cytochrome can undergo only single-electron transformations.[218]

In recent years, studies on the fine mechanism of the $C(sp^3)-H$ bond cleavage in dihydroazines have received new impetus due to the design of new pharmaceuticals and technical materials, enzyme reactors, bioelectrochemical systems and molecular devices (switches, antennas, sensors, *etc*.) based on these compounds and the use of partially hydrogenated heteroarenes as reagents for stereoselective reduction of various unsaturated systems.

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