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Author's Review

Metalloporphyrins. The Nature of Ligand Bonding and the Mechanism of Replacements†

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The imidazole ring is an essential component of many biological systems (hemoglobin and myoglobin, nucleic acids, vitamin B_{12}, cytochromes, metalloenzymes, *etc.*). The nature of the bond between imidazole-nitrogen and the metal is therefore of biological interest. Imidazole is an electron-donating ligand in both σ and π sense, much more electron donating than the majority of nitrogen heterocycles. As ligands, most imidazoles are good σ donors and moderate π donors. They can also function as π acceptors if the imidazole ring has one or more electron-withdrawing substituents. Our recent study of bonding modes of pyridine and imidazole type ligands in the transition state of a Co^{III}(protoporphyrin IX) model complex enabled us to conclude that stabilization of the reaction transition state is more sensitive to the change in the strength of π bonding than in that of σ bonding. This observation is important for some metallo-enzymatic reactions. Mechanisms of replacements in porphyrin and in corrin rings are discussed.

INTRODUCTION

The imidazole ring is an essential component of many biological systems: in proteins as a part of the side chain of the amino acid histidine (hemoglobin and myoglobin), in nucleic acids as a part of the purine ring adenine and

† In memory of the late Professor Stanko Borčić.

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guanine, in cytochromes, in vitamin B_{12} coenzyme as benzimidazole, in metalloenzymes, as *e.g.* in carbonic anhydrase, in microperoxidase-8 (a heme octapeptide which catalyses the reduction of H_2O_2 making possible the oxidation of substrates not in direct vicinity of the active site).

The nature of the bond between iron and the imidazole-nitrogen of proximal histidine in hemoglobin has been extensively studied. Detailed elucidation of the way in which four hemoglobin subunit interactions give rise both to the cooperativity in O_2 binding and the so called Bohr effect (increase of oxygen-binding ability of hemoglobin at lower pH) was provided by John C. Kendrew (elucidation of the structure of myoglobin, 1958) and Max Perutz (structure of hemoglobin, 1960). Kendrew and Perutz shared the 1962 Nobel prize in chemistry. Complete analysis of their achievements is far too complex to be reviewed here, except to recall that the changes in the coordination sphere of the iron play a crucial role in the oxygenation of hemoglobin and the oxygen transfer to the cell and into the cell (myoglobin). This role is now understood and considered a great success of coordination chemistry. It is known that deoxyhemoglobin contains iron(II) in a high-spin state[1,2] with two electrons in the e_g orbitals. The iron bonding radius is too large to fit into the equatorial plane of the four nitrogen atoms of the protoporphyrin IX and, therefore, lies about 0.7 Å above this plane. Thus, the iron is pentacoordinated and square pyramidal, the imidazole-nitrogen atom from proximal histidine lying in the apex. When an O_2 molecule is bound in the opposite axial position, the iron atom goes into a low-spin state. The radius of the iron decreases and fits into the porphyrin plane. The lowering of iron into the equatorial plane causes movements of the attached imidazole-nitrogen of histidine and of the entire helical section, *i.e.* of all amine acid residues attached to it. These shifts are transmitted to other three subunits of hemoglobin, promoting the total oxygenation process.

It is interesting to mention that the porphyrin complexes of iron have been found in excrements of reptiles, about a hundred and fifty million years old, suggesting that the oxygen transfer mechanism in living beings did not essentially change during this enormously long period of time.

Besides the changes in the electronic structure of iron, the change in the bond structure between metal and imidazole-nitrogen of proximal histidine is also important. *E.g.* the pK_a of histidine-146 in deoxyhemoglobin is substantially increased by the presence of asparat-94 because the negative charge on asparat-oxygen facilitates the protonation of histidine-146.[3] The increase of pK_a of a ligand might change the ratio of σ/π bonds between this ligand and the metal. That such changes do occur, with substancial differences in reaction dynamics, was proved recently on model replacement reactions involving [Co^{III}(protoporphyrin IX dimethyl ester)(methoxo)(methanol)]*, where methanol ligand was replaced by various amine ligands of pyridine- and imidazole-type.[4]

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* [Dimethyl-3,7,12,17-tetramethyl-8,13-divinylporphyrin-2,18-dipropanoato(2-)]-(methanol)(methoxo)cobalt(III).

IMIDAZOLE BONDING MODES

Imidazole is an electron-donating ligand in both σ and π sense, much more electron donating than the majority of other nitrogen heterocycles.[5] As ligands, most imidazoles are good σ donors and moderate π donors.[6] Recently, the 2-aldehyde-substituted imidazole, 2-CHOimH, was shown to be a strong π-acceptor group with a π-acceptor power comparable to that of pyrazine.[7,8]

In all the mentioned biological systems, imidazoles function in a variety of roles, *e.g.* as a proton donor and/or acceptor site for hydrogen bonding, as a specific base or a nucleophilic catalyst, or as a site for metal ion coordination.[9–13] The imidazole moiety of histidyl residues in a large number of metalloproteins constitutes all or part of the binding sites of various transition-metal ions such as Mn^{2+}, Fe^{2+}, Fe^{3+}, Cu^{+}, Cu^{2+}, and Zn^{2+}.[12–14] It is known that 1-methylimidazole has a strong affinity for Mg^{2+}.[15–18] It has been suggested that Mg^{2+} coordinates to *N*-methylhistidine found in muscle myosin.[19,20] Asher *et al.*[5] pointed out that evaluation of the π-bonding ability of imidazole is important for understanding the effect of imidazole on the physicochemical properties of hemoproteins and how these properties might be »fine tuned« by changes in Fe-imidazole bond lengths and imidazole orientation, or by hydrogen bonding. The authors[5] also claim that structural features of *catena*-$[(H_2O)_2 \cdot (1\text{-}CH_3im)_2Mg(\mu CN)\text{-}Fe^{III}(CN)_4(1\text{-}CH_3im)] \cdot H_2O$ strongly indicate π bonding between 1-CH_3im and iron.

COMPARISION OF THE BONDING MODES OF IMIDAZOLE AND PYRIDINE

Imidazole is a considerably poorer π acceptor than pyridine.[21] There are cases where imidazole π donation is or is not important. For example $[(NH_3)_5Co(5\text{-}CH_3\text{-}imH)]^{3+}$ is a case where π donation is not important.[22,23] Co(III), a low spin d^6 ion, has no empty π orbitals at low energy and cannot be an effective π acceptor. Unlike Co(III), low spin Fe(III) and Ru(III) can act to accept π-electron density from a donor atom.[22] In contrast to the good π-donor properties of imidazole, pyridine is a much weaker π donor, because pyridine does not have a high energy HOMO as does imidazole.[21] The π acceptor properties of pyridine are moderate because its LUMO is not as low in energy as, *e.g.* that of pyrazine, known as a good π acceptor.[24] Since Co(III) has no empty π orbitals at low energy and cannot be an effective π acceptor it can be concluded that the modes of bonding of entering ligands into Co^{III}(porphyrin)-complexes are limited to σ bonding and cobalt to ligand π bonding only. This is the reason why we have systematically studied the nature of bonding of imidazole and pyridine type entering ligands of a model complex, cobalt(III)(protoporphyrin IX dimethyl ester)(methoxo)(methanol).[4,25] Methoxo-methanol complex was choosen because methoxo ligand is strongly bonded to cobalt while methanol ligand is weakly bonded and can be easily replaced by amine ligands in a dissociative manner.

REPLACEMENTS IN Co(III) PORPHYRINS

Several ligands can be easily coordinated in the axial position of Co(III) porphyrins in a variety of aprotic and mixed protic-aprotic solvents.[26] On the other hand, binding of amine ligands in the sixth position of Co(II) porphyrins is very unfavourable[27] because cobalt(II), a d^7 system, does not fit into the equatorial plane determined by four porphyrin nitrogen atoms, as already discussed in the introduction section for iron(II) (protoporphyrin IX). For example the binding of amine ligands in the sixth axial position of Co(II) porphyrins in toluene takes place at high ligand concentrations only, (*e.g.*, with piperidine a 10^5-fold excess over complex concentration is required); with ligands coordinating less strongly than piperidine, there is practically no binding to the sixth position at room temperature.[27]

In alcoholic solutions, in the presence of molecular oxygen, and in the presence of various amine ligands (L), the oxidation of cobalt(II) protoporphyrin IX dimethyl ester, [$Co^{II}P$], proceeds readily[28,29] by way of the reaction intermediate [$Co^{II}P(L)(O_2)$], the involvement of which has been widely recognized.[4,30–32] Even in the absence of amine ligands, [$Co^{II}P$] in methanol undergoes oxidation yielding mainly [$Co^{III}P(CH_3O)(CH_3OH)$] at a rate 10^2–10^3 times smaller than that with amine ligands.[33,34]

It should be stressed that the solutions of [$Co^{II}P$] in aprotic, non-coordinating solvents (*e.g.* chloroform, methylene chloride, benzene) in the presence of air are stable and can be used as stock solutions.[28] On the other hand, the alcoholic solutions of [$Co^{II}P$] are stable only in the absence of oxygen. In the presence of air, spectral changes indicate that the coordinated methanol acts as a weak electron donor, promoting electron transfer from cobalt to molecular oxygen. The spectral changes and the second-harmonic e.s.r. spectra indicate the following reaction stages:[34]

$$[Co^{II}P(CH_3OH)] + O_2 \longrightarrow [Co^{II}P(CH_3OH)(O_2)] \quad (1)$$

$$[Co^{II}P(CH_3OH)(O_2)] + CH_3OH \longrightarrow [Co^{II}P(CH_3OH)(O_2H)^+] + CH_3O^- \quad (2)$$

$$[Co^{II}P(CH_3OH)(O_2H)^+] + CH_3OH \longrightarrow [Co^{III}P(CH_3OH)_2]^+ + HO_2^{\cdot} \quad (3)$$

$$\uparrow\downarrow$$

$$[Co^{III}P(CH_3O)(CH_3OH)] + H^+ \quad (4)$$

If no acid or alkali is extra added to the methanolic solutions the methoxomethanol species widely predominates. Stage (2) of the above reaction scheme reveals the importance of protons of the protic solvent in the oxidation of cobalt(II) and the elimination of superoxide radical $HO_2^{\cdot}$. The methanolic solutions of [$Co^{III}P(CH_3O)(CH_3OH)$] can be also prepared by disol-

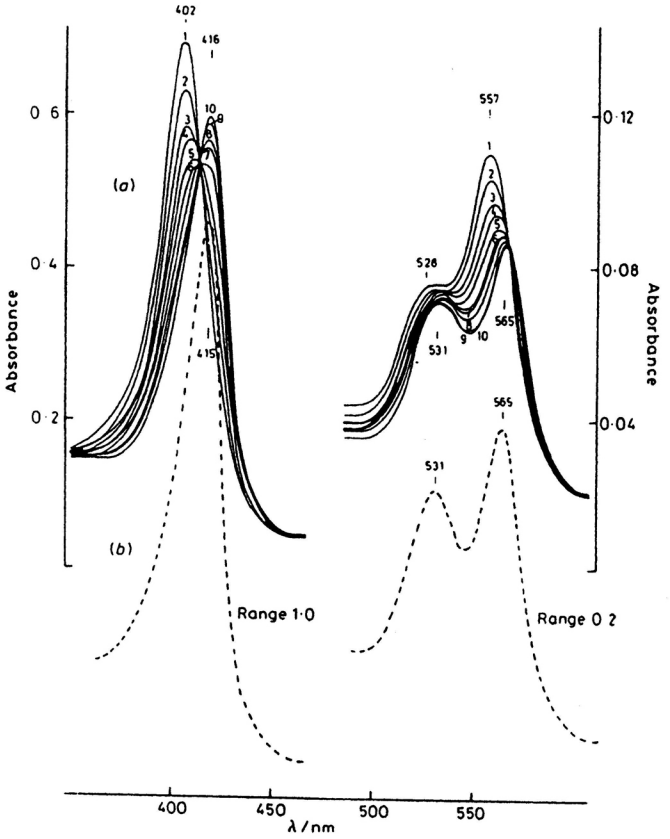

Figure 1. (a) Spectral changes of a solution (5×10^{-6} mol dm^{-3}) of [$Co^{II}P$] in methanol (φ = 3% of chloroform, in air) yielding [$Co^{III}P(MeO)(MeOH)$] (thickened line 10). (b) Spectrum of a solution of [$Co^{III}P(Cl)$] in methanol; upon dissolution the complex releases its chloride yielding [$Co^{III}P(MeO)(MeOH)$] (from Ref. 34).

ving [$Co^{III}P(Cl)$] (dark violet-red crystals) in methanol. Upon dissolution the complex releases its chloride practically instantaneously and equilibrates[34] as shown by equation (4), where the species [$Co^{III}P(CH_3O)(CH_3OH)$] predominates, as already said. The spectra of [$Co^{III}P(CH_3O)(CH_3OH)$] prepared either from [$Co^{II}P$] in methanol in the presence of O_2 or from [$Co^{III}P(Cl)$] in methanol are identical. Therefore, the solutions of the methoxo-methanol complex can be prepared in either of these two ways. Figure 1 shows the spectrum of [$Co^{II}P$] in methanol and the spectral changes due to the formation of the reaction product. It can be seen that the spectrum of this reaction product is identical with the spectrum of the solution of [$Co^{III}P(Cl)$] in methanol.

EVIDENCE FOR A D-MECHANISM IN THE SUBSTITUTION OF METHANOL IN [Co^{III}P(MeO)(MeOH)] BY PYRIDINE LIGANDS IN SOLVENT METHANOL

Distinction between D and I_d mechanisms in polar coordinating solvents is difficult. The most throughly investigated substitutions in this respect are the displacements of H_2O by L in $[Fe(CN)_5(H_2O)]^{3-}$ and other complex cyanides but the mechanism is still a matter of debate.[35–40] For several years substitution of X by L in $Co^{III}(CN)_5X$ was considered to occur *via* a D-mechanism, but later on an I_d mechanism was proposed[41] for various ligands L.

Replacement of MeOH by L in [Co^{III}P(MeO)(MeOH)] in methanol is one of the rare cases involving a D-mechanism. Arguments that the replacement of MeOH by pyridine ligands in methanol follows a D-mechanism (S_N1 limiting mechanism) were put forward some years ago,[33,34] being, in principle, the same as those arguments offered by Heim and Wilmarth[42] already in 1962 for replacement of H_2O in $[Co(CN)_5(OH_2)]^{2-}$ by N_3^- in water. They observed a tendency toward rate saturation when plotting k_{obs} *vs.* azide concentration. Later on, their results were revised, and a linear dependence for k_{obs} *vs.* azide concentration was established.[43] Therefore, it could not be determined whether a D or I_d mechanism was operating. Our results[33,34] prove the existence of penta-coordinated Co^{III}P(MeO) intermediate in methanol which lives long enough to discriminate between entering ligands, as shown in Table I.

It can be seen that the limiting rates are the same (57.8 s^{-1}) for all three entering ligands (4CN-py, py, 4Me-py), but the observed rate constants for a particular entering ligand differ (D-mechanism). The competition ratios k_2/k_{-1} for entering ligands L, 4CN-py, py, and 4Me-py, were 6800, 3700, and 2800, respectively, where k_2 is the rate constant of the reaction of the intermediate [Co^{III}P(MeO)] with L, and k_{-1} is the rate of reentry of MeOH into the intermediate.[34] High values of competition ratios are to be expected because the amine ligands are more reactive than methanol. On the other hand, the order of reactivity of the amine ligands is puzzling. One might expect that the most basic amine ligands would react at the highest rate but the case is just the opposite. Figure 2 shows that there is a linear dependence of the competition ratios logarithm on the pK_a of the conjugate acids of the entering amine ligands, but with a negative slope.

The Soret peak of the methoxo-methanol complex is at 415 nm (ε *ca.* 6.5 $\times 10^4$ dm^3 mol^{-1} cm^{-1} in methanol at 25 °C). The kinetics were measured at 417 nm, where the differences in absorption are the largest. Replacements of the MeOH and MeO^- ligands proceed consecutively in that order. The difference in the rates of the two replacements is large enough to permit independent determination of the first step.[34] Since k_{-1} has the same value in replacements with all three amine ligands, the plot in Figure 2 represents a linear free energy relationship. We drew the conclusion[25] that methoxide

TABLE I

Rates of replacements of CH_3OH (k_{obs}^{I}/s^{-1}) in [$Co^{III}P(CH_3O)(CH_3OH)$] with py, 4CN-py, and 4Me-py in methanol[a] (from Ref. 34)

10^4[L]	Entering ligand (L)		
mol dm^{-3}	4CN-py	py	4Me-py
1	3.47[b]	2.86	1.0
	0.15[c]	0.15	0.05
	5[d]	5	5
5	6.93	3.85	3.85
	0.35	0.2	0.2
	4	4	5
10	17.3	8.6	6.93
	0.8	0.4	0.3
	4	3	5
20	34.7	18.2	10.7
	1.6	0.7	0.6
	5	3	4
30		30.0	
		1.5	
		5	
40	53.3	38.5	
	3	2	
	3	5	
50		46.2	27.7
		3	1.8
		4	3
60	**57.8**[e]		
	4		
	4		
80	**57.8**	**57.8**	
	3.0	3.0	
	6	5	
100		**57.8**	49.3
		3.2	3
		4	4
500			**57.8**
			4
			4
1000			**57.8**
			4
			5

[a] Concentration of [$Co^{III}P(CH_3O)(CH_3OH)$] = 5×10^{-6} mol dm^{-3}; kinetics were followed by the stopped-flow technique at 430 nm; temperature 25 ± 0.05 °C. Results quoted as follows: [b] mean first-oreder reaction rate constant; [c] standard error of the mean; [d] number of kinetic runs; [e] bold figures represent limiting rates.

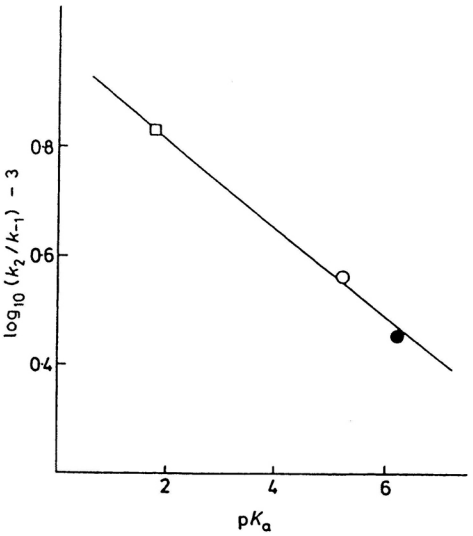

Figure 2. Dependence of log (rate ratio) on entering ligand basicity for reactions of intermediate [$Co^{III}P(MeO)$] with amine ligands (k_2) and methanol (k_{-1}). Reaction [$Co^{III}P(MeO)(MeOH)$] + L → [$Co^{III}P(MeO)(L)$] + MeOH; methanol solvent; complex concentration 5×10^{-6} mol dm^{-3}; λ = 430 nm; temperature 25 ± 0.05 °C. L = 4CN-py (□), py (o), 4Me-py (•) (from Ref. 34).

in the [$Co^{III}P(MeO)$] intermediate strongly increases the electron density at the *trans*-axial position, which favours the entry of the least basic amine ligand. In addition, the »soft« character of the cobalt porphyrin complex may make π back-bonding a more important interaction than might otherwise be the case with a metal(III)-ligand bond.[44]

Regarding the mechanism of replacement of CH_3O^- by L in [$Co^{III}P(CH_3O)(L)$], which is an about 50 times slower process than the replacement of CH_3OH, and must be carried out at increased entering ligand concentration, it has been pointed out[34] that a bimolecular mechanism can be excluded. If the replacements were bimolecular, the rates (slopes of the straight lines, Figure 3) would exhibit a much stronger dependence upon the nature of the entering ligand. The replacement of methoxide by L in a D [S_N1(lim)] mechanism, as well as in an I_d mechanism, *via* short-lived solvent-containing intermediate, should exhibit limiting rates. Therefore, these two mechanisms cannot operate. The authors explain[34] the linearity in Figure 3: (a) by assuming that CH_3O^- is replaced by L in an I_d mechanism with no solvent-containing intermediate; (b) by assuming that the replacement of CH_3OH by L takes place in the conjugate acid, [$Co^{III}P(L)(CH_3OH)$]$^+$, of the methoxo-complex. In this case, the conjugate acid is assumed to be formed in a fast proton transfer pre-equilibrium. This replacement can give a linear

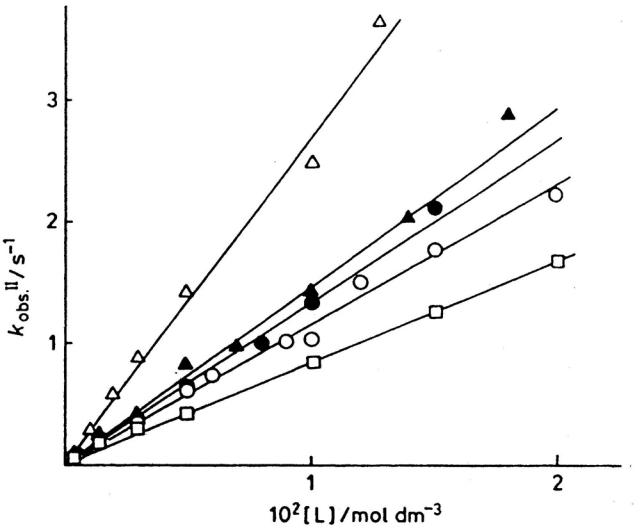

Figure 3. Dependence of k_{obs}^{II} on [L] for the reaction $[Co^{III}P(MeO)(L)] + L \rightarrow [Co^{III}P(L)_2]^+ + MeOH$. Complex (prepared from $[Co^{II}P]$) concentration *ca.* 5×10^{-6} mol dm^{-3}; L = 4CN-py (□), py (o), 4Me-py (•), nicotinamide (▲), $4NH_2$-py (Δ); methanol solvent; λ = 430 nm; temperature 25 ± 0.05 °C; stopped-flow technique (from Ref. 34).

dependence when either a D or an I_d mechanism is operative. The authors[34] prefer assumption (b). They have pointed out that several factors might influence the rates of replacements in Figure 3: L in the starting complex is different in all five cases and therefore the rates of dissociation of CH_3OH should be somewhat different; the rates of the reverse reactions should also differ, as well as the rates of reactions of the potential intermediate with L, either $[Co^{III}P(L)]^+$ in the case of a D mechanism, or $[Co^{III}P(L)(CH_3OH]^+$ in the case of an I_d mechanism. The directing axial ligand, which is a better electron donor, will promote a faster release of the ligand methanol. The authors have also pointed out[34] that the nature of the axial L might also influence the equilibrium concentration of the conjugate acid.They have also stressed that, in the replacement of methoxide by L, the magnitude of the slopes of the straight lines for $4NH_2$-py, 4Me-py, py, and 4CN-py, respectively, are in the order of their electron-donating ability, as normally expected for a dissociative type mechanism. It could be concluded that only the methoxide directing ligand causes the unexpected kinetic behaviour because of its extreme basicity and excellent electron donating ability in absolute methanol. Thus, the larger the pK_a of the entering ligand L, the smaller is the rate of its entry (Figure 2). The exceptional methoxide electron donation appears to promote cobalt to ligand π back-bonding, favoured by entering amine ligands of smaller basicity (smaller pK_a), *i.e.* smaller ability for donation. This observation will be further elaborated in the section to folow.

MECHANISM OF OCTAHEDRAL SUBSTITUTIONS ON TRANSITION METAL COMPLEXES

It is well established that substitution reactions of octahedral complexes occur by a predominantly bond-breaking mechanism, but the details vary from one case to another. In some cases a S_N1(lim) (or D) mechanism[45] is claimed to operate, forming a five coordinated intermediate, which lives long enough to discriminate between the entering ligands. In other cases a dissociative-interchange (or I_d)[45] mechanism operates, *i.e.* a dissociative type of exchange of the positions between particles in the first and second coordination spheres. For example, it has been postulated that induced aquations of $[Co(NH_3)_5(O_2CNH_2)]^{2+}$ by nitrous acid[46,47] and of $[Co(NH_3)_5X]^{2+}$ ($X = Cl^-$, Br^-, I^-) by Hg^{2+} proceed through a common five-coordinated intermediate[48,49], $[Co(NH_3)]_5^{3+}$. On the other hand, a spontaneus aquation of the $[Co(NH_3)_5Cl]^{2+}$ ion should proceed by an I_d mechanism.[50]An I_d interchange of leaving and incoming ligands has been also postulated for the Hg^{2+}-assisted removal of Cl^- from $[Co(NH_3)_5Cl]^{2+}$ in aqueous solutions of $NaNO_3$, $NaHSO_4$, H_3PO_4 and CH_3CO_2H and in three water + nonaqueous solvent mixtures.[51a] This supported an earlier observation that the assisted aquation of $[Co(NH_3)_5Cl]^{2+}$ by Hg^{2+} in sulphate media proceeds by paths involving Hg^{2+}, $HgSO_4$, $Hg(SO_4)_2^{2-}$ with intermediates having approximately 0.15 and 30% efficiencies, respectively, for conversion to $[Co(NH_3)_5SO_4]^+$, which are independent of solvent concentration.[51b] Similarly, it has been observed[51c] that the Hg^{2+}-assisted aquation of $[Co(NH_3)_5Cl]^{2+}$ in nitrate media proceeds by paths involving Hg^{2+} and $HgNO_3^+$ with intermediates having approximately 2 and 98% efficiencies, respectively, for conversion to $[Co(NH_3)_5(NO_3)]^{2+}$, independent of nitrate concentration. To avoid complications of ion-pairing anionic $[Co(CN)_5(OH_2)]^{2-}$ has been used[42,52–54] and it has been claimed that replacements of water by azide or thiocyanate ions occur by the D mechanism.

Aquations of *trans*-$Co(en)_2Cl^{2+}$ and of *trans*-$Co(en)_2(NO_2)Cl^+$ (en = ethylene diamine) proceed by a bond-breaking mechanism. The aquations have been studied in a range of binary mixed solvents, including methanol, ethanol, dioxan, and acetone-water content.[55] Both complexes aquated completely in water-rich mixtures and incompletely in solutions containing a higher percentage of organic components. The logarithms of rate constants correlated linearly with the Grünwald-Winstein solvent Y values, with slopes of $m = 0.32$ for the dichloro- and $m = 0.09$ for the chloronitro-complex. The lower susceptibility of the chloronitro-complex to solvent ionizing power indicates that the remaining bonding to the leaving chloride in the transition state is larger than in the dichloro-complex. It has been previously suggested that, in the aquation of the chloronitro-complex ion, the leaving chloride does not completely dissociate before the entering water molecule starts to associate. The term »solvent assisted dissociation« has been coined to de-

scribe this situation.[56] Alternatively, it could be claimed that the aquations of both dichloro- and chloronitro-complexes are I_d processes, where »accidental bimolecularity« resulted in different bond strenghts of the incoming water molecule to the central metal atom in the complex transition states.

There is often no sharp distinction between the D and I_d mechanisms in the octahedral replacements discussed. The extent of discrimination of a potential five-coordinate intermediate for entering reagents varies considerably with the nature of this intermediate. Whereas, *e.g.*, in $Fe(CN)_5X + Y^-$ the discrimination between reagents is mainly a function of the electrical charge of Y, the intermediates $Co(CN)_5^{2-}$ and $Co(NH_3)_4SO_3$ discriminate between reagents showing no marked correlation with charge.[57]

It is well known that the variations in reactivity of the iron centre in heme proteins are determined primarily by the axial ligands, the most common of which is imidazole (imH) from »proximal« histidine residue. We have already mentioned that the best known example of reactivity modulation is the trigger mechanism for hemoglobin cooperativity,[1] in which movement of the iron atom toward the porphyrin plane is restrained by the imidazole ring orientation.[58] Another way the proximal histidine can influence heme reactivity is *via* hydrogen bonding or deprotonation of the imidazole N-H proton. As the level of the hydrogen-bonding to a certain base increases, the donor ability of the imidazole imine nitrogen also increases, resulting in a stronger Fe-N bond and more electron density on the iron.[59] It is known that better coordination to the metal increases the acidity of the imidazole N-H proton by *ca.* 4 pK_a units in metmyoglobin.[60,61] Resonance Raman and NMR studies[62–65] of horseradish and turnip peroxidases suggest that the proximal histidine is strongly bonded or even deprotonated. X-ray structural and NMR data indicate similar results for cytochrome *c* peroxidase.[66,67] In hemoglobin and myoglobin, the hydrogen bonding is relatively weak.[62,64,67] It has been stressed[59] that variations in the proximal hydrogen-bond strength influence the thermodynamics and kinetics of ligand binding.

Fleischer *et al.*[68] followed the kinetics of the reaction between cobalt(III) and iron(III) hematoporphyrin with the anions thiocyanate and cyanide using the stopped-flow technique. Their kinetic data fit a reaction mechanism scheme that involves a dissociative mechanism with a five-coordinate intermediate. They have also observed that Co(III) hematoporphyrin is very labile with respect to substitution reactions as compared with the usual inert behaviour of the Co(III) complexes.

Difficulties in distinguishing between a limiting dissociative (D) and a dissociative interchange mechanism (I_d) have been encountered by Marques *et al.*,[69] who studied the kinetics of the reaction of aquacobalamin (vitamin B_{12a}) with azide anion and hydrazoic acid producing azidocobalamin. They followed the replacement rates by stopped-flow spectrophotometry, and by measuring the volume of activation for the reaction of aquacobalamin with azide from the pressure response of the rate constant. They concluded that the data obtained cannot be used to distinguish between the two possible

mechanistic pathways. Some other authors[70–72] also stressed that their results may be interpreted by either the D or I_d mechanism. On the other hand, some workers have favoured a limiting dissociative (D) mechanism in which the unimolecular dissociation of H_2O from the coordination sphere of Co(III) is rate limiting.[73–77] Other workers have favoured an interchange mechanism (I_d) with participation of the incoming ligand in the transition state.[78,79] Recently, Marques *et al.* have found[80] that the pseudo-first-order rate constants for the replacement of the H_2O in aquahydroxocobamide by azide, *N*-methylimidazole, pyridine and cyanide show a clear tendency to rate saturation. The saturation effects prove that all reactions proceed *via* a dissociative activation pathway. Furthermore, their observation that the saturating rate constant (and its activation parameters $\Delta H^{\neq}$ and $\Delta S^{\neq}$) depends on the identity of entering ligand L indicates that L participates in the transition state. This allowed them to conclude that the mechanism of replacement of H_2O in aquahydroxocobamide should be identified as a dissociative interchange (I_d). Further support for this conclusion was presented in a subsequent paper,[81] where the anionic ligands I^-, $S_2O_3^{2-}$, NO_2^-, SCN^- and N_3^- replaced the coordinated water. That the replacement of H_2O in aquacobalamin (vitamin B_{12a}) is an I_d process has been recently claimed[82] (the authors corrected their earlier claim[77] that a D-mechanism is operative). The entering ligands replacing water were thiourea and substituted thiourea. They observed that the volumes of activation of both the forward and reverse reactions have values between +6 and +10 $cm^3\ mol^{-1}$ and are accompanied by positive values for the entropy of activation.

It could be concluded that, at least in metalloporphyrin type systems, the replacements are most likely to follow the Id mechanism. The D mechanism is met when the »orienting« ligand (terminology used by C. K. Ingold)[83] is an excellent electron donor, as is the case with methoxide »orienting« ligand in methanol solution.[25,34] If the D-mechanism is operative, one expects to observe an equal limiting rate for all entering ligands, but the individual rates at which various ligands reach the limiting (saturation) rate should vary, indicating that the pentacoordinate intermediate lives long enough to descriminate between entering ligands. On the other hand, if the saturating rate constants depend on the identity of L, this indicates that incoming L participates in the transition state, and the mechanism could be identified as a dissociative interchange.

NATURE OF THE BONDING OF AMINE LIGANDS TO COBALT(III)

[Co^{III}(protoporphyrin IX dimethyl ester)(CH_3O)(CH_3OH)] is very suitable for studying the nature of bonding of amine ligands replacing the CH_3OH ligand. Replacements of CH_3OH by amine ligands L was measured spectrophotometrically at 417 nm, using stopped-flow technique.[4] Reactions half-

times vary approximately between 0.03 and 200 seconds (at 25 °C).[4] Replacements of the CH_3OH and CH_3O^- ligands proceed consecutively in that order. The difference in the rates of the two replacements is large enough to permit independent determination of the first step. The reactions follow the D [S_N1(lim)] mechanism.[33,34,84] The observed rate constant (k_{obs}) is given by the equation (5)

$$k_{obs} = k_1k_2[L]/(k_{-1}[CH_3OH] + k_2[L]) \quad (5)$$

where k_1 and k_{-1} are rate constants of dissociation and association of ligand CH_3OH, respectively, and k_2 is the rate constant of the reaction of the intermediate [$Co^{III}P(CH_3O)$] with L. Since the concentrations of L were small and equal (0.002 mol dm^{-3}), and the concentration of CH_3OH was large (CH_3OH is the solvent), it follows

$$k_{obs} = k_1k_2[L]/k_{-1}[CH_3OH] \quad (6)$$

and equation (7) must hold

$$k_{obs}{}^{L'}/k_{obs}{}^{L''} = k_2{}^{L'}/k_2{}^{L''} \quad (7)$$

Equation (5) can be modified into equation (8)

$$1/k_{obs} = (k_{-1}[CH_3OH]/k_1k_2) \cdot 1/[L] + 1/k_1 \quad (8)$$

from which the ratios k_2/k_{-1} were determined by the least-squares method, using a computer programme.[4]

The dependence of $\ln(k_2/k_{-1})$ on increased pK_a values of pyridine type entering ligands shows a minimum at a pK_a of about 5. The plot of $\ln(k_2/k_{-1})$ *vs.* pK_a of imidazole type entering ligands shows that between pK_a = 6.5–8 the rates are only slightly dependent on the basicity of L. As already pointed out with pyridine and imidazole entering ligands and their derivatives, for orbital energy reasons, we have to consider ligands σ bonding, and Co(III) → ligand π bonding only.

Since electron withdrawing ligands will promote π bonding, while electron donating ligands favour σ bonding, stabilization of the transition state between the reaction intermediate [$Co^{III}P(CH_3O)$] and the entering ligand L should have its minimum at a certain pK_a of LH^+, as indeed observed.[4] It can be inferred that the Co(III) → ligand π bonding in the transition state is more important (higher rates) than ligand σ bonding. Such an observation has recently been made for the ground state of the low-spin [(tetramethylporphynato) iron(III)L_2], where L is a pyridine type ligand of various σ-basicity.[85]

As early as 1984, we found[28] that the [$Co^{III}P(CH_3O)$] intermediate favours the entry of the least basic amine ligand, not the most basic, as commonly observed, which we elaborated in subsequent papers.[4,25,33,34] The observation was explained by the fact that the methoxide group, being a very strong electron donor, increases the electron density in the *trans* axial position of the [$Co^{III}P(CH_3O)$] intermediate, which favours the entry of the least basic amine ligand.

With imidazole entering ligands, there is no maximum rate as with pyridine type ligands,[4] showing that σ versus π bonding abilities of pyridines and imidazoles are different.

Recently, equilibrium constants K for the substitution of coordinated H_2O in the iron(III)-porphyrin microperoxidase-8 by various azoles have been determined[86] in 20% aqueous MeOH and a linear dependence was found of log K on pK_a of LH^+. The authors have pointed out that important factors which determine the preference of iron(III) porphyrins for imidazole (as histidine) over pyridine and amines are: »group specific factors« > basicity > π bonding. The equilibrium constant K for the substitution of coordinated H_2O in the cobalt(III) corrinoid-aquacyanocobinamide (vitamin B_{12}) by various amines and six-membered heterocycles in aqueous solution, determined by the same authors,[87] has a special relevance to our work. In their experiments, the CN^- ligand is very firmly held and can be considered as inert (at least in the dark), while the H_2O ligand is kinetically very labile. Their reaction took place in aqueous solution and is dissociative in nature (I_d-type).[81] Analogously, in our [$Co^{III}P(CH_3O)(CH_3OH)$] replacements, methoxide is firmly held while the CH_3OH ligand is kinetically labile. The solvent is methanol, and the mechanism is also dissociative (D-type).[33] Of course, the chelate is different and, what we consider most important, the »orienting« ligand *trans* to the leaving ligand is different: in our case, this is methoxide, one of the excellent electron donors, as already pointed out, while in the mentioned vitamin B_{12} replacements the »orienting« ligand is cyanide, one of the strong electron withdrawing ligands. Thus, replacements in vitamin B_{12} show the linear free energy relationship $\log K = a \cdot pK_a + b$, while in our replacements the dominant trend is: the smaller the pK_a, the larger is the k_{obs}.

It should be mentioned that high rates of CH_3OH replacements, attributed to strong π bonding in the reaction transition state, are related to negative entropies of activation, $\Delta S^{\neq}$, (increased »order« due to π bonding and solvent association).

It can be concluded that, besides all the mentioned factors that direct the metal → ligand bonding, such as α-effect, group specific factors, basicity of L and π bonding,[86] there can be a dominant influence of the orienting ligand *trans* to the leaving ligand, as in the case of [$Co^{III}P(CH_3O)(CH_3OH)$] complex.

One might try to find an alternative explanation of the presented kinetic data in the supposition that the kinetics we followed are in fact related to the π-π interaction between the porphyrin ring and the entering ligand, *e.g.* pyridines. The idea of the π-π interactions in porphyrin systems was first put forward by Mohr and Scheler.[88] They observed that, in an alkaline aqueous solution (pH > 10) protohaemin forms a green coloured pyridine complex containing two ligands per haemin dimer. They also found that similar haemin complexes are formed by *N*-alkyl-pyridinium halides, the absorption spectra being nearly identical to those of the corresponding pyridine complexes, although there is no possibility of interaction with the positively charged haemin iron. Moreover, pyridinium cations developed a higher affinity towards haemin than the neutral pyridines. They attributed this behaviour to electronic attractions between the propionylic groups of porphyrin and the positively charged pyridinium salts. They also found that the substitution of pyridine in position 4 by a cyano group increased the affinity towards haemin. Marques, Byfield and Pratt[89] studied the coordination of ammonia, aniline and pyridine by the iron(III) porphyrin microperoxidase-8 (MP-8) and found that all these ligands bind through coordination to the metal replacing coordinated H_2O and not through the π-π interaction with the porphyrin ring. They found obvious similarities in the spectra between all three entering ligands which supported the conclusion. On the other hand, the adduct of MP-8 at pH = 12 with 1-methylpyridinium (which cannot act as a ligand) showed a totally different spectrum, suggesting some formation of a π-π adduct at this high pH. The same authors also stressed that the adduct formation should be promoted by the presence of a strong donor ligand on the Fe^{III}. Therefore, one might claim that a π-π adduct formation might be an alternative explanation for our observation that the ligands of low basicity can yield high rates of MeOH replacements due to the metal → ligand π bonding. We shall prove in the following section that this supposition is wrong.

It was pointed out more than twenty years ago[90] that the ingression by L into the transition state of replacements in cobalt corrinoids may be influenced by the nature of the »orienting« ligand Z. For example, as the donor power of Z increases, a five-coordinated ground state in which 5,6-dimethylbenzimidazole is displaced becomes progressively more favoured. In a series of CN-Co-Z complexes the stretching frequency of coordinated CN^- decreases.[91] Also the stability constants for L-Co-Z, where L = CN^-, N_3^-, pyridine, *N*-methylimidazole or 3-aminopropan-1-ol decrease.[92] From this literature survey, it can be concluded that the π-π adduct formation as an alternative explanation of our kinetic results has no support indeed. The orginal observation by Mohr and Scheler[88] relates only to the alkaline aqueous solution (pH > 10) of protohaemin. As already mentioned, they attributed the π-π interaction to electrostatic attraction between the propionylic groups of porphyrin and the positively charged pyridinium ion. In our case, the

propionylic groups are blocked in the form of dimethyl esters. The above mentioned paper by Marques, Byfield and Pratt[89] shows that all the ligands investigated bind through coordination to the iron of MP-8 replacing coordinated H_2O. Only at pH = 12, with 1-methylpyridinium, which cannot bind to iron, they report a green π-π adduct formation, with a Soret band at 394 nm, *i.e.* with a totally different spectrum. They concluded that in the pH region studied, pyridine and aniline both act as ligands to the Fe^{III} in MP-8, though the formation of some π-π adduct cannot be entirely excluded.

Formation of the π-π adduct should be an associative process, while we clearly measured the kinetics of reactions (9) and (10). Reaction (9) is a dissociative process

$$[Co^{III}P(MeO)(MeOH)] + L = [Co^{III}P(MeO)(L)] + MeOH \quad (9)$$

$$[Co^{III}P(MeO)(L)] + L = [Co^{III}P(L)_2]^+ + MeO^- \quad (10)$$

of the D [S_N1(lim)] type: the pyridine type ligands (4CN-py, py, 4Me-py) gave ideal limiting rates (k_{obs} = 57.8 s^{-1} at 25 °C).[33,34] The π-π adduct formation could not produce such a kinetics.

The spectrum of [Co^{III}P(MeO)(MeOH)] has a Soret peak at 417 nm, and α and β peaks at 565 and 532 nm. All spectral changes due to replacements (Eqs. 9 and 10) are similar. There are slight changes of and peaks and a bathochromic shift of a Soret peak of about 4–10 nm, depending on the ligand nature.

It appears that the π-π adduct formation is limited to some special circumstances only, described in the papers mentioned.[88,89] Because of all the reasons quoted, we must reject the idea of the π-π adduct formation as an explanation of our kinetic results.

Regarding the basicity of the methoxide »orienting« ligand, we have already stressed that the alkoxides are excellent electron donors. We observed the following sequence: methoxide < isopropoxide < *sec*-butoxide. One should bear in mind that our replacements were preformed in absolute methanol. In pure liquid, methanol, ethanol and other simple alcohols are weaker acids than when dissolved in an aqueous solution.[93] The pK_a for methanol as a pure liquid is approximately 17 (K_{MeOH} = $[CH_3OH_2^+][CH_3O^-]$ = 1.2 × 10^{-17} M^2). Thus, methoxide in methanol is a stronger base than hydroxide in water,[94] and obviously an excellent electron donor, much better than hydroxide in aqueous solution. The smaller K_{MeOH}, as compared with K_w, comes largely from the lower dielectric constant of methanol (32.6 : 78.5). Greater energy is required to separate methoxide from proton (or from a positive metal centre) in methanol than for analogous separation of hydroxide in aqueous solution. But the relative acidities and basicities of alcohols are also important.[94]

M. Tobe and his coworkers studied the influence of L on the rate of acid hydrolisis of $Co^{III}(en)_2LCl^+$ yielding $Co^{III}(en)_2LH_2O^{2+}$. They arranged groups L in an order of decreasing tendency to donate electrons to cobalt and increasing tendency to accept electrons.[95] The hydroxide ion is considered the strongest electron donor among the 21 ligands listed. The electron donating ability of CN^- is placed much below that of OH^-. On the other hand, there are reports[80,91] that CN^- is a better donor than OH^-. Of course, there is no unique ligand electron donor scale, since electron donating ability depends also on the electron accepting system. Besides, it is difficult to discern the bonding modes of ligands, which can ligand-to-metal σ bond, and metal-to-ligand and ligand-to-metal π bond.

SOME MODELS OF METALLOENZYMES

In recent years there has been a great deal of research devoted to metalloenzymes.[96–98] For instance, carbonic anhydrase (CA) is an efficient catalyst for converting CO_2 into hydrogen carbonate and *vice versa*.[99] In the active site of CA, the zinc ion is coordinated to three imidazole groups (belonging to histidine residues and a water molecule,[99] Figure 4). The classical work of Riepe and Wang[100] led to an understanding of the CA activity. At physiological pHs CO_2 is converted to the bicarbonate ion HCO_3^- by attack of zinc bound OH^- on CO_2. The water molecule bound to zinc is more acidic than water in aqueous solutions of free (fully hydrated) Zn^{II} ions.[98] The pK_a decreases from *ca.* 9 in aqueous solutions to *ca.* 7 in CA. Deprotonation of this water molecule gives an OH^- group that acts as a nucleophile towards CO_2, converting it to HCO_3^-. A reaction so simple as the conversion of $CO_2 + H_2O$ to H_2CO_3 needs, in biological systems, an enzymatic catalysis and the CA makes it one of the fastest enzymatic reactions known. Every enzyme molecule can convert 10^5 molecules of CO_2 to HCO_3^- in a second, which enables an effective transfer of CO_2 from the tissue into blood.

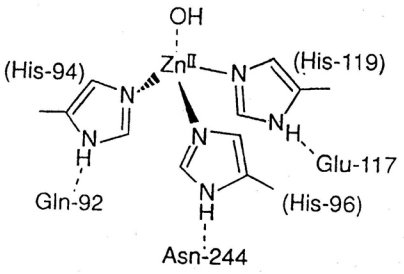

Figure 4. Carbonic anhydrase is an efficient catalyst in red blood cells for converting CO_2 into hydrogen carbonate ($k_{cat} \approx 10^7$ mol dm^{-3} s^{-1} at 25 °C). Every enzyme molecule can convert 10^5 molecules of CO_2 per second making the reaction one of the fastest known.

The observation we made in studying the σ *vs.* π bond ratio upon changing the pK_a of imidazole type ligands suggests that the increased acidity of water in carbonic anhydrase is a consequence of the Zn → imidazole nitrogens π-bonding. The result is a reduced electron density on the metal, and increased bonded water acidity.

An interesting approach to modelling CA is that by Valeur and Bardez,[98] based on reverse micelles. The reverse micelles are, in principle, formed in apolar solvents from surfactants whose polar heads occupy the core of the structure while hydrocarbon chains extend outward into the surrounding solvent. One common anionic surfactant that forms reverse micelles is sodium bis(2-ethylhexyl) sulphosuccionate, (AOT). Valeur and Bardez replaced the sodium counterions in AOT with zinc ions and then complexed the zinc with imidazole. They found that the lower the water content of the surfactant, the more stable was the complex. Under certain circumstances, the complexed zinc was tetra-coordinated. The imidazole ring, they found, was hydrogen bonded through either the SO_3^- or ester carbonyl groups. By adding a little water, they could perform hydrolysis reactions, in principle by a mechanism similar to that of carbonic anhydrase.

It appears that the bridging imidazole molecules play an important role in these catalytic hydrolyses by the ability of changing the σ *vs.* π bonding modes to the metal complex centre, depending on the pK_a of the substituted imidazole moiety.

SEVERAL STABLE PORPHYRIN ISOMERS HAVE BEEN RECENTLY SYNTHESIZED

In 1929, Hans Fischer, Professor at the High Technical School in Munich, completed the synthesis of hemin (Nobel prize 1930). In 1986 Emanuel Vogel of the Institute for Organic Chemistry of the University of Cologne, Germany, synthesized porphycene, the first nonnatural porphin isomer.[101] Prior to this, nobody had succeeded in forming a stable macrocycle other than porphin from four pyrroles and four sp^2-hybridized carbon atoms. It is not entirely clear why nature chose porphyrin, as opposed to one of its isomers.[102]

After the synthesis of porphycene, several other porphin type isomers have been synthesized, as pointed out by S. Borman.[103] The previous idea that isomers of porphin would be unstable and not available, to nature proved now to be wrong. Due to the fact that several porphin isomers are available a great deal of research is being devoted to the study of the effects of geometry, core size steric strain, metal coordination and macrocycle deformation of porphyrin-like compounds in order to find the answer – why only porphyrin in nature.

A STRING OF PORPHYRINS MIGHT FUNCTION AS A MOLECULAR PHOTONIC WIRE

J. S. Lindsey and his co-worker R. W. Wagner[104] prepared a string of porphyrins serving as a molecular photonic wire. According to R. Dagani,[105] Lindseys inspiration came from light-harvesting complexes containing chlorophyll that plants use for photosynthesis. These complexes absorb sunlight and quickly convey it to reaction centres, where it is converted into chemical energy. In order to mimic the process, Lindsey designed a simple linear array of five porphyrin-based pigments that absorb and emit light in solution. At one end of the »wire« is a boron-dipyrromethene dye (a porphyrin fragment) that absorbs blue-green light. The resulting excited state is transmitted through a string of three zinc porphyrins to a fluorescent metal-free porphyrin, which emits a photon of red light. The signal transmission efficiency is 76%. The »molecular photonic wire« shows some features similar to a molecular-scale fibre-optic device. One day it might be used to transmit signals between molecular-scale devices engaged in information processing.

CONCLUSION

It is well known that the changes in the coordination sphere of the iron play a crucial role in the oxygenation of hemoglobin and oxygen transfer to the cell, and into the cell (myoglobin). Besides the changes in the electronic structure of iron, the change in the bond structure between metal and imidazole-nitrogen is also important, as we have shown on the cobalt(III) protoporphyrin IX (methoxo)(methanol) model complex. The methoxo-methanol complex was chosen because methoxo ligand is strongly bonded to cobalt while methanol ligand is weakly bonded and can be easily replaced by amine ligands in a dissociative manner. The MeO^- »orienting« ligand, an excellent electron donor, favours entry of the least basic L, and not the most basic as usually observed. The plot of ln k_{obs} *vs.* pK_a of pyridine and its derivatives exhibits a minimum rate at pK_a of about 5. The »V« diagram is explained as being due to a change in the electronic structure of the transition state, from predominantly π bonding (descending branch) to the predominantly σ bonding (ascending branch). Imidazoles show similar trends but their rates level off for pK_a values above 7. The free energy of activation for the reaction between [Co^{III}(protoporphyrin IX dimethyl ester)(MeO)] and the entering ligand L is more sensitive to the change in the strength of the π bond than to that of the σ bond. This is manifested in the steeper negative slope of the descending branch of the »V« diagram, as compared with the slope of the ascending branch of the »V«.

The distinction between D [S_N1(lim)] or I_d (interchange dissociative) mechanisms in polar coordinating solvents is difficult. A survey of this problem is given. It is well established that substitution reactions of octahedral

complexes occur by a predominantly bond-breaking mechanism. In most cases, an I_d mechanism operates, *i.e.* a dissociative type of exchange of positions between particles in the first and the second coordination sphere. If an I_d mechanism operates the tendency for rate saturation should be expected, which is indicative of a dissociative activation patway. In addition, the observed saturation rate constants (and the activation parameters $\Delta H^{\neq}$ and $\Delta S^{\neq}$) should depend on the identity of the entering ligand, showing that L participates in the transition state. On the other hand, if a D mechanism operates, the observed saturation rates should be equal for all entering ligands L, but the individual rates with which various ligands reach the limiting (saturation) rate should vary, indicating that the pentacoordinated intermediate lives long enough as to discriminate between the entering ligands. Examples for both D and I_d mechanisms in porphyrin replacements reactions are given.

The π-π interaction between the porphyrin ring and the entering ligands, *e.g.* pyridines, is discussed. It appears that the π-π adduct formation is limited to some special circumstances (alkaline aqueous solutions of pH > 10), and it cannot explain the kinetic results of replacements of MeOH and MeO^- in [Co(III)P(MeO)(MeOH)] in methanol solvent.

In recent years, there has been a great deal of research devoted to models of metalloenzymes. Examples are given.

A recent observation that a string of porphyrins might function as a molecular photonic wire is described.

Considering that several stable porphyrin isomers have been recently synthesized, it remains unanswered why only the porphyrin structure is found in nature.

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SAŽETAK

Metaloporfirini. Narav vezivanja liganda i mehanizam zamjene

Smiljko Ašperger i Biserka Cetina-Čižmek

Imidazolski prsten bitna je komponenta mnogih bioloških sistema: u proteinima kao dio pokrajnog lanca aminokiseline histidina (hemoglobin i mioglobin), u nukleinskim kiselinama kao dio purinskog prstena adenina i gvanina, u citokromima, u vitaminu B_{12} koenzimu kao benzimidazol, u metaloenzimima, npr. karboanhidraza, mikro-peroksidaza-8, i drugo.

Imidazol je kao ligand donor σ i π elektrona, i to mnogo bolji elektron-donor od većine dušikovih heterocikla.

Većina imidazola su kao ligandi dobri σ-donori, a osrednji π-donori. No oni mogu biti i π-akceptori, ako imidazolski prsten ima supstituente koji upijaju elektrone. Proučavali smo načine vezivanja liganada tipa piridina i imidazola u prijelaznom stanju modelnog spoja Co^{III}protoporfirin IX dimetilester(metokso)(metanol). Mogli smo zaključiti da je stabilizacija reakcijskog prijelaznog stanja, između međuprodukta nastalog disocijacijom labilno vezanog metanola i ulaznih liganada piridinskog i imidazolskog niza, osjetljivija na promjene jakosti π-vezivanja metal → ligand, nego jakosti σ-vezivanja. To ima značenja u tumačenju reakcijskog mehanizma nekih metaloenzimskih reakcija. Diskutira se o mehanizmima supstitucije u porfirinskom i korinskom prstenu, napose o razlikovanju D i I_d mehanizma.