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# Catalytic Electron Transfer

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The possibilities of obtaining catalysts and catalytic systems for redox hydrogen-transfer reactions are discussed. Use is made of the method of analogy with enzymatic catalysis and modern ideas on electron-transfer reactions. The general requirements to be satisfied by an "optimal" catalyst for hydrogen transfer, the conditions for rapid electron transfer, and some characteristic features of electron transfer in a biochemical oxidation chain are examined. The promising possibilities revealed by this approach for the selection of catalysts and catalytic systems for various reductions are demonstrated. The bibliography contains 206 references.

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## I. INTRODUCTION

One possible approach to the development of a scientific basis for the preparation of catalysts and catalytic systems is to use the method of analogy with enzymes. Results obtained in enzymology make it possible to explain many features of the structure and mechanism of action of coenzymes and enzymes on the basis of the ideas of organic and coordination chemistry. This makes it possible to reach definite conclusions regarding the chemical characteristics of the components of the active centres of enzymes, the principles of their activation and the activation of substrates, and the organisation of the individual components into more complex structures. On this basis it is possible, with a sufficient degree of reliability, to formulate some of the general principles determining the structure and catalytic properties of enzymes. It appears to us that it is now possible to realise these principles and to prepare corresponding analogues and analogue systems of various levels of organisation.

It may be assumed that the development of this approach will open up extensive possibilities for the preparation of new effective catalysts and catalytic systems for various reactions.

In the present review we have considered, for the example of redox reactions, some problems of the preparation of catalysts and catalytic systems using the method of analogy with enzymes.

We shall first analyse the general requirements to be satisfied by catalysts for redox reactions. The simplest catalytic hydrogen-transfer cycle consists of a reaction between a hydrogen donor ($AH_2$) and a catalyst (Q) (stage 1) and the reactions of the reduced forms of the catalyst with an acceptor (B) (stage 2):

$$AH_2 + Q \xrightarrow{k_1} QH_2 + A, \quad (1)$$

$$QH_2 + B \xrightarrow{k_2} Q + BH_2. \quad (2)$$

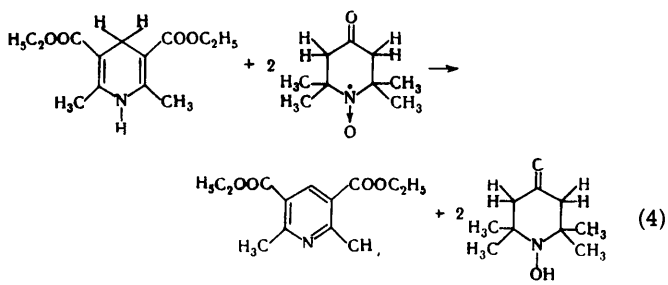
The best catalyst for the catalytic cycle corresponds to the maximal value of the rate of catalytic transfer ($w$).

The rate $w$ is related to the constants $k_1$ and $k_2$ by the equation

$$w = \frac{k_1 k_2 [AH_2][B][Q]_0}{k_1[AH_2] + k_2[B]} \quad . \qquad (3)$$

The value of $w$ is determined by the absolute values of the constants, and also by the ratio between them. It follows from an analysis of Eqn. (3) that if $k_1 \gg k_2$ (or $k_2 \gg k_1$), we have $w = k_2[B][Q]_0$ (or $w = k_1[AH_2][Q]_0$), that is the rate of the catalytic transfer of hydrogen in the limiting cases is proportional to one of the constants $k_1$ or $k_2$, and in the intermediate range of values of the constants, a maximum is observed in the range where $k_1$ and $k_2$ are approximately equal. For the same redox substrate pair, characterised by a definite decrease in free energy $\Delta F^0$, the constants $k_1$ and $k_2$ are not independent, but are related to one another by the expression $\Delta F^0 = \Delta F_1^0 + \Delta F_2^0$, where $\Delta F_1^0$ and $\Delta F_2^0$ are the free energy changes in reactions (1) and (2). Although in general there is no simple relationship between thermodynamic and kinetic constants, it follows from the last relationship that with improvement of the acceptor properties of the catalyst (in the thermodynamic sense) there is a simultaneous deterioration in its ability to act as a donor. Thus for the given catalytic cycle there exists an "optimum" catalyst, exhibiting strong donor and acceptor properties with respect to the substrates.

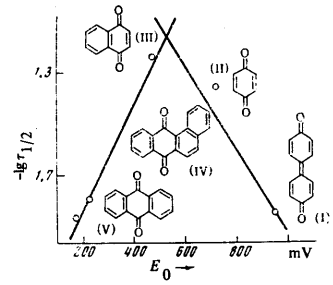
The literature contains examples illustrating the existence of an optimal dependence of the overall rate of catalytic reactions on the values of the individual constants for stages (1) and (2). Thus for the catalytic transfer of hydrogen in the reaction



(4)

the most effective catalysts correspond to a limited range of catalyst redox potentials 0.4–0.6 V.[1,2] The Figure demonstrates the dependence of the rate of the catalytic transfer of hydrogen in reaction (4) for a series of para-quinones on the redox potential of the quinone. When quinones are used as catalyst-transfer agents in hydrogenation, derivatives of 9,10-anthraquinone are more active than derivatives of 1,4-naphthaquinone and 1,4-benzoquinone[3]. A similar relationship with a catalytic efficiency maximum is also found for enzyme systems[4]. Moreover, the greater the redox potential of the quinone, the greater the rate at which it is reduced, and the lower the rate of oxidation of the corresponding hydroquinone. Analogous relationships were observed[5] in the catalytic decomposition of hydrogen peroxide by metal complexes.

It may be concluded that in general the realisation of a catalytic cycle involving two (or more) successive stages with comparable rates always leads to the existence of an optimal dependence of the overall rate of catalysis on the values of the rates of the separate stages, or, in the final analysis, on the thermodynamic characteristics of the catalysts. This principle of redox catalysis has an analogy in other types of catalysis, in particular heterogeneous catalysis[6]. For example, from the principle of energetic correspondence of Balandin's multiplet theory it follows that "if a process involving a catalyst is represented as taking place in a number of stages, the most favourable path will be that in which the energetic effects of the stages are equal".[7] Note that to obtain the "optimum" catalyst it is also necessary to satisfy the condition of a minimum value for the energetic effects of the stages.




Dependence of the rate of transfer of hydrogen in reaction (4) on the redox potential of the para-quinones used as catalysts for the reaction.

As a result, there are two requirements to be satisfied by catalysts for greatest activity in any specific reaction: firstly, it is necessary to select a catalyst which will satisfy the optimum condition for a given catalytic cycle, and secondly, the structure of the catalyst should be such that the rate constants $k_1$ and $k_2$ have the maximum possible values. For example, catalysts for reaction (4) include $o$-naphthaquinone (redox potential $E_0 = 0.58$ V) and Methylene Blue ($E_0 = 0.534$ V), which satisfy the optimum condition for the reaction. The constants $k_1$ and $k_2$ have the values 30 litre mole$^{-1}$ min$^{-1}$ and 30 litre mole$^{-1}$ min$^{-1}$ respectively for $o$-naphthaquinone and $2.6 \times 10^3$ litre mole$^{-1}$ min$^{-1}$ and $4.1 \times 10^3$ litre mole$^{-1}$ min$^{-1}$ respectively for Methylene Blue (at 30°).[8]

One possible way of predicting the values of the rates of reactions (1) and (2) is by using linear relationships between the thermodynamic and kinetic parameters of these reactions.

The large amount of data on the rate constants of redox reactions enables examples of a linear relationship between the free energy change in the redox act and the free energy of activation to be found[9-16].

Proportionality between the kinetic parameters is observed, for example, for electron-transfer reactions with similar mechanisms, when the transmission coefficient (of activated complex theory) is approximately constant in the series of reactions being compared and when the contribution of electrostatic interactions to the free energy of activation differs little on going from one reaction to another[12-17].

The reactions of a given reagent with a series of structurally similar compounds obviously satisfies these requirements. It is for such series of reactions that correlations have been observed between the free energy of activation and the change in free energy for the process.

Relationships of this kind have been found, for example, for reactions of electron transfer between $Fe^{2+}$ and various complexes of $Fe^{3+}$ (and other ions),[17] the reactions of the $HO_2^-$ ion with various metal ions[5], the reaction of the $Fe^{3+}$

ion with various hydroquinones[5,12-16], the transfer of hydride ion between xanthone and a series of triarylmethyl cations[18], the reduction of quinones by derivatives of 1,4-dihydropyridine[19], the transfer of hydrogen to quinones from hydrazo-compounds and 1,4-dihydronaphthalene[20,21], and the reduction of various flavins by dihydrolipoic acid and dihydronicotinamide adenine dinucleotide[22]. Other examples can be found in the literature[11,23,24].

The optimum condition limits the choice of catalysts for a given reaction to a definite range of catalyst redox potentials. In this connection, important significance for redox catalysis is acquired, on the one hand, by factors favouring rapid electron transfer in reactions characterised by relatively small changes in free energy, and, on the other hand, by the principles of the functioning and organisation of the catalyst systems, since it must apparently be assumed that high rates of electron transfer in each elementary act with the above limitations can be observed only for a definite range of donors and acceptors.

The transfer of electrons in inorganic systems usually takes place at rates of $10^{-2}-10^{2}$ litre mole$^{-1}$ s$^{-1}$, with activation energies of 15–21 kcal mole$^{-1}$.[25,26]. Rates of electron transfer equal to $10^{7}-10^{8}$ litre mole$^{-1}$ s$^{-1}$ and even greater than $10^{9}$ litre mole$^{-1}$ s$^{-1}$ are observed only in individual instances for simple systems.

On the other hand, for enzyme systems the rates of electron transfer are generally extremely high. For example, the oxidation of a number of metabolites in mitochondria takes place in the presence of catalyst–enzyme systems at rates of $\sim 10^{7}-10^{8}$ litre mole$^{-1}$ s$^{-1}$, with activation energies of 7–8 kcal mole$^{-1}$.[31]

Enzyme systems are distinguished by the fact that a high rate of electron flow is maintained along a chain of several catalyst–transfer agents. The decrease in the free energy of the reaction in each elementary act of electron transfer along the enzymatic chain is relatively small compared with ordinary redox systems[32].

It is natural to assume that enzymes effectively satisfy the requirements made of them as redox catalysts, and that the structure of the coenzymes and the functional groups forming part of the active centres of the enzymes are extremely well adapted to the functions of rapid electron transfer. This makes it possible to select and prepare catalysts for redox reactions by making use of data on the structure, mechanism of action, and methods of organisation of enzymes.

First of all let us consider briefly the conditions for the rapid transfer of electrons. The basic theoretical principles of the mechanism of electron-transfer reactions have been considered by Libby[33], Eyring and coworkers[25], Weiss[34], Laidler[35], Marcus[12], Halpern and Orgel[36], Levich and Dogonadze[37,38], and others[39-41]. Excellent reviews of experimental results and theoretical conclusions have been published[42-45].

## II. CONDITIONS OF RAPID ELECTRON TRANSFER

### 1. Thermodynamic Criterion of Transfer

According to this criterion, the greater the decrease in the free energy of a reaction, the greater the probability of a high reaction rate. The possibility of using this criterion in redox catalysis is limited, as can be seen from the foregoing discussion.

It may also be noted that the rate of a redox reaction may vary considerably, depending on the detailed mechanism of the process. Thus despite favourable thermodynamic relationships at room temperature, electron transfer does not take place without catalysts in the systems $Sn^{II}-Fe^{III}$, $Tl^{I}-Ce^{IV}$, dihydronicotinamide adenine dinucleotide (and its simple analogues)—molecular oxygen, sodium hydridoborate—nitroso-compounds, etc.[46-49]

### 2. Principle of Equivalent Exchange by Electrons[50-52]

According to this principle, first put forward by Shaffer, a reaction is rapid if in the course of the reaction the molecules of the oxidising agent and reducing agent respectively take up and give up the same number of electrons. If these numbers differ, the reaction is slow. This criterion is of considerable importance for the qualitative prediction of the rates of redox reactions. It leads to an extremely important consequence, directly related to redox catalysis: reactions in which there is equivalent exchange by electrons and which take place at a low rate will be accelerated by compounds capable of acting simultaneously as one-electron and two-electron oxidising agents and reducing agents.

In enzymatic catalysis, extensive use is made of structures capable of undergoing reversible one-electron and two-electron oxidation and reduction (flavones, quinones, cobalamines).[53-55]

Until recently, only isolated examples of catalytic reactions in which the principle of equivalent exchange is observed had been published[50-52,56-58].

This principle has been applied most fully and extensively in work on the development of new catalysts and catalytic systems for various redox reactions[1,2,59-63].

For example, it has been shown that the rate of the reaction between dihydropyridine compounds (hydride reducing agents) and molecular oxygen or the stable radical of 2,2,6,6-tetramethylpiperidone-4 (a one-electron oxidising agent) is increased considerably in the presence of flavins, quinones, and similar compounds[1,2,59]. The selection of a catalyst may be made on the basis of the values of the redox potentials[1,2]. It has been found that this type of catalysis may extend to other reducing agents: metal hydrides and molecular hydrogen activated by hydrogenation catalysts[3,59,62-66]. In the presence of these catalysts it is also possible, by means of hydride reducing agents, to reduce aromatic nitroso- and nitro-compounds, compounds with positive halogen, and complex compounds of metals with variable valency[60-62,66].

When Shaffer's principle is used, it is necessary to make allowance for the fact that the types of reacting compounds, ligands, and medium influence the ability of, for example, the donor to act as a hydride or one-electron reducing agent. Thus a change in the medium, influencing the stability of the intermediate states of oxidation of the catalyst or substrate, and complex formation, leading to stabilisation of intermediate states of oxidation, may alter both the mechanism and the rate of a redox reaction.

The catalytic oxidation of the dianions of organic compounds in common media was studied by Russell and coworkers[67]. The increase in the rate of the catalytic transfer of hydrogen as a result of the possible formation of a complex of the donor with a $\pi$-acceptor and a complex of an intermediate state of the catalyst with a metal ion has been studied[68,69].

### 3. Energy of Coulombic Interaction and Energy of Franck–Condon Rearrangement

The energy of the Coulombic interaction between the donor and the acceptor and the energy of the Franck–Condon rearrangement, that is the energy required for rearrangement of the ligand and solvate environment of the donor and acceptor in the change to the activated complex, appear in the free energy of activation of the redox reaction and determine it completely [12-16,42]. A decrease in the sum of these two terms leads to an increase in the rate of electron transfer.

As a rule, the rates of electron transfer between oppositely charged ions or between an ion and a neutral molecule are much greater than those between ions of the same sign. For example, the rate of the reaction of $Fe^{2+}$ with $IrCl_6^{2-}$ is greater by an order of magnitude than the rate of the reaction of $Fe^{2+}$ with the 1,10-phenanthroline complex of $Fe^{3+}$, which has the same $\Delta E^0$ value [17]. The activation energies of these reactions are comparable (1.9 kcal mole$^{-1}$ and 0.8 kcal mole$^{-1}$), but the entropy of activation is much smaller for $IrCl_6^{2-}$ than for the phenanthroline complex of $Fe^{III}$.

Very high values ($\sim 10^9$ litre mole$^{-1}$ s$^{-1}$) are observed for the rates of exchange by electrons in both the forward and back directions in the tris-(4,7-dimethyl-1,10-phenanthroline) $Fe^{II}$–$IrCl_6^{2-}$ system [27]. The reactions of $Fe^{3+}$ with the anions of hydroquinones is more rapid than the same reactions in acid media [12-16]. The rate constants for the disproportionation of neutral benzosemiquinones and the anions of benzosemiquinones are $10^9$ litre mole$^{-1}$ s$^{-1}$ and $5 \times 10^6$ litre mole$^{-1}$ s$^{-1}$ respectively [70].

A fact of importance for redox catalysis is that the rate of electron transfer between ions of identical sign is usually increased if the bridging group in the activated complex (that is the group joining the donor and the acceptor) is a ligand with the opposite sign ($Cl^-$, $Br^-$, $I^-$, $OH^-$, etc.). [42,71,72] The dimensions of the bridging group influence the forces of electrostatic repulsion between ions of the same sign [42,43,72].

Let us now consider the factors which decrease the energy of the Franck–Condon rearrangement. Firstly, if the reagents have similar structures and show little change in the solvate sheath, the rate of electron transfer in these systems will be maximal [34]. This explains the rapid electron transfer between the $MnO_4^{2-}$ and $MnO_4^-$ ions, which have identical structures, and the slow exchange between $AsO_4^{3-}$ and $AsO_3^{3-}$, which have different structures. Secondly, since the greatest contribution to the energy of the Franck–Condon rearrangement is made by the energy used in the rearrangement of the inner and outer coordination spheres of the reagents, the introduction of, for example, the iron ion into the rigid structure of the porphyrin in cytochromes increases its ability to undergo redox reactions, compared with hydrated iron [34]. High rates of electron transfer ($10^8$–$10^9$ litre mole$^{-1}$ s$^{-1}$) are observed between ions containing bulky ligands with extensive $\pi$-electron systems [17,27]. The activation energies of these reactions are very low and coincide with the activation energies of reactions whose rates are limited by diffusion. Thirdly, strong electronic interaction between the reagents and a bridging group, in Sutin's opinion [44], can stabilise the activated complex and decrease the total free energy required for rearrangement of the inner and outer coordination spheres of the reagents on electron transfer.

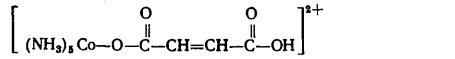
Finally, according to Libby [33], the rate of electron exchange is increased if it is possible to produce an activated complex whose geometry remains symmetrical to within the vibrational amplitudes involved in zero point motion ("symmetry principle").

### 4. Degree of Electronic Coupling Between the Reagents (Linearity of the Trajectory of the Electrons) [73]

The existence of an activated complex and low values for the Coulombic repulsion and the energy of the Franck–Condon rearrangement do not guarantee high rates of electron transfer—the possibility of sufficient electronic interaction between the reagents in the activated complex is necessary. In this connection it is important to emphasise the significance of bridging groups for the electronic coupling of reagents. Bridging groups provide orbitals of suitable symmetry, in which the electrons of the reducing agent may be delocalised and then transferred to the oxidising agent. If an electron moves from a $t_{2g}$ orbital of the reducing agent to a $t_{2g}$ orbital of the oxidising agent, we should expect easy transfer through bridging groups containing $\pi$-electrons, since these orbitals effectively overlap the $\pi$-orbitals of the bridging group. If the transfer involves $e_g$ orbitals, the limitations of symmetry greatly reduce the efficiency of the process. Thus for redox catalysis it is important that the catalyst be a compound–bridging group with a structure ensuring the necessary electronic coupling between the reagents through the electronic system of the catalyst and the formation of various complexes (chelates, $\pi$-complexes, etc.).

Published data show that the existence, in the bridging group, of positions for the additional binding of reagents in the activated complex favours electron transfer [74,75]. For $Co^{III}$ complexes containing bridging groups capable of forming chelate structures with the $Cr^{II}$ cation–reducing agent, the observed rates of transfer are higher than those for $Co^{III}$ complexes whose bridging groups do not have positions for binding $Cr^{II}$. [74,75]

As a rule, bridging groups containing $\pi$-systems favour electron transfer to a greater extent than bridging groups containing $\sigma$-systems [71,76]. The classical example illustrating this conclusion was described by Taube [71]: the rate of reduction of the complex



by the $Cr^{II}$ ion is greater by two orders of magnitude than the rate of reduction of the complex



A high rate of electron exchange was observed in the reduction of the $Fe^{3+}$ ion by the complex $(Fe-N_3)^{2+}$ in aqueous medium [77]. The bridging group provides its unshared pairs for bonding with the metal ion. The rate of electron transfer in the $Co(phen)_3^{2+}$–$Co(phen)_3^{3+}$ system is greater by six orders of magnitude than that in the corresponding ammines [71] (phen represents 1,10-phenanthroline).

A higher rate of electron transfer is observed in the case of the hexakis(phenyl isonitrile) complexes of $Mn^+$ and $Mn^{2+}$, compared with the ethyl and t-butyl isonitrile complexes [78]. It is assumed [78] that the activated complex has a structure in which there is overlap of the $\pi$-system

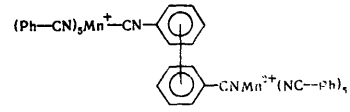
Rate constants for electron transfer in various reactions of organic compounds with the corresponding radical-anions.

| Compound | Solvent | $k$, litre mole$^{-1}$ s$^{-1}$ | $E_{act}$, kcal mole$^{-1}$ | Temp., °C | References |
|---|---|---|---|---|---|
| Benzene | THF:DMF = 2:1 | $7.7\cdot10^7$ | 2.8±0.6 | 18 | 80 |
| Naphthalene | DME | $1.6\cdot10^9$ ($\sim10^9$) | 5 | 23 | 79, 81 |
| Ditto | THF | $2\cdot10^9$ ($8\cdot10^7$) | 5 | 23 | 79, 81 |
| Naphthalene[a] | THF | $3\cdot10^7$ ($1.8\cdot10^7$) ($5.7\cdot10^7$) | | 23 | 79, 81, 90 |
| Naphthalene[b] | THF | $6\cdot10^7$ ($5.7\cdot10^7$) | | 23 | 79, 81 |
| Ditto | DME | $1\cdot10^8$ | | 23 | 81 |
| Anthracene | | $1.2\cdot10^9$ | 3.0 | | 80 |
| 1,4-Benzoquinone | DMF | $3.8\cdot10^8$ | | | 28, 85 |
| Duroquinone | DMF | $6.2\cdot10^7$ | | | 28, 85 |
| Vitamin B | DMF | $1.6\cdot10^7$ | | | 85 |
| 1,4-Naphthaquinone | DMF | $4.2\cdot10^8$ | | | 85 |
| Vitamin $K_3$ | DMF | $4\cdot10^8$ | | | 85 |
| Vitamin $K_{1(20)}$ | DMF | $1.3\cdot10^8$ | | | 85 |
| Tetracyanoethylene | THF | $2.1\cdot10^8$ | | | 82 |
| Anthracene | DMF | $4.8\cdot10^8$ | | | 82 |
| Nitrobenzene | DMF | $3\cdot10^7$ | | | 28 |
| Ditto | DMF + 10% $H_2O$ | $3.2\cdot10^8$ | | | 28 |
| *p*-Dinitrobenzene | DMF | $6\cdot10^8$ | | | 28 |
| *m*-Dinitrobenzene | DMF | $5.2\cdot10^8$ | | | 28 |
| *p*-Chloronitrobenzene | DMF | $7.9\cdot10^7$ | | | 28 |
| *m*-Chloronitrobenzene | DMF | $8.8\cdot10^7$ | | | 28 |
| 3,5-Dichloronitrobenzene | DMF | $1.6\cdot10^8$ | | | 28 |
| Radical-anion of cyclo-octatetraene[c] | THF | $10^9$ | | | 87 |
| Cyclo-octatetraene | THF | $\sim10^4$ | | | 87 |
| Tri-*p*-nitrophenylmethane | ($Na^+$)DME | $4.35\cdot10^9$ | 2.04 | 25 | 83 |
| Ditto | ($K^+$) | $5.99\cdot10^9$ | 1.99 | 25 | 83 |
| " | THF($Na^+$) | $4.56\cdot10^9$ | 0.86—2.63 | 25 | 83 |
| " | THF($K^+$) | $4.7\cdot10^9$ | 2.25 | 25 | 83 |
| " | Pyridine($Na^+$) | $6.79\cdot10^9$ | 2.03 | 25 | 83 |
| " | Pyridine($K^+$) | $8.7\cdot10^9$ | 1.95 | 25 | 83 |
| " | Acetonitrile($Na^+$) | $16.3\cdot10^9$ | 1.04 | 25 | 83 |
| " | ($K^+$) | $13.8\cdot10^9$ | 1.12 | 25 | 83 |
| *p*-Xylene | DME | $\sim2.8\cdot10^7$ $10^{12}\exp(-6200/RT)$ | 6.2 | 25 | 88 |
| Xanthone[d] | DMF | $4.56\cdot10^8$ | 5.1 | 37 | 84 |
| | THF | $4.48\cdot10^8$ | 4.3 | 25 | |
| | THP | $4.68\cdot10^8$ | | 7 | |
| | Me-THF | $4.32\cdot10^8$ | | 0 | |
| Xanthone[e] | DME | $2.5\cdot10^8$ | | 25 | 84 |
| Benzophenone[f] | DMF | $1.10\cdot10^8$ | 6.3 | 25 | 84 |
| | THF | $1.14\cdot10^8$ | 6.0 | 12 | |
| Benzophenone[g] | DME | $1.56\cdot10^8$ | | 25 | 84 |
| Benzophenone[h] | THF | $\sim2.5\cdot10^8$ | | 25 | 84 |
| Xanthone | $CH_3Cl$ | $\sim10^9$ | | 25 | 84 |
| Benzophenone[i] | DME | $<10^8$ | | 25 | 84 |
| | Me-THF | | | | |
| | Dioxan | | | | |
| 1-(α-Naphthyl)-1-phenylethane | DMF | $6.8\cdot10^7$ | 1.6 | 25 | 89 |
| | THF | $1.9\cdot10^7$ | 2.3 | | |
| Tri-t-butylphenol | $CCl_4$ | $6.6\cdot10^2$ | | 27 | 91 |
| Tetrabutylindophenol | $CCl_4$ | $1.4\cdot10^3$ | | 27 | 91 |
| | Cyclohexane | $2.2\cdot10^3$ | | | |
| Diphenylhydroxylamine | $CCl_4$ | $>10^7$ | | 27 | 91 |
| Di-t-butylhydroxylamine | $CCl_4$ | $3.2\cdot10^2$ | | 27 | 91 |
| | Chlorobenzene | $2.4\cdot10^2$ | | | |
| t-Butyl-2,6-dimethoxy-phenylhydroxyl-amine | Chlorobenzene | $5.2\cdot10^3$ | | 27 | 91 |
| | Chloroform | <20 | | | |
| | $CH_2Cl_2$, acetone | | | | |
| Hexahelicene | THF | $k_{dd}=1.2\cdot10^{10}$ $k_{dl}=3\cdot10^9$ | | 23 | 92 |
| Fluoranil[j] | 90% THF + 10% acetonitrile | $\sim10^8$ | | —75 | 86 |

[a]Reaction with naphthalenide ($Na^+$). [b]Reaction with naphthalenide ($K^+$). [c]Reaction with the di-anion of cyclo-octatetraene. [d]Reaction with the xanthone radical-anion ($Na^+$). [e]Reaction with the xanthone radical-anion ($Rb^+$). [f]Reaction with the benzophenone radical-anion ($Na^+$). [g]Reaction with the benzophenone radical-anion ($Rb^+$). [h]Reaction with the benzophenone radical-anion ($K^+$). [i]Reaction with the complex of the benzophenone radical-anion, the metal ion, and the neutral benzophenone molecule. [j]Reaction with the fluoroanil anion.

THF—tetrahydrofuran, DME—dimethoxyethane, DMF—dimethylformamide, THP—tetrahydropyran, and Me-THF—methyltetrahydrofuran.

of the benzene rings and which cannot be achieved in the case of alkyl isonitrile ligands

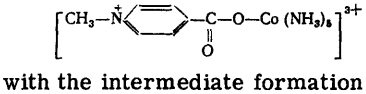


An unusually high rate of electron transfer is observed between tris-(4,7-dimethyl-1,10-phenanthroline)-$Fe^{II}$ and hexachloroiridate(IV).[27] The rate constants for transfer in the forward and back directions are $10^9$ litre mole$^{-1}$ s$^{-1}$ and $4\times10^9$ litre mole$^{-1}$ s$^{-1}$ respectively. The most probable mechanism of transfer involves delocalisation of the electron over all three phenanthroline ligands and overlap of the appropriate orbitals of the chloride ions with the π-system of the phenanthroline ligands. The high rate of electron transfer suggests that the overlap is sufficient to make possible the ready transfer of an electron, accompanied by rearrangement of the ligands in the solvate sheaths. High rates of electron exchange are observed between neutral organic molecules and their ions[28,79-92].

All the organic systems of this type which have been studied up to the present have extensive electronic systems, the ready overlap of which ensures high rates of transfer. The values of various rate constants for electron transfer between radical-ions and neutral molecules are given in the Table.

The above discussion leads to the following qualitative conclusion—the more extensive the conjugated system in the organic compound, the greater the rate of transfer. The rate constants for the reaction increase in the order: benzene < naphthalene ~ anthracene. An important feature is that in the reactions given in the Table, the change in free energy is equal to zero.

The transfer of electrons through bridging groups may be accompanied by oxidation or reduction of these groups[93-96]. Sometimes the lifetime of these states is greater than the half-reaction time for the individual electronic reactions, and sometimes it is so great that chemical changes in the bridging group are possible, for example cis-trans isomerisation in the reduction of the pentamminemalato-complex of $Co^{III}$ by $Cr^{II}$ ions[92,94]. The rapid reduction, by $Cr^{II}$ ions, of the complex



takes place with the intermediate formation of the radical-cation, stabilised by conjugation[95,96]. The easier the reduction and oxidation of the bridging group, the greater the observed rate of electron transfer[74,93-96]. The ligands which are readily reduced and oxidised are generally extensive conjugated systems.

## 5. Spin Preservation Rule

Spin preservation is an important factor influencing the rate of redox reactions: systems for which changes in spin are expected are characterised by low rates of electron transfer. Preservation of spin on electron transfer to the activated complex requires the use of high-lying excited electron orbitals, so that high rates are impossible. The difference in the rates of reactions involving molecules with more than one unpaired electron can apparently be explained on the basis of this forbidden case[97].

---oOo---

The above conditions for rapid electron transfer can be used in the selection of catalysts for the catalytic cycle described above [reactions (1) and (2)]. Since its characteristic feature is that the most effective catalysts have redox potentials lying in a definite range, an important significance for the estimation of the rate constants $k_1$ and $k_2$ is acquired by an equation obtained by Marcus [12-16], relating the rate constant of the forward reaction $k_{12}$ between a donor $A^-$ and an acceptor B

$$A^- + B \underset{k_{21}}{\overset{k_{12}}{\rightleftarrows}} A + B^-$$

to the equilibrium constant $K_{12}$ (it also defines the redox potential) and the rate constants of the one-electron exchange reactions $k_{11}$ and $k_{22}$

$$A^- + A \overset{k_{11}}{\rightarrow} A + A^-$$

$$B^- + B \overset{k_{22}}{\rightarrow} B + B^-$$

The constants $k_{11}$ and $k_{22}$ may either be measured by physical methods (EPR, NMR) or predicted on the basis of the conditions for rapid transfer.

Following Marcus, we can write

$$K_{12} = (k_{11}k_{22}k_{12} \cdot f)^{1/2} \qquad (5)$$

where

$$\ln f = \frac{(\ln K_{12})^2}{4 \ln (k_{11} \cdot k_{22}/z^2)},$$

$z$ is the frequency of bimolecular collisions in the solution ($z \sim 10^{11}$ litre mole$^{-1}$ s$^{-1}$ and $f$ is often close to unity).

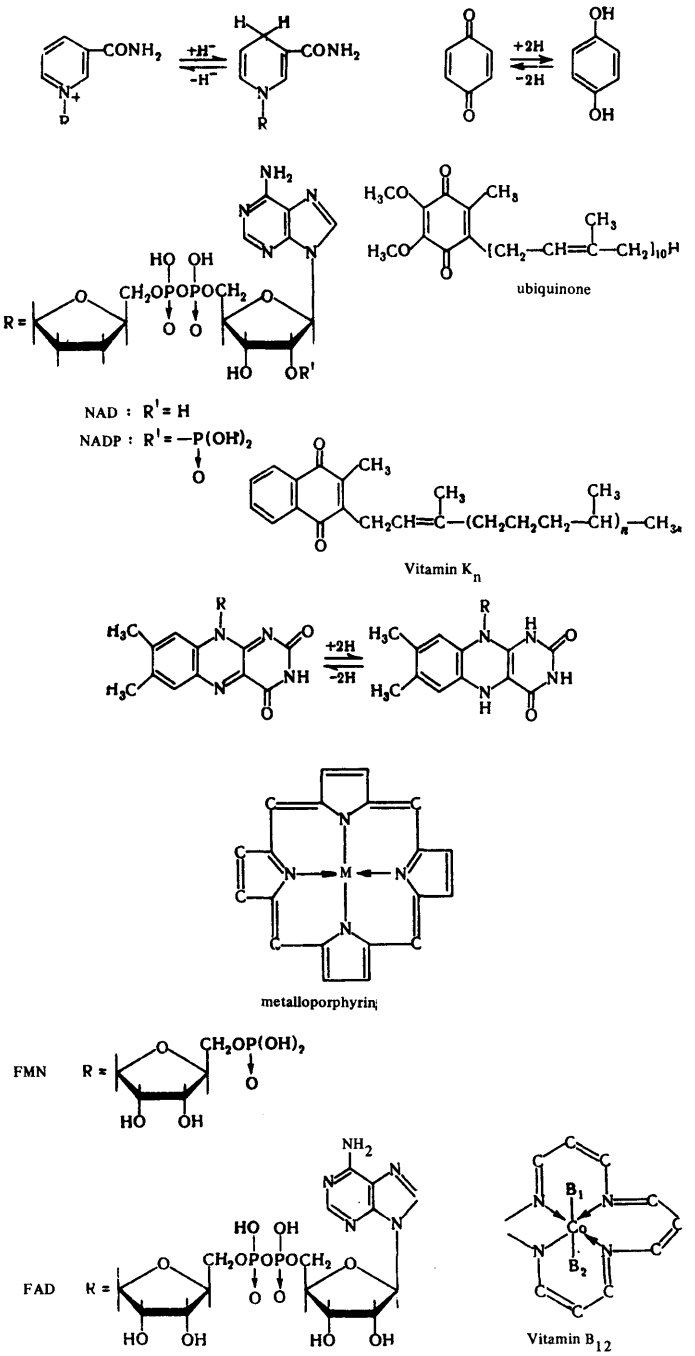
Although the theoretical calculations were carried out by Marcus for a definite model of the reaction, in which rupture or formation of chemical bonds does not take place (electron transfer by the so-called outer-sphere activated complex mechanism) it must be assumed that its conclusions can be extended to many systems. This conclusion is confirmed by experimental results [17,42,85,98]. For example, Eqn. (5) has been used to estimate the relative rate constants for redox reactions of biologically important quinones—vitamins $K$ and $E$—compared with 1,4-naphthaquinone and duroquinone. The relationship between these constants and the length of the side chain of vitamins $K$ and $E$, and the possibility that they take part in the biochemical respiration chain as electron transfer catalysts has been discussed on this basis [85]. In simpler systems, quinones in fact act as effective catalysts for the transfer of an electron from various reducing agents to a large number of acceptors [1,3,59,61,63,66,99-101].

In concluding this section, we may point out that despite the large number of redox reactions studied, there are extremely few examples of catalytic reactions in which criteria of rapid electron transfer have been used. At the same time, enzymatic redox catalysis is a process which is organised in a definite fashion and in which conditions for rapid electron transfer are realised and use is made of structural elements which are well adapted for carrying out the functions of catalysts for redox reactions. Consequently, it is of interest to examine the general principles of the construction and functioning of enzymes of redox reactions, with the aim of producing new catalysts and catalytic systems on this basis.

## III. SOME CHARACTERISTIC FEATURES OF ENZYMATIC TRANSFER OF ELECTRONS (HYDROGEN)

### 1. Structure of Groups in the Active Centre of Enzymes (Coenzymes)

Of the coenzymes used in enzymatic redox catalysis, of which there is a limited number [102], mention may be made of nicotinamide adenine dinucleotide (NAD), nicotinamide adenine dinucleotide phosphate (NADP), flavin mononucleotide (FMN), flavin adenine dinucleotide (FAD), metal–porphyrin complexes, ascorbic acid, lipoic acid, coenzyme Q (ubiquinone), vitamin K, and vitamin $B_{12}$, the structures and reactions of which are given below:



The coenzymes show the following characteristic structural features.

The highly universal action of coenzymes [103] is due to the fact that in these coenzymes, the properties of various classes of compound are combined. All the coenzymes are (or contain) conjugated heterocyclic systems with acid–base centres and various groups adapted for reversible bond and complex formation. As a result, they may be effective bridging groups (catalysts) or contain such groups.

The presence in the coenzymes of extensive $\pi$-electron systems is directly related to their catalytic functions. In Bersuker's opinion [104], redox enzymes can be regarded as characteristic electronic systems of high capacity, since they can readily take up and give up electrons without significant change in energy. For example, the iron–porphyrin complex can act as a powerful acceptor and also as a no less powerful donor, taking effective part in electron transfer. On the other hand, conjugated systems can increase the rates of electron transfer as a result of conduction through the system of $\pi$-bonds.

The ready conversion of one systems of conjugated bonds into another is responsible, for example, for the functioning of the coenzymes NAD, NADP, FMN, FAD, and also coenzymes with quinone structures. Here, an apparently general principle is the principle of minimal breakdown of the $\pi$-system of the coenzyme with the introduction of the entire conjugated system into the reaction. Calculations [105-107] show that the oxidised form of the coenzyme is a very effective electron acceptor, and the reduced form an effective electron donor. The formation of various complexes with the coenzyme alters its donor–acceptor properties considerably (see, for example, the review of the flavins [108]).

The possibility of maintaining a steady-state concentration of catalytically active forms (semiquinones–QH) through the equilibrium between the completely oxidised (Q) and reduced ($QH_2$) forms of the coenzyme (flavins and quinones) $QH_2 + Q \rightleftharpoons 2QH$, in which the rates of electron exchange between the various oxidised forms of the coenzyme are extremely high [85], is an important property of enzyme–transfer agents.

In the case of vitamin $B_{12}$, the highly reactive state of $Co^{II}$, with one or several unpaired electrons, exists [55] as a result of the equilibrium $Co^{II} + Co^{I} \rightleftharpoons 2Co^{II}$.

The various possibilities for stabilisation of the catalytically active forms of coenzymes by delocalisation of the unpaired electrons over the conjugated systems, and the formation of complexes with metal ions or $\pi$-acceptors, are also related to the characteristic features of the structure of coenzymes [108-116].

## 2. Role of $\pi$-Complexes in Enzymatic Catalysis [117-122]

The formation of $\pi$-complexes leads firstly to an increase in the extent of the conjugated system and hence to the possibility of electron transfer over considerable distances, and secondly to stabilisation of the catalytically active forms of the coenzymes.

Most of the available published data on this subject relates to the detection and identification of the $\pi$-complexes of dihydronicotinamide adenine dinucleotides, flavins, quinones, and other coenzymes with conjugated systems. The biological role of coenzymes is undoubtedly due to their ability to form various $\pi$-complexes.

Thus it is assumed [123-125] that the transfer of electrons in mitochondria and chloroplasts is brought about by $\pi$-complexes of the metalloporphyrin–quinone or chlorophyll–quinone types respectively. The values of the measured formation constants for the formation of $\pi$-complexes between vitamin $K_3$ and biologically important electron donors—Co-mesoporphyrin-IX-dimethyl ether and chlorophyll—show that these complexes are quite capable of existing under the conditions of enzymatic reactions and of influencing electron transfer.

The formation of $\pi$-complexes between NAD-$H_2$ and flavins has been studied [110,125]; identical $\pi$-complexes may also be obtained in the reaction of reduced flavin with NAD.

Molecular complexes of NAD and its simple analogues with various electron donors, $I^-$, indole, tryptophan, and serotine† have been studied [126].

Of considerable importance for an understanding of the role of $\pi$-bonding in enzymatic catalysis are various facts [127-129] which indicate electronic interaction of the "charge transfer" type between the adenine and nicotinamide (or isoalloxazine) rings within the enzyme itself.

Study of the complexes of indole with the pyridinium ion showed that the absorption spectra of these systems are similar to the spectra of the enzyme glyceral-3-phosphate dehydrogenase. It is suggested [130] that the bond between NAD and the protein in the enzyme is produced as a result of the formation of a $\pi$-complex. Similarly, the bond between flavin and a protein may be produced through a $\pi$-complex with tyrosine [131,132]. A large number of $\pi$-complexes are formed by the isoalloxazine ring, which can often be regarded not only as an electron acceptor (complexes with purines, HI, dihydropyridines, hydroquinones, phenols, and other compounds) but also as a $\pi$-electron donor (complexes with tetracyanoethylene or 2,3-dichloro-5,6-dimethyl-1,4-benzoquinone). Dimethylalloxazine, for example, behaves in this way, and the ability of this compound to act as donor or acceptor shows a correlation with the energies of the higher occupied and lower vacant orbitals [183]. Isoalloxazines and related dyes are known to form molecular complexes with purines, pyrimidines, indoles, phenols, and other compounds of biological interest [110,134-137].

Finally, molecular complexes of quinones are widely known [121,138-140]. The complexes of quinones with flavins and cytochromes are of greatest interest, since they are active groups of enzyme–transfer agents, which come into direct contact in electron transfer processes.

Although it can definitely be stated that the $\pi$-complexes of many redox coenzymes take part in biochemical reactions as intermediate structures, there is almost no direct proof of this. Some of the difficulty is due to the fact that even in those instances where the accumulation of reaction products takes place in the same sense as the change in the concentration of the intermediate $\pi$-complex [140], it cannot be guaranteed that the chief reaction path is that involving the formation of the $\pi$-complex, and does not by-pass it.

$$A + B \xrightarrow{[\pi\text{-complex}]} \text{products}$$

† It is not clear whether seroten or serotonin is intended here (Ed. of Translation).

It can be said that the factors corresponding to the formation of $\pi$-complexes favour electron transfer from the donor to the acceptor.

It may be noted that the existence of $\pi$-bonding between the substrate and the enzyme tyrosinase under anaerobic conditions [120] shows that this complex is apparently an intermediate in the oxidation of substrates by molecular oxygen. The examples of the participation of NAD and FAD in intramolecular complexes, in $\pi$-complexes with aromatic aminoacids, and in complexes with one another may indicate not only the nature of the bonding between the coenzyme and the apoenzyme, but also the existence of intermediate catalytically active states involving reducing agents, for example NAD-$H_2$ (source of hydrogen) and the hydrogen acceptor FMN, FAD, or quinone.

### 3. Role of Semi-quinones in Enzymatic Catalysis

As indicated above, a characteristic feature of enzymatic catalysis is the existence of a steady-state concentration of catalytically active intermediate forms (semi-quinones, $Co^{II}$, etc.) through the equilibrium between the completely oxidised and reduced forms of the coenzyme. The maintenance of a steady-state concentration of catalytically active forms is due to the structural characteristics of the coenzymes. In this connection, a factor of considerable importance in redox catalysis by enzymes undoubtedly is the possibility of additional stabilisation of intermediate radical and highly active biradical states of the coenzymes, and also reactive low-valency and other states of metal ions, as a result of the inclusion of the corresponding $\pi$- or $d$-electrons in conjugated systems of sufficient extent.

At an early date, Michaelis [141] suggested the existence of radical–enzyme complexes as a necessary condition for the essential one-electron transfer in enzymatic redox reactions.

Current data indicate that there is stabilisation of the radicals as a result of the formation of $\pi$-complexes under conditions of both non-enzymatic [108-116] and enzymatic [111-113,115,116] reactions. Stable complexes of flavin radicals with iodine and phenol were recently obtained [114].

It may be assumed that in many instances the detection of radicals under the conditions of enzymatic reactions is related to additional delocalisation of the unpaired electron either on a suitable conjugated system of the protein or on suitable orbitals of the metal ion.

The chief theories on the role of free radicals are associated with the name of Michaelis, who considered that all biological redox reactions must have a stage involving one-electron transfer, the intermediate compounds being free radicals [141].

At the present time, the role of radical intermediate forms in enzymatic catalysis remains the subject of a large amount of discussion [112,113,115,116,141,142], since even with modern methods of study it is not always possible to relate the facts of the detection, identification, and behaviour of radicals under various conditions to the actual mechanism of enzymatic catalysis. The problem is also complicated by the variety of ways in which free radicals can be stabilised and destabilised, for example by $\pi$-bonding, complex formation with metal ions, concurrent chemical reactions which do not affect the free valency, etc.

As already indicated, a characteristic feature of the reversible flavin–dihydroflavin reaction and the analogous quinone–hydroquinone reactions is the ready formation of free radicals as intermediate compounds. The mechanism of formation of radicals in these systems is based on the equilibria

$$QH_2 + Q \underset{k_{21}}{\overset{k_{12}}{\rightleftarrows}} [QH_2 \cdot Q] \underset{k_{32}}{\overset{k_{23}}{\rightleftarrows}} 2\,QH,$$

where $QH_2$, QH, Q, and $[QH_2.Q]$ represent the reduced, the semi-quinone, and the oxidised forms of the flavin or quinone, and the intermediate complex, which is usually a $\pi$-complex.

Depending on the medium, these equilibria are superimposed on the reversible reactions of addition and removal of a proton from the various forms of flavin or quinone [112,115,116,144,145]. In aqueous and aqueous-alcoholic media, hydroxide ions may act as possible reducing agents to semi-quinones [146-149].

The temperature-jump method has been used to study the reaction between FMN and FMN-$H_2$ at pH = 4.7 and a temperature of 298°K. [150] The values of the constants $k_{12}$, $k_{21}$, $k_{23}$, and $k_{32}$, equal to $> 10^9$ litre mole$^{-1}$ s$^{-1}$, $> 10^6$ s$^{-1}$, $5 \times 10^3$ s$^{-1}$, and $6 \times 10^6$ mole$^{-1}$ s$^{-1}$ respectively, show that the rates of electron transfer in the two directions approximately coincide. The data on the isotope effect evidently indicate that transfer of an electron to the intermediate complex is less probable than transfer of a hydrogen atom.

It is of particular interest to compare the rates of one-electron exchange and transfer of hydride ion in quinone–hydroquinone systems. The constants $k_{21}$ and $k_{23}$ can apparently be regarded as proportional to the rates of hydride ion transfer and one-electron exchange, since in the intermediate complex the hydrogen atoms which undergo exchange are equivalent with respect to the two flavone (or quinone) rings, present in the complex.

If this is so, the rate of transfer of two electrons in the FMN–FMN-$H_2$ system is much greater than the rate of exchange by an electron in the same system. It may be assumed that the rates of electron transfer are markedly dependent both on the structure of the flavin or quinone and on the nature and degree of the binding of the coenzymes in reactions of enzymatic catalysis.

Unfortunately, in other systems these rate constants for electron transfer are unknown, although the rates of one-electron transfer in the forward and back directions have been measured [70,151-155]:

$$QH_2 + Q \underset{k_{-1}}{\overset{k_1}{\rightleftarrows}} 2\,QH\,.$$

The values of the constants $k_1$ and $k_{-1}$ are fairly high ($10^7$–$10^{10}$ mole$^{-1}$ s$^{-1}$).

Usually, as expected, the QH$^{\cdot}$ radical disproportionates much more rapidly than its deprotonated form Q$^{\cdot}$. [70,155]

The complexity of the study of electron transfer in the Q + $QH_2$ system is also due to the need to make allowance for redox reactions of exchange by electrons

$$Q + QH \rightleftarrows QH + Q$$
$$QH + QH_2 \rightleftarrows QH_2 + QH\,.$$

This reaction takes place at a high rate (values of the constants up to $10^{10}$ litre mole$^{-1}$ s$^{-1}$) (see Table on page 107 and Refs. 28 and 85).

The oxidised, semi-quinone, and reduced forms of the flavins or quinones readily form various complexes: $\pi$-complexes with one another and various $\pi$-acceptors and $\pi$-donors, and complexes with metal ions and other complex-forming species [108,110-114,120,121,124-141,157-159].

As a result of complex formation, there is an increase in the effective concentration of intermediate radical forms.

For example, the maximal concentration of flavosemiquinones is observed in acidic and alkaline media [115,116] and does not exceed several percent of the total concentration of flavin, whereas the maximum concentration of flavosemiquinones in the presence of various metal ions is observed in neutral media and may amount to almost 100% of the flavin concentration [113].

The oxidised form of flavin reacts specifically with a metal ion, whereas the reduced form is inert [113]. Thus flavin forms very stable chelates only with $Ag^+$ and $Cu^+$ ions, and in the complex of flavin with $Cu^+$, reversible electron transfer takes place between the partners. The spectra of the complexes $[Fl^-.Cu^+] \Longleftrightarrow [Fl^{2\cdot}.Cu^{2+}]$ and $[Fl^-.Ag^+]$ correspond to the isoelectronic spectrum of the protonated flavosemiquinone $[Fl^{\cdot}.H_2^+]$. [160,161]

$Fe^{2+}$ and $MoO^{3+}$ ions react equally strongly with flavin, but in contrast to the situation with the $Ag^+$ and $Cu^+$ compounds, the flavin in the complexes with $Fe^{2+}$ and $MoO^{3+}$ is completely reduced to the semiquinone [113,162].

It should be emphasised that the semiquinones of flavins are able to form complexes with, as a rule, many more metal ions than the oxidised or reduced forms [163,164]. With diamagnetic metal ions ($Zn^{2+}$, $Cd^{2+}$) the flavosemiquinone gives an EPR spectrum with a hyperfine structure which is quite different from that of free flavosemiquinone, although the absorption spectra in the visible range are approximately identical [159,163,165]: this indicates a marked change in the electron density in the flavosemiquinone on complex formation with metal ions.

It has been suggested that the role of metal ions in enzymatic catalysis possibly involves the stabilisation of the flavin semiquinone [163].

Bray and coworkers [166], in a study of reactions catalysed by xanthine oxidase (a flavin enzyme containing Fe and Mo), showed by the EPR method that in the anaerobic reduction of xanthine oxidase and the aerobic oxidation of xanthin, the flavosemiquinone and $Mo^V$ are formed as intermediate products. The results indicate that this radical is joined to the protein or the metal [166].

In view of the marked ability of semiquinones to form various complexes, proofs of direct electron transfer in systems containing flavins and quinones must be approached with some caution.

Study of the EPR spectrum of the $\pi$-complex $[NAD\text{-}H_2.FMN]$ [167] showed the presence of free radicals, associated only with the flavin part of the complex. This was explained on the basis of the following reaction scheme

$$NAD\text{-}H_2 + FMN \rightleftharpoons [NAD\text{-}H_2^+.FMN^-] \rightleftharpoons NAD\text{-}H_2^+ + FMN^-$$
$$2NAD\text{-}H_2^+ \rightleftharpoons NAD\text{-}H^+ + NAD\text{-}H_2 + H^+$$
$$FMN^- + H^+ \rightleftharpoons FMN\text{-}H^{\cdot}.$$

The intermediate free radical $NAD\text{-}H_2^+$ immediately undergoes disproportionation, to form the completely reduced and oxidised pyridine nucleotides. Thus the result of the overall reaction is the reduction of FMN at the expense of the $NAD\text{-}H_2$, to the semiquinone, without the formation of free radicals of $NAD\text{-}H_2$.

On the other hand, there exists the possibility of complete reduction of the flavin in the $\pi$-complex, the formation of semiquinones through the equilibirium between the oxidised and reduced forms of the flavin, and stabilisation of the resulting flavosemiquinone by its inclusion in a $\pi$-complex with the oxidised form of nicotinamide adenine dinucleotide.

This mechanism of stabilisation of semiquinones may also be realised in reactions of N-benzyldihydronicotinamide with quinones, where semiquinones have been detected [168]. The authors cited consider that this proves one-electron transfer, since the semiquinones were not detected by the EPR method under the same conditions in the quinone–hydroquinone system. Allowance must be made, however, for the fact that the reaction between dihydropyridine and 1,4-benzoquinone is fairly slow [169], whereas the attainment of equilibrium in the quinone–hydroquinone system is a very rapid process [70,134-137,151-156]

Because of complex formation, it is not always possible to observe correlations between the appearance of an EPR signal and the absorption bands assigned to the semiquinone [112]. It was found, for example, that the absorption spectra of the enzyme lipoyl dehydrogenase are the same for the reduction by dithionite and by the substrate, but an EPR signal is not observed, because of the formation of a complex between the flavosemiquinone and a sulphur-containing radical, formed in the enzyme. This complex plays a central role in processes catalysed by the enzyme lipoyl dehydrogenase; it is a catalytically active intermediate complex. The completely reduced enzyme is catalytically inert, at least in reactions with physiological substrates.

In a study of the mechanism of action of the oxidase of D-aminoacids it was found that the catalytically active intermediate product is a complex between the semiquinone form of the flavin and a radical of the aminoacid; in agreement with this, the concentration of the flavosemiquinone increased with increase in the concentration of the aminoacid [112].

Although many conclusions are still controversial, it may be taken that the formation of complexes by radicals increases the effective concentration of the radicals—this may have a significant influence on the overall rate of electron transfer [170].

On the other hand, complex formation by radicals may alter considerably the electron distribution in the radicals [113,159,170] and this in turn influences the rate and specificity of the process.

Ehrenberg [115,116] detected free radicals by means of the EPR method in the reaction between "old yellow" enzyme and $NAD\text{-}H_2$. He showed that the radicals are combined with a slowly vibrating protein molecule. The unpaired electron is localised chiefly in that part of the isoalloxazine molecule which is not combined with the protein. This electron density distribution is extremely sensitive to the smallest changes in the structure of the environment of the radical.

The action of the enzyme on the free radicals formed in a number of instances from the substrates is of interest [171]. Nakamura [172] established that in the oxidation of hydroquinone by the copper-containing enzyme laccase, a semiquinone is formed as the primary reaction product. The formation of free radicals in the oxidation of hydroquinone, pyrogallol, pyrocatechol, and other compounds was observed by a number of authors in processes involving peroxidase [173] and phenol oxidase [174].

Work illustrating the specific behaviour of semiquinones compared with other redox forms is of particular interest.

The important role of semiquinones is emphasised by Yamasaki and Ohnishi [153], who showed that the rate of the reduction of cytochrome C by hydroquinone is greatly increased in the presence of quinone. This increase was attributed to the formation of para-benzosemiquinone. The reduction of cytochrome C by the semiquinone is rapid

and plays an important role in the redox equilibrium between the ferro-ferricytochrome C and quinone–hydroquinone systems. A kinetic study by the EPR method showed the following reaction mechanism:

$$QH_2 + Q \rightleftarrows 2QH$$

QH + ferricytochrome C ⇌ quinone + ferrocytochrome C.

The same result was previously obtained in a study of simpler systems [175].

The rapid reduction of cytochrome C in reactions of oxidases (peroxidase, ascorbic acid oxidase), which catalyse the two-stage oxidation of hydrogen donors, is also associated with the formation of semiquinone free radicals from the donor molecule [176].

The autocatalysis of the oxidation of reduced flavin by molecular oxygen may indicate a high rate of reaction of the flavosemiquinone with oxygen, compared with the reduced flavin [177]. The addition of the oxidised flavin to the FMN-$H_2$–$O_2$ system increases the rate of oxidation [177].

This was proved experimentally with other systems. An interesting feature is the behaviour of the semiquinone of thionine (a dye structurally similar to the flavins) in the reduction of the $Fe^{3+}$ ion. The rate constants [151] for the oxidation of thionine semiquinone and its reduced form by $Fe^{3+}$ ions are $7.9 \times 10^4$ litre mole$^{-1}$ s$^{-1}$ and $2.6 \times 10^2$ litre mole$^{-1}$ s$^{-1}$ respectively.

The reactivity of the semiquinone is determined by many factors. Thus it has been established that the flavin semiquinone produced by the action of various flavoproteins is oxidised by hexacyanoferrate(III) with great difficulty in the presence of a substrate; is however the substrate is absent, the oxidation is instantaneous [162,170,178].

Various flavosemiquinones are so strongly stabilised by a protein or a metal ion that they undergo extremely slow oxidation by molecular oxygen, and reduction by $S_2O_4^{2-}$ ions [112,113].

## 4. Catalytic Electron Transfer Chains

A characteristic feature of enzyme catalysis is the use of so-called catalytic chains, that is systems consisting of several enzymes [31,179,180]. For example, the oxidation of a number of metabolites in mitochondria takes place in the presence of a system of catalysts consisting of nicotinamide adenine nucleotide enzymes, flavoproteins, quinones, cytochromes, and metalloproteins. The chief sections of this chain are shown in the following scheme:

$$\text{RH} \rightarrow \text{NAD-protein} \rightarrow \text{flavoprotein} \rightarrow \text{Vitamin K} \longrightarrow \left\{\begin{array}{l}\text{Cytochrome}\\ \text{Ubiquinone}\\ \text{Metalloprotein}\\ \text{containing iron}\end{array}\right\} \rightarrow \left\{\begin{array}{l}\text{System of cytochromes}\\ \text{and also ubiquinone}\end{array}\right\} \rightarrow O_2$$

At different ends of the respiratory hydrogen transfer chain, there is preliminary activation of the substrates: the hydrogen donor RH and the hydrogen acceptor molecular oxygen, and electron transfer along the chain takes place at a very high rate ($10^7$–$10^8$ mole$^{-1}$ s$^{-1}$, activation energy 7–8 kcal mole$^{-1}$ [31]) and is highly specific. The term activation is understood to mean the formation of enzyme–substrate complexes in which the necessary rearrangement of the electronic structure of the hydrogen donor or acceptor and an orientation of the reagents convenient for the reaction take place. The formation of enzyme–substrate complexes leads to an increase in the rate and specificity of the enzymatic reaction. In particular cases a coenzyme may act as substrate.

It should first of all be emphasised that the key sections of the respiratory chain are those in which interaction of pyridine nucleotide and flavin enzymes with hydrogen donors and acceptors (particularly molecular oxygen), and also reaction of these enzymes with one another, take place. It is the study of these sections which may show why redox systems use not one universal catalyst but a chain of catalysts. This problem of course applies to other biochemical systems. It is natural to assume that the chief advantages of the catalytic chain lie in the fact that these chains are best able to satisfy the specific conditions of the reaction—the rates of electron transfer along the chain are high, and the reagents are activated and separated in space. This makes it possible to overcome the limitations imposed by the diffusion of reacting species to the active centre and also to generate reaction products in definite positions, so that their possible influence on the course of the reaction may be reduced to a minimum [179].

We may note the characteristic features of the biochemical respiratory chain given above. In the initial section of the chain, the substrate is oxidised by the direct transfer of hydrogen to the nicotinamide coenzyme. Most of the data on the mechanism of oxidation under the conditions of both model and enzymatic reactions indicates that hydrogen is transferred to nicotinamide coenzymes in the form of hydride ion [181], but no specific theories regarding the details of the mechanism of this reaction exist [102].

The final substrate of the electron transfer chain is molecular oxygen in aerobic organisms and nitrates and nitrites in anaerobic organisms. The mechanism of the reduction of these acceptors is apparently a one-electron mechanism (see Ref. 182 for oxygen).

Most of the available data [180] indicate that systems involving cytochromes function as one-electron transfer agents, although other possibilities can be pictured. For example, it was recently shown that the ferrogem–ferrigem electrode reaction is a two-electron process [186]. [This reference does not mention the stated reaction. (Ed. of Translation)].

Flavin and quinone-containing enzymes, on the other hand, take part in both one-electron and two-electron reactions. Under ordinary conditions, for example, flavins are apparently reduced by a hydride-ion mechanism under the influence of NAD-$H_2$, [22,53,54,181,184,185] and dihydrolipoic acid [22]. The dependence of the hydride-ion and hydrogen-atom mechanisms for the reduction of quinones on the reaction conditions has been discussed [186].

From the reduced nicotinamide coenzymes NAD-$H_2$ and NADP-$H_2$, hydrogen is transferred chiefly by a hydride-ion mechanism to many substrates, including flavins and quinones [53,54,181,187].

This fact is of importance in the explanation of the high rates of electron transfer in redox chains involving dihydropyridine and flavin enzymes. It may be assumed that in the catalytic chains the process is separated into stages differing in their chemical mechanisms—at one end of the chain, hydride ion is transferred from the substrate to the nicotinamide coenzyme, and at the other end, one-electron reduction of the acceptor takes place. Between the two ends of the chain there are systems containing flavin and quinone coenzymes capable of being reduced by a hydride-ion mechanism and oxidised with transfer of a hydrogen atom or an electron [53,54].

The separation of the process into stages with different chemical mechanisms not only leads to an increase in the

rate of electron transfer as a result of observation of the principle of equivalent exchange by charges, but also ensures specificity of the reduction process relative to substrates which tend to undergo definite types of interaction.

## IV. CATALYTIC ASPECTS OF ELECTRON TRANSFER

The conclusions reached in the previous sections are extremely useful in the search for catalysts for electron transfer reactions. We shall illustrate this for the examples already mentioned in the present review.

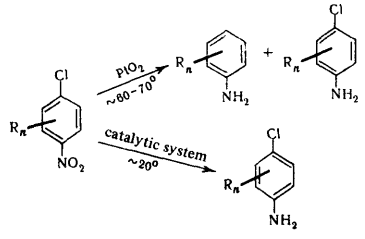
The rates of reactions of hydrogen transfer from reducing agents chiefly of the hydride type to probable one-electron acceptors, according to Shaffer's principle, should be increased by compounds capable of acting as one- and two-electron oxidising agents and reducing agents. In enzymatic catalysis, coenzymes with quinone and isoalloxazine structures, and also vitamin $B_{12}$, are compounds of this type.

For example, if dihydropyridine compounds, which are predominantly hydride ion donors [19,187-201] and whose reducing power is no less than that of molecular hydrogen [202], are used, the range of compounds reduced by NAD-$H_2$ and its models is greatly extended, and the rates of hydrogen transfer are increased in the presence of flavins, quinones, and similar dyes as catalysts [1,2,59-61]. Molecular oxygen [59], the stable radical of 2,2,6,6-tetramethylpiperidone-4 N-oxide [1,2], nitro- and nitroso-compounds [60,61], nitramine [61], N-bromosuccinimide [61], the acetylacetonato-compounds of $Co^{III}$, $Fe^{III}$, $Mo^{VI}$, and $V^{V}$, and also cyclopentadienyltitanium dichloride and cyclopentadienylvanadium dichloride [61]. The results obtained made it possible to apply the same principles of searching for organic catalysts with the isoalloxazine and quinone structures to the reaction of transfer of hydrogen from metal hydrides [59,61,63], organoelemental hydrides [203], formamidinesulphinic acid [62], dianions (organic and inorganic), [62] etc.

The next step in the use of the analogies with enzymes in catalysis is the development of catalytic systems which are more effective than the individual components [3,61,64-66,68,69]. Thus by taking account of the ability of the dihydropyridine ring to form $\pi$-complexes with various $\pi$-acceptors, it has been possible to find catalytic systems including $\pi$-acceptors and catalyst–transfer agents and having a higher efficiency in reaction (4) than the individual components of the system [69]. Published work [69] indicates that the mechanism of action of these catalytic systems apparently involves the formation of a $\pi$-complex between the reducing agent (1,4-dihydropyridine or cyclohexa-1,4-diene) and a $\pi$-acceptor (tetracyanoethylene, tetracyanoquinodimethane, 1,3,5-trinitrobenzene, etc.), in which there is a change in the ability of the reducing agent to act as a hydride ion and hydrogen atom (electron) donor.

Other effective catalytic systems for reaction (4), consisting of a catalyst–transfer agent and a metal ion, increase the rate of reduction of 2,2,6,6-tetramethylpiperidone-4 N-oxide and oxygen, possibly as a result of the ability of the semiquinones to form complexes with metal ions [68].

Catalytic hydrogenation systems, in the presence of which there is a marked change in both the rate and the specificity of hydrogenation [9,64-66,203,204], are of considerable interest. Catalytic systems of the first type consist of ordinary hydrogenation catalysts (heterogeneous or homogeneous) and catalyst–transfer agents, which can include quinones [3,66] and dimethylglyoximato-complexes of cobalt [64,65] and rhodium [203]. These catalytic systems are many times more effective in the hydrogenation of nitro-, nitroso-, azo-, azoxy, and hydrazo-compounds, compared with ordinary catalysts. In the hydrogenation of various halogenonitrobenzenes in the presence of, for example, the $PtO_2$–sodium anthraquinone-2-sulphonate catalytic system, the rate of reduction of the nitro-group increases, and the dehalogenation is completely suppressed, since the hydrogenation takes place at room temperature, and in the presence of a transfer agent there is a decrease in the duration of contact between the substrate and the heterogeneous catalyst [205]:




Other catalytic hydrogenation systems, instead of catalyst–transfer agents, contain activating substrates as a result of the formation of various complexes [204,206]. On this basis, selective catalytic systems have been developed for the hydrogenation of unsaturated ketones, acrolein, and cinnamaldehyde.

These results lead to the following conclusions.

1. In a number of instances it is possible to obtain effective catalysts for various reactions on the basis of an analysis of the characteristic features of the structure and mechanism of action of enzymes.
2. For the rational selection of catalysts for a given process, it is necessary to take account of the thermodynamic characteristics of the catalyst and the structural correspondence between the reagents and the components of the catalytic systems in the limiting stage of the process.
3. The use of catalyst–transfer agents in redox reactions is extremely promising for carrying out various chemical processes at a high rate with high specificity under mild conditions.

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