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Enantioselective Effects in Coordination Compounds

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The present Review represents the first attempt to unify and systematise the numerous data on the development of enantioselective effects in the formation and chemical reactions of coordination compounds, as well as in their catalytic and adsorption properties. Enantioselectivity (thermodynamic or kinetic), while being a consequence of the chiral structure of the inner coordination sphere of the complex, may develop even in processes involving only the ligands of the outer coordination sphere. The present state of the chemistry of coordination compounds not only permits but even requires that enantioselective effects should be considered separately from all types of stereospecific effects. A list of 307 references is included.

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I. INTRODUCTION

During recent decades the stereochemistry of coordination compounds has been a field of intense research by chemists of the most diverse schools and specialisation. On it converge the interests of biochemists attempting to understand the role of metal ions in the steric peculiarities of the action of metal enzymes, inorganic chemists investigating the electronic structure of coordination compounds and the nature of the metal–ligand bond, investigators of macromolecular compounds studying the part played by catalysts in stereoselective and stereospecific polymerisation, and finally organic chemists using asymmetric induction in complexes to effect asymmetric syntheses.

II. REFINEMENT OF STEREOCHEMICAL TERMINOLOGY

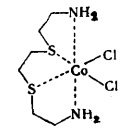
The variety of approaches to the stereochemistry of coordination compounds has led to ambiguity in the interpretation by different scientists of the same stereochemical terms. In many cases careless terminology makes an inadequate understanding of the stereochemical peculiarities of the processes investigated; moreover, it causes a substantial delay in the transition from a descriptive, qualitative study of these features to their accurate quantitative measurement.

The Reviewers consider that it is first necessary to delimit perfectly clearly the regions of application of the terms "selectivity" and "specificity": the former should be used for the characteristics of selection, of the choice of potential reactants present in the system; and the latter term to represent the specific direction of the reaction.

Processes should be termed *stereoselective* when a reactant species is able to select for reaction one of several stereoisomers of a second component. For example, we have a particular case of stereoselectivity—enantioselectivity—if the choice is made between two enantiomers. Such selection can be made, of course, only by a chiral reactant species. Thus we imply by *enantioselectivity* a difference between two molecules (or structures), which are optical enantiomers, in their interaction with a third chiral molecule (or structure).

The term *stereospecific* should be applied to processes leading to the preferential formation of one or more possible stereoisomers of the reaction product. For example, we have a particular case of stereospecificity—enantiospecificity—when a new asymmetric centre predominantly of one of two possible configurations appears in the reaction product. Asymmetry can be induced, of course, only when the initial compounds contain at least one chiral centre. Thus we shall understand by the *enantiospecificity* of a process the ability of chiral centres present in a system to dictate a certain configuration to newly formed chiral centres.

Among stereoselective processes, in the broad meaning of this term, we must include e.g. the selective reaction of boric acid (or acetone) only with those vicinal glycols whose hydroxy-groups are in the *cis*-position. An example of a stereospecific process is the exclusive formation of the symmetrical (±)-*cis*-complex of 3,6-dithiaoctane-1,8-diamine with cobalt(III)



although other stereoisomers of this complex are theoretically possible.

The stereochemical characteristics of reactions may be governed both by kinetic and by thermodynamic factors. Kinetic enantioselectivity, for example, is apparent in a difference in the rates of interaction of a chiral structure with enantiomers of a second reactant. Thermodynamic enantioselective effects are shown by differences in the stability or other properties of two labile diastereomeric adducts formed. Typical examples of kinetically and

thermodynamically enantioselective processes are respectively the difference in the rates of enzymic hydrolysis of the L- and D-isomers of amides of α-amino-acids and the difference in the adsorbability of these isomers on the surface of optically active quartz. The selective oxidation of D-isomers of amino-acids by D-amino-acid oxidase isolated from pigs' kidneys is an example of a kinetically enantioselective process leading to a decrease in the number of asymmetric centres in a system.

Enantiospecificity can by definition occur only in processes in which the number of chiral centres increases. For example, (+)-propylenediamine-*NNN'N'*-tetra-acetic acid interacts enantiospecifically with Co^{2+} ions to form the complex $(-)_{5461}$-[Co(+)-PDTA]$^{2-}$, in which the configuration of the asymmetric cobalt is unambiguous. Asymmetric syntheses are also the result of enantiospecific processes.

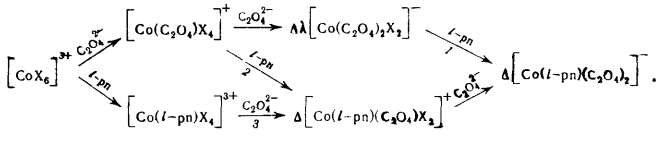
The delimitation of the concepts "selectivity" and "specificity" permits quantitative characterisation both of the selective ability of reactant species and of the directional nature of a process by use of the "degree of stereoselectivity α_{sel}" and the "degree of stereospecificity α_{sp}" respectively. The necessity of such discrimination is dictated by the fact that many processes exhibit both stereoselective and stereospecific effects, usually with different values of α_{sel} and α_{sp}.

Thus processes involving racemates and leading to an increase in the number of asymmetric centres in the system may be characterised by both enantioselectivity and enantiospecificity. In the reaction between racemic propylenediamine (*dl*-pn) and Co^{3+} ions in the presence of activated carbon, for example, Dwyer and his coworkers observed the formation of only four structures:

$$Co^{III} + dl\text{-pn} \begin{cases} \nearrow \Lambda(+)\,[Co(d\text{-pn})_3]^{3+} + \Delta(-)\,[Co(d\text{-pn})_3]^{3+} \\ \searrow \Delta(-)\,[Co(l\text{-pn})_3]^{3+} + \Lambda(+)\,[Co(l\text{-pn})_3]^{3+} \end{cases}$$
$$85\% \qquad 15\%$$

These data show that the degree of enantiospecificity of the process $\alpha_{sp} = (85 - 15)/(85 + 15) = 70\%$ is lower than the degree of enantioselectivity $\alpha_{sel} = 100\%$, since *d*-isomers of propylenediamine react only with those isomers of the complexes which already contain ligands of the same *d*-configuration, but form final tris-complexes of both Λ- and Δ-configurations.

It must be emphasised that knowledge of the reactants and the final reaction products alone may be insufficient for analysis of the steric aspects of the process. Thus the reaction of cobalt(III) with *l*-propylenediamine and oxalate ions leads to preferential formation of Δ-[$Co(C_2O_4)_2$*l*-pn]$^-$, which can be represented formally by the scheme



Only a knowledge of the reaction mechanism can indicate whether the final result is a consequence of enantioselective effects at stage *1* or of enantiospecific effects at stage *2* or *3*.

Previous reviewers of aspects of the stereochemistry of coordination compounds [1-7] have used the motley terminology of the original sources, and have not attempted to systematise the experimental results in conformity with the nature of stereochemical phenomena. The present Review is confined to a survey of enantioselective effects in coordination compounds. Enantiospecific aspects will be touched on only to the extent to which they appear in stereoselective processes.

III. ENANTIOSELECTIVITY IN COMPLEXES OF α-AMINO-ACIDS AND THEIR DERIVATIVES

Stereoselective and stereospecific effects in the equilibrium systems formed by kinetically labile complexes of copper, nickel, zinc, manganese, cobalt(II), aluminium, and iron with ions of alkali and alkaline-earth metals should be thermodynamic in nature. In non-equilibrium (reacting) systems of these complexes, however, the observed stereoselective and stereospecific effects would probably result from a combination of thermodynamic and kinetic contributions, as in the formation of kinetically inert complexes of cobalt(III), chromium(III), platinum-group metals, and several others.

1. Thermodynamic Effects

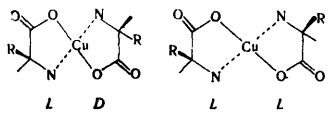
In contrast to tetrahedral and octahedral structures, the metal atom in square planar bis-complexes of copper with α-amino-acids (Aa) is not an independent centre of asymmetry. These complexes can therefore exhibit only enantioselective effects connected with the difference between the D- and L-isomers of the amino-acid in their interaction with an asymmetric structure such as the complex of the copper ion with one asymmetric amino-acid ligand. Enantioselectivity may thus occur at the stage of formation of the bis-complex. It should be apparent in a difference in thermodynamic stability between the optically active structure [$Cu(L\text{-}Aa)_2$] and the *meso*-structure [Cu(D-Aa)(L-Aa)] or in a difference in some properties of their solutions. Since the complexes are not stable diastereomers in solution, even a difference in their electronic spectra† must be ascribed to enantioselectivity, for a change in position of the energy levels of the *d*-orbitals of the copper ion indicates a difference in interaction between ligands within these two structures. Spectral differences may in principle be connected also with displacement of the *cis-trans* isomeric equilibrium, but bis-complexes of copper with bidentate α-amino-acids are assumed to have a *trans*-structure in dilute solutions [9-11].

It must be emphasised that the difference in properties between the crystalline complexes [$Cu(L\text{-}Aa)_2$] and [Cu(D-Aa)(L-Aa)]—including their solubilities—cannot be identified with the stereoselectivity of their formation. The properties of the solid phase are determined by the totality of other interactions, which, although characterised by exceptionally high stereoselectivity, are only indirectly related to the processes involved in formation of the complexes.

A conformational examination of complexes of α-amino-acids led Corey and Bailar [12] to the conclusion that five-membered chelate rings formed by the ligand with the central metal ion have an almost planar structure. There is then hardly any interaction between two chelate rings

†The molar extinction of a racemate would in general differ from that of the optically active enantiomers in the region in which the latter exhibit circular dichroism [8]. In most cases, however, this difference is vanishingly small.

in a complex. Substituents R attached to α-carbon atoms of ligands in square planar bis-complexes are separated by considerable distances



L D *L L*

and are also unable to produce stereoselective effects. Later calculations of the conformation of five-membered amino-acid chelate rings have shown[13] considerable flexibility, absence of any one preferred puckered conformation, and insignificant interactions between two chelate rings. In fact, most of the experimental results obtained until recently supported this theoretical conclusion that stereoselectivity was absent in amino-acid complexes of copper.

The slight difference (2–3%) in molar extinction observed originally[14] between solutions of copper complexes of optically active and of racemic alanine (Ala) and phenylalanine (Phe) was disproved by the later investigations of Gillard and his coworkers, who showed[15,16] that the spectral characteristics of the D-alanine and L-alanine complexes were unaffected when their solutions were mixed in equal proportions, and that the pH dependence of the spectra of the L-alanine and DL-alanine complexes was the same, which suggests that the homogeneous and mixed complexes—[Cu(L-Ala)$_2$] and [Cu(D-Ala)(L-Ala)]—have the same stability (degree of formation).

The absence of enantioselective effects leads to a purely random distribution of ligands, in which the equilibrium concentrations of the bis-complex structures [M(D-Aa)$_2$], [M(D-Aa)(L-Aa)], and [M(L-Aa)$_2$] are in the proportions[17] 1 : 2 : 1, and those of the tris-complex structures [M(D-Aa)$_3$] [M(D-Aa)$_2$(L-Aa)], [M(D-Aa)(L-Aa)$_2$], and [M(L-Aa)$_3$] are[18] 1 : 3 : 3 : 1. In both cases the potentiometric titration curves of L- and DL-amino-acids in the presence of metal ions M coincide exactly.

Table 1. Formation constants for mono- and bis-complexes ($\lg\beta_1$ and $\lg\beta$) of metals with alanine ($pK_1 = 2.54 \pm 0.04$ and $pK_2 = 9.93 \pm 0.06$) and with phenylalanine ($pK_1 = 2.41 \pm 0.04$ and $pK_2 = 9.35 \pm 0.06$) in 0.37 M $NaNO_3$ at 20 ± 0.1 °C.

Ion	Configuration of ligand	Alanine		Phenylalanine	
		$\lg\beta_1$	$\lg\beta$	$\lg\beta_1$	$\lg\beta$
Cu^{2+}	*L*	8.16	14.98	7.93	15.10
	D	8.14	15.00	8.00	15.08
	DL	8.20	15.04	8.03	15.14
Ni^{2+}	*L*	5.23	9.91	5.23	9.72
	D	5.22	9.87	5.24	9.70
	DL	5.21	9.96	5.19	9.66
Cd^{2+}	*L*	4.09	7.40	3.90	6.73
	D	4.00	7.40	3.87	6.72
	DL	3.98	7.40	3.84	6.75
Pb^{2+}	*L*	4.20	9.34	4.02	8.86
	D	4.16	9.40	3.99	8.88
	DL	4.08	9.42	4.03	8.79
Zn^{2+}	*L*	4.63	~9	4.43	~8.5
	D	4.62	~9	4.43	~8.5
	DL	4.65	~9	4.41	~8.5

Simeon and Weber tried to detect enantioselectivity in the formation of the bis-complexes of alanine and phenylalanine with several metals[19], making a careful potentiometric titration of these systems with the use of D-, L-, and DL-amino-acids. The formation constant of the bis-complex ($\lg\beta$ in Table 1) was independent of the steric configuration of the ligands, within the limits of experimental error (±0.05 for copper and nickel, and ±0.10 for the remaining ions). This applies not only to the square planar complexes of copper but also to the more complicated structures formed by metal ions of coordination number exceeding 4.

Potentiometric titration did not reveal enantioselectivity in complexes of copper with alanine, valine (Val)[16,20], proline (Pro)[16], or leucine (Leu), nor in bis-complexes of nickel with alanine, valine, and leucine[20]. Study of the optical rotatory dispersion of bis-complexes of copper with several L-amino-acids and their mixed complexes with optically inactive ligands led to the conclusion[21] that steric interactions between the two ligands in the [Cu(L-Aa)$_2$] system are so small that the Cotton effect is almost unaffected. While reaching this conclusion, the authors do not comment on their earlier report[22,23] of some difference in the pH dependence of the electronic spectra of complexes with optically active and with racemic alanine, valine, and especially proline, indicating that the homogeneous structures are less stable than the *meso*-complex [Cu(D-Aa)(L-Aa)].

The long standing view[1-4] that enantioselectivity is absent from copper complexes with bidentate amino-acids was not inconsistent with the difference (within the limits of experimental error) between the stability constants of mixed copper complexes of L-proline with L- and D-valine ($\lg\beta = 16.89 \pm 0.09$ and 17.00 ± 0.20 respectively) calculated from the optical rotatory dispersion of the system[24]. Nor was this view disproved by some difference[25,26] in the electron spin resonance spectra of vitrified aqueous–methanolic solutions of copper complexes of L- and DL-alanine, -valine, -proline, and -serine (Ser), since there was no certainty that microcrystals of these complexes differing markedly in the e.s.r. properties were not formed when the solutions were cooled.

The first measurements of the stability of copper complexes of the terfunctional α-amino-acid–asparagine (Asp-NH_2)—potentiometric titration showed that the homogeneous structures—[Cu(D-As-NH_2)$_2$] and [Cu(L-Asp-NH_2)$_2$]—were more stable than the mixed complex [Cu(D-Asp-NH_2)(L-Asp-NH_2)], and that the quantities of the former in the equilibrium solution exceeded the concentration of the mixed complex fourfold[27]. However, more careful potentiometric measurements of the stability constants have shown that enantioselectivity is absent from the bis-complexes of copper with such terfunctional amino-acids as asparagine[28-30], aspartic acid (Asp), glutamine (Glu-NH_2), glutamic acid (Glu)[29,30], 2,3-diaminopropionic acid, and histidine (His)[20,31], as well as from mixed complexes[32] of histidine with threonine (Thr).

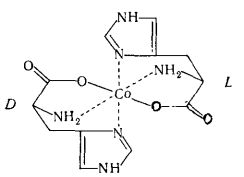
The presence of thermodynamic enantioselectivity in octahedral bis-complexes of cobalt(II) with terdentate histidine was first demonstrated in 1963 by McDonald and Phillips[33]. These workers observed, in the proton magnetic resonance spectra of solutions of the complex with DL-histidine, signals that were absent from solutions of the optically active complex, and they attributed the signals of the *meso*-complex [Co(D-His)(L-His)]. Study of the dependence of their intensity on the concentration ratio of D- and L-isomers of the ligand led to the calculated constant $K = 11.5$ for the equilibrium

$$[Co(L\text{-}Aa)_2] + [Co(D\text{-}Aa)_2] \rightleftharpoons 2[Co(L\text{-}Aa)(D\text{-}Aa)]$$

(in the absence of enantioselectivity $K = 4$[17]). Thus the mixed complex is formed preferentially in this system, its stability exceeding that of the homogeneous complex by 0.32 kcal mole^{-1}.[34] These results have been confirmed

by potentiometric titration[20,31,34]. Selectivity is still greater in complexes of histidine with nickel(II): the difference $\delta\Delta G^\circ$ in the Gibbs free energies of the individual structures reaches 0.49 kcal mole^{-1}.[34] The contents of the mixed structure in the complexes of DL-histidine with bivalent cobalt, nickel, zinc, cadmium, and copper are respectively 62%, 72%, 63%, 53%, and 50%,[31] corresponding to degrees of enantioselectivity of 24%, 44%, 26%, 6%, and 0. The high enantioselectivity observed with the nickel complexes is apparent also in their spectral properties: the absorption bands of the complex with L-histidine at 356 and 556 nm are rather wider and below the bands of the racemic complex, which moreover are somewhat displaced to longer wavelengths[31].

Enantioselectivity in octahedral histidine complexes is attributed[30,31,34] to the tendency of the bulky imidazole and similarly charged carboxylate donors to occupy *trans*-positions, which is possible only if the two histidine molecules have opposite configurations:



The degree of enantioselectivity then depends on the regularity of the octahedron and on the diameter of the central metal ion[30,31]. It is interesting that the rates of formation of $[MHis_2]$ complexes in which M = Ni, CoII, Zn are independent of the configuration of the ligands. The poorer stability of the structures $[M(D\text{-}His)_2]$ and $[M(L\text{-}His)_2]$ than of [M(D-His)(L-His)] is evident in higher rate constants of the reverse reaction (dissociation) for the homogeneous structures[35,36]. It is noteworthy that, in contrast to the situation existing in solution, the crystalline complexes of nickel and zinc with DL-histidine are constructed from the homogeneous structures $[M(D\text{-}His)_2] + [M(L\text{-}His)_2]$.

No stereoselectivity has been found in octahedral bis-complexes of terdentate 2,3-diaminopropionic acid with nickel[31], aspartic and glutamic acids with nickel and cobalt[29,30], and cysteine (CySH) with nickel and zinc[30,37]. On the other hand, Ritsma[30] has observed considerable intensification of enantioselective effects in histidine complexes on the introduction of alkyl substituents into the α-amino-group (Table 2). Benzyl- and dimethyl-histidine exhibit appreciable enantioselectivity even on coordination with copper, but the resulting complexes undoubtedly differ in structure from the square complexes of α-amino-acid type. Furthermore, Ritsma[30] finds that the optically active protonated complexes of copper with histidine are rather more stable, whereas at pH > 6 the *meso*-structure is apparently slightly more stable[32].

Barnes and Pettit studied the thermal effects accompanying the formation of copper complexes of alanine, valine, proline[38], and aspartic acid, copper and nickel complexes of glutamic acid and histidine, and also the zinc complex of histidine[38,39]. Enantioselective effects were observed only with histidine: differences between calculated enthalpies of formation of the individual *meso*-complex and the optically active complexes $\delta\Delta H^\circ$ were +0.67 ± 0.17, +0.57 ± 0.05, and −0.67 ± 0.17 kcal mole^{-1} with nickel, zinc, and copper respectively. Thus the enhanced stability of the symmetrical *meso*-complexes of nickel and zinc is mainly an enthalpy effect, as is suggested by the closeness of the values of $\delta\Delta H^\circ$ and $\delta\Delta G^\circ$

Table 2. Difference in Gibbs free energies $\delta\Delta G^\circ$ (in kcal mole^{-1}) of mixed and homogeneous structures—[M(D-Aa)(L-Aa)] and $[M(L\text{-}Aa)_2]$—from results of potentiometric titration with μ = 0.1 M at 25°C. Negative values indicate that the mixed structure is the less stable[30].

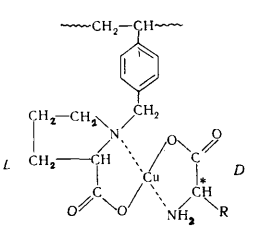
Amino-acid	Co^{II}	Ni^{II}	Cu^{II}	Zn^{II}
Histidine	+0.32	+0.49	0.0	+0.28
N-Methylhistidine	+0.69	+1.03	0.0	+0.49
N-Benzylhistidine	+0.28	+0.74	−0.25	<0.0
NN-Dimethylhistidine	+1.06	+1.62	+0.56	+1.20
N-*o*-Hydroxybenzylalanine	−0.71	−0.83	0.0	<0.0
Cysteine		0.0		~0.0
Penicillamine		−0.55		>0.0

(Table 2). With copper, on the other hand, complexes with ligands of the same configuration should be preferred. (This unexpected result was ascribed to the tendency of copper to form tetragonal *cis*-structures in which histidine is coordinated through the imidazole ring and the amino-group.) However, the considerable enthalpy effect is probably balanced by entropy factors.

Complexes of cobalt(II) with L- and with DL-histidine differ not only in thermodynamic stability but also in the rate constants of their reversible oxidation[40] by molecular oxygen to the structure $[CoHis_2]_2O_2$.

The presence of enantioselectivity in complexes of bifunctional amino-acids was first shown unambiguously by Davankov and Rogozhin[41,42], by using a new method—ligand-exchange chromatography[43]—for studying kinetically labile mixed complexes. If one ligand (stationary) is bound covalently to an insoluble polymeric support, chromatography of a mixture of mobile ligands on such a sorbent in the presence of complexing metal ions permits determination of the relative thermodynamic stabilities of all the mixed complexes whose formation involves the stationary ligand. The stability of these mixed complexes increases in the same sequence as the affinity of the mobile ligands for the sorbent. Racemic amino-acids were subjected to chromatography, in the presence of copper, nickel, or zinc ions, on sorbents having chiral amino-acid groups. These ions become centres for the formation of mixed sorption complexes of the stationary chiral ligands of the sorbent and the mobile ligands, i.e. molecules of the separable racemate. Thermodynamic enantioselective effects in the formation of these sorption complexes are responsible for the separation of the isomers of the racemate, which is transported by the mobile phase in a column of such sorbent.

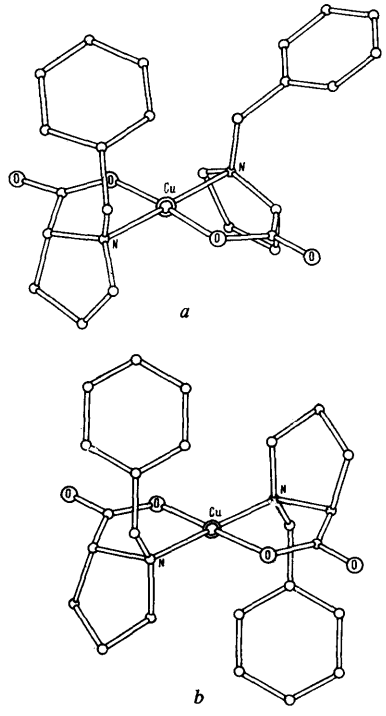
In the presence of copper ions, for example, a sorbent obtained by reaction between L-proline (or L-hydroxyproline) and a chloromethylated macrocellular styrene copolymer forms considerably more stable mixed complexes with D-than with L-amino-acids[44]:



If the mobile ligands are D- and L-proline, the difference in their free energies of sorption reaches $\delta\Delta G^\circ$ = 0.45 kcal

mole^{-1} (determined under static conditions)[45,46]. The simplicity and great sensitivity of ligand-exchange chromatography enabled thermodynamic enantioselectivity to be detected in many labile complexes of bi- and ter-dentate amino-acids, hydroxy-acids, amino-alcohols, and other compounds[47,48].

The presence of enantioselectivity in solutions of complexes of several bifunctional amino-acids with copper was then demonstrated also by classical methods. Davankov et al. first studied complexes of *N*-benzylproline as a model of the unit in the dissymetric sorbent used. Potentiometric titration indicated[49,50] that an equilibrium is established with *N*-benzyl-DL-proline in aqueous solution, in which the concentration of the *meso*-complex [Cu(*N*-$C_6H_5CH_2$-D-Pro)(*N*-$C_6H_5CH_2$-L-Pro)] exceeds that of each of the two homogeneous complexes by factors of 14 ± 4. This corresponds to a degree of enantioselectivity of complex formation α_{sel} = 75%, or $\delta\Delta G^\circ$ = 1.15 kcal mole^{-1}. The poorer stability of the homogeneous structure [Cu(*N*-$C_6H_5CH_2$-L-Pro)$_2$] is conclusively supported by spectrophotometric investigations and by polarimetric titration, the latter of which can also be used[50] to calculate α_{sel}. X-Ray examination of the complexes[51-54] suggests that the benzyl radicals tend to occupy apical positions in the coordination sphere of copper, which is possible (see diagram) for both ligands only if they differ in configuration[54].



Structures of the complexes: *a*) [(*N*-$C_6H_5CH_2$-L-Pro)$_2$Cu]; *b*) [(*N*-$C_6H_5CH_2$-D-Pro)(*N*-$C_6H_5CH_2$-L-Pro)Cu].

The enantioselectivity of formation of copper complexes of amino-acids is a consequence of unequal interaction between the two ligands in the structures [Cu(D-Aa)(L-Aa)] and [Cu(L-Aa)$_2$]. Such interaction can occur by direct contact between individual fragments of the ligands (as in the *N*-benzylproline complexes), through solvent molecules coordinated in axial positions, or finally through the solvent sheath (outer coordination sphere). Interligand interactions may lead to distortion of the chelate unit of the complex, which is clearly apparent in a difference between the electronic spectra of [Cu(L-Aa)$_2$] and [Cu(D-Aa)(L-Aa)], or distortion of the conformation of the ligands and purchasing of the five-membered chelate rings. If such distortions occur in the optically active complex [Cu(L-Aa)$_2$], they can easily be detected by comparing its optical rotatory dispersion or circular dichroism spectra with those of the mixed complex with glycine [Cu(L-Aa)Gly]. The intensity ratio of these spectra is exactly 0.5 (without displacement of the maxima) only in the absence of distortion in the [Cu(L-Aa)$_2$] structure. This method has been used to investigate complexes of alanine, valine, proline, and hydroxyproline (Hypro) containing various combinations of methyl and benzyl substituents in the amino-group[55]. Maximum interligand interactions (and hence stereoselective effects) are observed in complexes of amino-acids containing two substituents in the amino-group, e.g. in complexes of *N*-benzylproline, *N*-benzyl-*N*-methylalanine, and hydroxy-*N*-methylproline.

Transmission of interligand interactions through axially coordinated water molecules must be adduced e.g. to explain why the complex [Cu(*N*-$C_6H_5CH_2$-L-Pro)(L-Pro)] is less stable than [Cu(*N*-$C_6H_5CH_2$-L-Pro)(D-Pro)]. The value $\delta\Delta G^\circ$ = 0.9 ± 0.2 kcal mole^{-1} calculated for this system from the circular dichroism spectra[56,57] agrees satisfactorily with ligand-exchange sorption data[45].

Solvation of the complexes also has a very considerable influence on interligand interactions, until the sign of the enantioselective effect is reversed on passing from one solvent to another[58]. The first example of the successful study of the influence exerted on enantioselective effects by the structure of the outer coordination sphere may well be an investigation[59] of the e.s.r. spectra of the [Cu(*N*-$C_6H_5CH_2$Pro)$_2$] complexes in methanol and in a chloroform–toluene mixture.

The work of Davankov, Rogozhin, and Kurganov has shown that enantioselectivity is extremely widespread in the copper complexes of α-amino-acids, but only after thorough investigation by potentiometric and polarimetric titration, spectrophotometry, circular dichroism, etc. can the presence or absence of enantioselectivity in a particular system be stated with certainty. The most sensitive method, however, is ligand-exchange chromatography.

Bernauer et al.[60] used this method to show that the chiral complex of iron(III) with 2′-hydroxyethyl-D-propylenediaminetriacetic acid L-[Fe(D-HEPDTA)]$^-$ forms mixed complexes more readily with the D-isomers of acetyl and benzoyl derivatives of leucine, alanine, phenylalanine, and methionine (Met) than with their enantiomers ($\delta\Delta G^\circ$ falls in this sequence from 0.10 to 0.02 kcal mole^{-1}). In the reaction of the (–)- and (+)-isomers of α-methylbenzylamine with the copper, nickel, and zinc complexes of D(–)-propylenediaminetetraacetic acid $\delta\Delta G^\circ$ reaches 0.3 kcal mole^{-1} [61] (investigation of the same system by partition between water and heptane gives $\delta\Delta G^\circ \simeq 0.14$ kcal mole^{-1}). Thus enantioselectivity is revealed even with unidentate ligands, which probably replace one of the acetate groups in the complexes of the above multidentate ligands.

Angelici and his coworkers have made a series of studies on the enantioselectivity of complex formation by α-amino-acids whose amino-group contains substituents

tending to coordinate with a metal, e.g. the carboxymethyl (Cm) and pyrid-2-ylmethyl (Pc) groups. Potentiometric titration showed[62] that *N*-carboxymethyl-L-valine forms somewhat more stable mixed copper complexes with L-leucine, L-phenylalanine, L-alanine, L-serine, D-valine, and L-leucine ethyl ester than with their enantiomers. *N*-Carboxymethyl derivatives of L-isoleucine (Ileu), L-serine, *N*-benzyl-L-alanine, and *N*-benzyl-L-leucine also form mixed copper complexes preferentially[63] with the L-isomers of valine, leucine, and threonine. *N*-Carboxymethyl-L-aspartic and *N*-carboxymethyl-L-glutamic acids, on the other hand, show greater affinity for the D-isomers of amino-acids. The authors attempted to explain the observed effects by the *cis*-structure of the bisamino-acid complex of copper, in which the *N*-carboxymethyl group occupies an axial position[63]. However, X-ray examination has shown[64] that the carboxymethyl group in the complex $[Cu(N\text{-Cm-L-Val})(H_2O)_2]$ is situated in the main plane of coordination. It is equally difficult to explain the fact that *N*-pyrid-2'-ylmethyl-L-aspartic acid and its *N*-6'-methylpyrid-2'-ylmethyl analogue form more stable mixed copper (and nickel) complexes with the L-enantiomers of alanine, phenylalanine, tryptophan (Try), threonine, leucine, and valine[65]. The situation is somewhat clearer with the bis-complexes of nickel and cobalt(II) with the *N*-*o*-hydroxybenzylalanine, where the homogeneous structures are more stable (Table 2). All three donor atoms of this ligand are clearly located in the same plane [sic], but nevertheless Ritsma[30] is rightly cautious in interpreting interligand interactions in its complexes.

Enantioselective effects obviously result from the action of many factors, whose contributions are at present still difficult to assess. Only detailed and comprehensive investigation will enable enantioselectivity to be explained even in the simplest systems, e.g. the fact that with *N*-benzylvaline the homogeneous complex $[Cu(N\text{-}C_6H_5CH_2\text{-L-Val})_2]$ is the most stable[58], where as with *N*-benzyl-D-proline, in contrast, the *meso*-structure $[Cu(N\text{-}C_6H_5CH_2\text{-D-Pro}).(N\text{-}C_6H_5CH_2\text{-L-Pro})]$ is the more stable.

2. Kinetic Effects

In an interesting case of kinetic enantioselectivity reported by Hix and Jones[66] catalysis of the alkaline hydrolysis of a histidine ester by histidinatonickel(II) is preceded by formation of the mixed complex $[NiHisHisOCH_3]^+$. The overall rate of hydrolysis is 40% lower when histidine and its ester have the same configuration than when the ligands have opposite configurations. The bidentate ligand $HisOCH_3$ can add to the complex $[NiHis]^+$ in six different ways, but only in one case—with the ligands having opposite configurations—can the preferred *trans*-structure be formed with the ester group in a position favourable for coordination. Since thermodynamic enantioselectivity is not observed in a mixed complex, the differences in rates of hydrolysis result from coordination of the ester carbonyl. It is significant that enantioselectivity is absent if complexes of histidine with copper are used for catalysis[67,68]: the coordination number 4 of copper ions leaves no vacant positions for the coordination of ester groups.

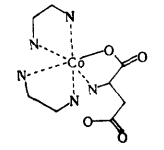
Blackburn and Jones[69-71] extended study of catalysis of the hydrolysis of amino-acid esters by complexes of nickel with amino-acids to another seventeen different systems, but only in one system $[NiTryHisOCH_3]^+$ was appreciable enantioselectivity found. Nevertheless, Angelici[62] observed that the complex $[Cu(N\text{-Cm-L-Val})]$ catalyses hydrolysis of the methyl esters of D-leucine and D-phenylalanine rather more strongly than that of the L-isomers. Similar though smaller effects were observed in catalysis by the copper complex of *N*-carboxymethyl-D-phenylglycine.

A difference (2–4-fold) has been observed in the rates of hydrolysis of the methyl esters of D- and L-phenylalanine in the presence of a copper complex of poly-L-lysine. The catalytic effect becomes stronger with increase in the molecular weight of the polymer. It is supposed[72,73] that at pH 7 hydrolysis is catalysed in a mixed complex, which is more easily formed with D-phenylalanine. Finally, there are indications[74] that the ethyl ester of L-phenylalanine is hydrolysed more rapidly in the presence of *trans*-$[CoCl_2(l\text{-pn})_2]Cl$ than in the presence of its enantiomer *trans*-$[CoCl_2(d\text{-pn})_2]Cl$. The mechanism of this process is quite complicated, and the stage at which stereoselective effects develop is difficult to assess.

In 1929 Shibata and Tsuchida[75] discovered that the laevorotatory complex $[CoClNH_3en_2]^{2+}$ accelerates selectively the oxidation of L-3',4'-dihydroxyphenylalanine (dopa). Although a subsequent check[76] on this report has not shown the presence of enantioselectivity, but has merely established a general catalytic effect by the complex independent of its configuration, the enantiomers of dopa are in fact oxidised at different rates in the presence of a mixed copper complex of protoporphyrin with L-histidine or with its cyclic dimer[77] and also in the presence of a copper complex of poly-L-lysine[78-80].

A special group of kinetically enantioselective processes are involved in the formation of inert complexes of cobalt(III) from compounds of which one is a racemate, while the other is optically active. Enantiospecificity is usually also observed in these processes. Unfortunately, most authors omit both a detailed analysis of the stereochemical features of these reactions and also the important experimental data (e.g. conversion and yield of product) required for much analysis.

The fact that the Λ-isomers of the complexes are the first to react when L-glutamic acid interacts with racemic $\Delta\Lambda$-$[CoCO_3en_2]ClO_4$[81] and with racemic $\Delta\Lambda$-$[Co(H_2O)_2en_2].(ClO_4)_3$[82] must be regarded as a case of kinetic enantioselectivity. The preferentially formed Λ-$[Co(L\text{-Glu})en_2].ClO_4$, furthermore, is sparingly soluble, and separates in optically pure form. Analogous enantioselectivity is observed when *d*-tartaric acid is used[81,82] instead of L-glutamic acid, but is absent when bidentate amino-acids[81,83] and lactic acid[81] are employed. Gillard and his coworkers[81,82,84] attributed this to three-point interaction of L-glutamic acid with the complex by formation of a hydrogen bond between the γ-carboxyl and an amino-group of ethylenediamine, which is possible only when the complex itself has the Λ-configuration:



However, X-ray examination has shown[83] that such a hydrogen bond is not formed, at least in the crystalline state.

Even the fact of kinetic enantioselectivity in the systems studied by Gillard has since been subjected to criticism[85,86]. The proportions of Λ- and Δ-complexes in the final equilibrium mixtures from the reactions of $\Delta\Lambda$-$[CoCO_3en_2]^+$ with L-glutamic and L-aspartic acids in the presence of

activated carbon were found to be 70 : 30 for $[Co(L\text{-}Glu)en_2]^+$ and 60 : 40 for $[Co(L\text{-}Asp)en_2]^+$. The observed effects are regarded [85] as thermodynamic in character. From a check on these results and study of the alkaline epimerisation of L-glutamic acid in the final complex it has been concluded [86] that no selective or specific effects occur in this system at all.

The absence of kinetic enantioselectivity in the interaction of racemic *cis*-bisethylenediaminecobalt(III) with optically active alanine [81-83], leucine, and phenylalanine [83] is fully consistent with the absence of enantiospecificity observed earlier [87] in the formation of a chiral configuration of cobalt on the reaction of symmetrical *trans*-$[CoCl_2en_2]Cl$ with the L-isomers of these amino-acids.

Among the 24 possible structures each containing 2 amino-acid residues which may result from the reaction of a hexanitrocobaltate(III) with DL-alanine, only the 4 complexes

$(+)_{589}[Co(L\text{-}Ala)_2(NO_2)_2]^-$ $(+)_{589}[Co(D\text{-}Ala)_2(NO_2)_2]^-$
$(-)_{589}[Co(L\text{-}Ala)_2(NO_2)_2]^-$ $(-)_{589}[Co(D\text{-}Ala)_2(NO_2)_2]^-$

are formed stereospecifically [88]. In the main coordination plane they contain two carboxylate anions and two nitro-groups in *cis*-positions [89]. Enantioselectivity is apparent in this system in the identical configuration of the two amino-acid residues in each structure. The enantiospecificity of complex formation is less marked: the two L-alanine molecules produce only slight predominance of the $(-)_{589}$-complex over the $(+)_{589}$-structure.

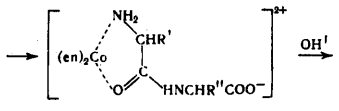
A very complicated mixture of complexes $[CoAla_{3-n}(L\text{-}Asp)_n]^{n-}$ ($n = 0$–3) is formed by the reaction of $[Co(CO_3)_3]^{3-}$ with L-aspartic acid and DL-alanine in the presence of activated carbon [90]. Here selective and specific effects should be examined separately for each group of structures. The mer-Λ-structures of the complexes $[CoAla(L\text{-}Asp)_2]^{2-}$ contain mainly L-alanine, but the fac-Δ-structures contain D-alanine. The analysis for a system containing L-proline and D- or L-aspartic acid is just as complicated [91].

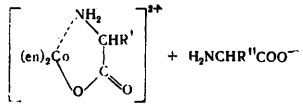
Contrary to expectation, enantioselectivity has not been found in the kinetically controlled reaction of L-proline with racemic β-$[CoOH(H_2O)trien]^{2+}$ or with its dichloro-analogue [92-94]: in both cases roughly equal quantities of Δ- and Λ-isomers of β_2-$[Co(L\text{-}Pro)trien]^{2+}$ are formed. X-Ray examination has shown [93,95] that steric interactions between ligands are in considerable measure eliminated by distortion of the angles of the coordination octahedron.

Nor have departures from a random distribution of complexes been observed in the reaction of *trans*-*NN'*-ethylenebisacetylacetoniminatodiaquocobalt(II) with DL-alanine, DL-valine, and DL-α-methylbenzylamine respectively [96]. In the final complexes two unidentate amino-acid ligands coordinated through the amino-groups occupy *trans*-positions in the coordination octahedron, and are unable to influence each other.

Nor is kinetic enantioselectivity observed in the reaction of the dipeptide L-leucylglycine with racemic $[CoOH(H_2O)en_2]^{2+}$. [97] If, on the other hand, an L-amino acid is a *C*-terminal group, as e.g. in glycyl-L-phenylalanine and glycyl-L-tyrosine, such a dipeptide reacts with the Δ-isomer of the complex twice as rapidly as with the Λ-enantiomer:

$$[Co(en)_2(H_2O)(OH)]^{2+} + H_2NCHR'CO{-}HNCHR''COO^- \longrightarrow$$





However, the dipeptide L-leucyl-L-tyrosine, which contains two L-amino-acids, reacts almost exclusively with the Λ-complex [97]. (It may be mentioned here that thermodynamic enantioselectivity has not been observed in the copper complex of glycylphenylalanine [98].)

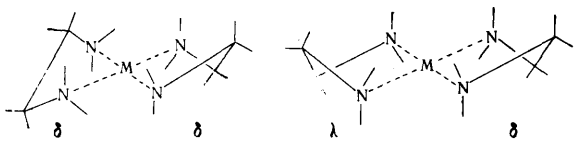
IV. COMPLEXES OF DIAMINES AND THEIR DERIVATIVES

Enantioselective effects were discovered considerably earlier in diamine complexes than in amino-acid complexes. In 1920 Smirnoff [99] detected only the two complexes Δ-$[Pt(l\text{-}pn)_3]^{3+}$ and Λ-$[Pt(d\text{-}pn)_3]^{3+}$ in the products of the reaction of platinum(IV) salts with *dl*-propylenediamine: i.e. the reaction occurred with complete enantioselectivity and enantiospecificity. Analogous situations were found in the formation of complexes of cobalt(III) with propylenediamine [100] and of cobalt(III) and rhodium(III) with cyclopentane-*trans*-1,2-diamine (cpn) [101]. The instability of complexes containing ligands differing in configuration is confirmed by their ease of disproportionation into homogeneous structures. For example, only Λ-$[Co(d\text{-}cpn)_3]^{3+}$ and Δ-$[Co(l\text{-}cpn)_3]^{3+}$ are formed by the action of *l*-cyclopentanediamine on Λ-$[CoCl_2(d\text{-}cpn)_2]^+$. [101,102] High selectivity is already observed at the stage of formation of the bis-complexes. Thus the oxidation of cobalt(II) in the presence of *dl*-cyclopentanediamine leads to the formation of *trans*- or *cis*-$[CoCl_2(d\text{-}cpn)_2]^+$ and $[CoCl_2(l\text{-}cpn)_2]^+$, but not that of $[CoCl_2(d\text{-}cpn)(l\text{-}cpn)]^+$. [101,103] The results of these investigations led Jaeger [104] to the conclusion that complexes of mixed structure are not in general stable, while the optical configuration of the metal atom is determined unambiguously by the configuration of the ligand.

However, the formation of diamine complexes does not always follow this rule strictly. Thus Werner [105] was able to obtain all eight theoretically possible isomers of $[Co(NO_2)_2enpn]^+$. Both possible isomers Δ- and Λ-$[Co(l\text{-}cpn)en_2]Cl_3$ are also formed by the action of *l*-cyclopentanediamine on ΔΛ-*cis*-$[CoCl_2en_2]Cl$, although only two of the four possible structures—Δ-$[Co(l\text{-}cpn)en_2]^{3+}$ and Λ-$[Co(d\text{-}cpn)en_2]^{3+}$—are formed enantioselectively by racemic *dl*-cyclopentanediamine [101,106]. Thus kinetic enantioselectivity, which undoubtedly occurs in the formation of octahedral tris-complexes with diamines, may remain unnoticed, as occurs in the first case, where the reaction conditions constrain *l*-cyclopentanediamine to react not only with Δ-$[CoCl_2en_2]^+$ but also with its Λ-enantiomer. Reaction of *d*-tartaric acid with both enantiomers of $[CoCO_3en_2]^+$ can be achieved in just the same way [107,108], although the Δ-isomer is the first to react [108], forming Δ-$[Co(d\text{-}tart)en_2]^+$. Both isomers of *dl*-tartaric acid can be made to react with Δ-$[CoCO_3(l\text{-}pn)_2]^+$, [109] whereas, when excess of tartaric acid is used, the complex reacts selectively with *d*-tartaric acid to form stable Δ-$[Co(d\text{-}tart)(l\text{-}pn)_2]^+$. [110] Its less stable diastereomer Δ-$[Co(l\text{-}tart)(l\text{-}pn)_2]^+$, being in contact with excess of the *dl*-acid, exchanges its acid ligand selectively for *d*-tartrate, so that the uncomplexed tartaric acid is considerably enriched with the *l*-enantiomer [110,111]. Similarly Δ-$[CoCO_3(l\text{-}pn)_2]^+$ prefers to exchange its carbonate ligand for the (−)-enantiomer of α-chloro- or α-bromo-propionic acid and for the (−)-lactate ion [110], which can be used for the partial resolution of racemates of these acids. On the

other hand, optically active lactic acid resolves the racemate of $[CoCO_3en_2]^+$, undergoing ligand exchange only with one isomer [112]. Nevertheless, appreciable enantioselectivity was not observed [106] in the exchange of Δ-$[CoCO_3(l\text{-pn})_2]^+$ with DL-alanine.

Corey and Bailar in their classic paper [12] made a conformational analysis of the complexes of diamines in order to elucidate the causes of the enantioselective and enantiospecific effects. Since the angle in a complex is only 86–88°, the theory of these workers indicates that the five-membered chelate ring should be puckered considerably more strongly than the cyclopentane ring, and there should be a clear difference between equatorial and axial positions for substituents. Interaction between the two chelate rings occurs through the hydrogen atoms of the chelated amino-groups. In square planar structures this interaction is about 1 kcal mole^{-1} smaller with the same conformation of the two rings, e.g. $\delta\delta$, than in a *meso*-structure, e.g. $\delta\lambda$



The difference in energy in tetrahedral structures is rather smaller. In octahedral tris-complexes interaction between the three rings is minimal when they have the same configuration: $\delta\delta\delta$- and $\lambda\lambda\lambda$-conformations of the rings are preferred respectively for the Λ- and Δ-configurations of chiral tris-complexes. The energy of the isomeric complexes increases by 1.8 kcal mole^{-1} in the sequence

$$\Lambda[\delta\delta\delta] < \Lambda[\delta\delta\lambda] < \Lambda[\delta\lambda\lambda] < \Lambda[\lambda\lambda\lambda] .$$

Interaction between chelate rings and a tendency for substituents to occupy an equatorial position may lead to the appearance of enantioselective effects in complexes of substituted 1,2-diamines. In tetrahedral and in octahedral *cis*-biscomplexes, as well as in octahedral tris-structures, moreover, enantiospecific formation of the configuration of the metal atom itself must be expected.

Satisfactory agreement with theory has since been found [95,113] in experimental verification of the views developed by Corey and Bailar. Dwyer, Sargeson, et al. made a detailed study of complex formation by cobalt(III) [114–119] and platinum(IV) [120,121] with propylenediamine. In contrast to earlier investigations, they discovered the existence of complexes containing ligands differing in configuration [117, 118,121] and even the formation of diastereomeric pairs of tris-*l*-propylenediamine [117,114,120,121]. On the hypothesis that thermodynamic equilibrium is established among all structures in the reaction mixture with cobalt(III) complexes in the presence of activated carbon, the authors calculated the differences in their free energies, which reached 1.6 kcal mole^{-1}, close to the values calculated by Corey and Bailar (Table 3).

Closely similar values have been obtained [122] by cobalt-59 nuclear magnetic resonance spectroscopy, which enables the composition of a mixture of trispropylenediaminecobalt(III) complexes to be analysed. The same method shows that, in the presence of activated carbon, equilibrium is displaced towards statistically more probable though energetically less favourable structures. However, it remains unproven whether carbon enables true equilibrium to be established. Diastereomers may well possess different sorbabilities of carbon, but hence also different rates of conversion. In any case it is clear that in this system kinetic enantioselective and enantiospecific effects differ from thermodynamic effects.

A more detailed study has begun of the composition of complexes of cobalt(III) and chromium(III) with cyclopentane-*trans*-1,2-diamine [123] and of cobalt(III) with cyclohexane-*trans*-1,2-diamine (chn) [95].

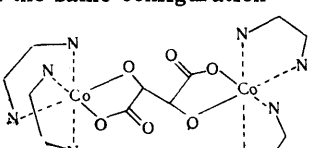
Table 3. Differences in Gibbs free energies $\delta\Delta G^\circ$ (kcal mole^{-1}) of diastereomers of complexes of cobalt(III) with propylenediamine.

Complex	Diastereomers		$\delta\Delta G^\circ$	Ref.
$[Co(l\text{-pn})(C_2O_4)_2]^-$	Λl	Δl	0.27	116
$[Co(l\text{-pn})_2(C_2O_4)]^+$	Λll	Δll	0.20	116
$[Co(en)_2(pn)]^{3+}$	Λl	Δl	0.45	117
$[Co(en)(pn)_2]^{3+}$	Λll	Δll	1.2	117
$[Co(pn)_3]^{3+}$	Λlll	Δlll	1.6	117
	Λddl	Λddd	0	118
	Δddl	Λddl	0.52	118
	Λlll	Λdll	0.53	118

The conformational ideas of Corey and Bailar have since been re-examined by Gollogly and Hawkins [124,125], who conclude that the chelate ring of a 1,2-diamine can assume many energetically similar conformations and that the $\Lambda(\delta\delta\delta)$ structure for $[M\,en_3]$ is more favourable than $\Lambda(\lambda\lambda\lambda)$ by at most 0.85 kcal mole^{-1}, while there is hardly any difference in energy between the $(\lambda\delta)$- and $(\delta\delta)$-structures for the *trans*-biscomplex. This last conclusion is consistent with the absence of thermodynamic enantioselectivity in complexes of propylenediamine, cyclohexane-*trans*-1,2-diamine, butane-2,3-diamine, and stilbenediamine with copper and nickel [126,127]. This unexpected result was obtained by calorimetric, potentiometric, and spectrophotometric methods.

Good examples of kinetic enantioselectivity are the reactions of $\Lambda(+)_{5461}$-$[CoEDTA]^-$ [128] and $\Lambda(-)_{5461}$-$[Co(+)\text{-PDTA}]^-$ [129] with racemic *dl*-propylenediamine, resulting in the formation of $\Lambda(+)$-$[Co(d\text{-pn})_3]^{3+}$, while the optically pure *l*-diamine remains in solution, since it does not undergo ligand exchange. When racemic $[CoEDTA]^-$ is treated with optically active *l*-propylenediamine, on the other hand, only the Δ-complex undergoes exchange [128].

A molecule of *d*-tartaric acid, on reacting in acid medium with racemic $\Delta\Lambda$-$[CoCO_3en_2]^+$, at once replaces carbonate ions in two complexes, always selecting a pair of complexes of the same configuration [108,130], e.g.



Enantioselectivity was unexpectedly high in electron transfer from $[Cr\,phen]^{2+}$ to $[Co\,phen_3]^{3+}$, where "phen" denotes 1,10-phenanthroline. When Λ-$[Co\,phen_3]^{3+}$ was used as oxidant, the racemic chromium complex yielded Δ-$[Cr\,phen_3]^{3+}$ of optical purity 92%. [131] A possible explanation is that only Δ-$[Cr\,phen_3]^{2+}$ undergoes oxidation, while the Λ-enantiomer is rapidly racemised. Very slight (1–2%) enantioselective effects have been observed [132] on the exposure of $[CrC_2O_4phen_2]^+$, $[Cr(C_2O_4)_2phen]^-$, and $[Cr\,bipy_3]^{3+}$ to the circularly polarised beam of an argon laser. The rates of isomerisation of enantiomers are

obviously different under these conditions. Ordinary light has a similar effect on the complex $[Cr\,phen_3]^{3+}$ if antimony *d*-tartrate is present in solution[133].

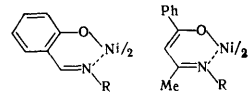
The Pfeiffer effect, first discovered in complexes of zinc with phenanthroline and with bipyridyl[135], is closely connected with enantioselective phenomena[134]. Three principal aspects—asymmetric induction, asymmetric transformation, and asymmetric synthesis—are distinguished at the present time[136], among which the first process has no connection with stereoselectivity. Asymmetric transformation involves a displacement, under the influence of an optically active compound, of the equilibrium between two labile enantiomers[137]. With the racemate of *cis*-$[CoCl_2en_2]^+$ in (−)-butane-2,3-diol, for example, the proportions of (+)- and (−)-isomers become 4 : 1.[138] The *trans*-$[CoCl_2en_2]^+$ complex can exist as three conformers (δδ, δλ, λλ), one of which is a *meso*-structure, while the other two are enantiomers distinguished by opposite puckering of the chelate rings. One of these chiral forms is stabilised in the optically active solvent, and the complex exhibits the Cotton effect[136]. A similar explanation applies to the appearance of Cotton effects with *cis*-$[CrCl_2en_2]^+$ and *cis*-$[CoCl_2trien]^+$ in (−)-butane-2,3-diol[136], with trisphenanthroline complexes of nickel, zinc, and cadmium in the presence of *l*-lactic acid[139,140] and of mercury in that of dibenzoyl-*d*-tartaric acid[139], and with $[Ni\,bipy_3]^{2+}$ in the presence of *l*-lactic acid[140]: the asymmetrising action of the optically active component is attributed to the difference in energy of its interaction (solvation or association) with the enantiomers of the complex. In the case of the diastereomeric ion-pairs of $[Ni\,phen_3]^{3+}$ with *d*-α-bromocamphorsulphonic acid this difference is $\Delta\delta G^\circ = 0.07$ kcal mole^{-1}.[141] Such considerable enantioselective effects with complexes are explained by the inclusion of the optically active component in the outer coordination sphere. In individual cases a chiral solvent may probably play a direct part in ligand exchange, as in the dissolution of *cis*-$[CoCl_2en_2]^+$ in *l*-propane-1,2-diol, which replaces chloride ions predominantly in the Λ-complex[142].

In the case of the Pfeiffer effect asymmetric synthesis implies the conversion of a non-chiral compound into an optically active structure. For example, the complex *trans*-$[CoOHCl\,en_2]^+$, which dissolves in (−)-butane-2,3-diol when heated to 70 °C, exhibits absorption and circular dichroism spectra identical with those of the optically active *cis*-$[CoOHCl\,en_2]^+$ in aqueous–methanolic solution. The degree of enantiospecificity of this isomerisation is evidently quite high[136].

A difference in the interaction of two enantiomeric complexes with an optically active solvent may also be evident in a difference in solubility[138]. The presence of an optically active con ponent in solution may change significantly the diffusion constants of the enantiomers[143–145]. Enantioselectivity in the association processes underlying such phenomena was demonstrated on the systems formed by *d*-tartaric acid with the enantiomers of $[Co\,en_3]^{3+}$[146] and by the enantiomeric tartaric acids with Λ-$[Co(d\text{-}pn)_3]^{3+}$.[147]

V. COMPLEXES OF SCHIFF BASES

Less detailed study has been made of enantioselective phenomena in complexes of Schiff bases. Fundamental investigations were made by Holm and his coworkers, who showed[148–151] that an equilibrium is established between tetrahedral and square planar forms of bis-complexes of Schiff bases with nickel(II) in non-coordinating solvents. The position of equilibrium depends mainly on the size and type of radical R attached to the nitrogen atom. Since the square planar form is diamagnetic, while the tetrahedral form is paramagnetic, signals from the two forms are easily distinguishable in the nuclear magnetic resonance spectrum. In the latter case the signals from *meso*-structures and optically active molecules, formed when a racemic Schiff base is used, can also be distinguished. Three pairs of diastereomers

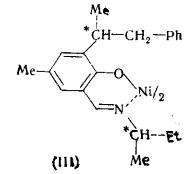


(I) (II)

are then formed, but complexes with optically active ligands give only one series of signals owing to rapid inversion[151,152] of the tetrahedral configuration $\Delta \rightleftharpoons \Lambda$.

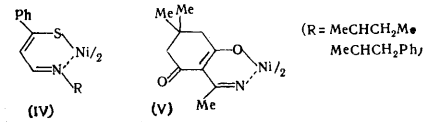
$$\Delta(ll),\ \Delta(dd),\ \Delta(ld) \equiv \Lambda(dd),\ \Lambda(ll),\ \Lambda(dl).$$

With *NN'*-disubstituted disalicylideniminatonickel(II) complexes (I: R = $CH_3CH_2CH(CH_3)$ or $C_6H_5CH_2CH(CH_3)$) the total concentration of *meso*(*dl*)-complexes (in square planar and tetrahedral forms) is roughly double the total concentration of each of the optically active structures[149,151]. With the *meso*-structure, however, the equilibrium is shifted further towards the tetrahedral form than with the optically active structures[148–152]. This difference is especially marked with nickel and zinc complexes of types (I) and (II) having a bulky substituent attached to nitrogen (R = $C_6H_5CH(CH_3)$): in this case the tetrahedral *meso*-complexes are more stable than the tetrahedral optically active structure by 0.08 kcal mole^{-1}.[152]



(III)

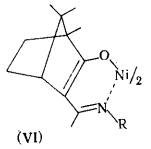
Six pairs of diastereoisomers may be formed by tetrahedral complexes of the Schiff base (III), which contains two asymmetric atoms[153]. Signals characteristic of each pair have been observed in the nuclear magnetic resonance spectrum, and the free energy of interconversion of planar square into tetrahedron has been determined from the temperature dependence of the signals. As in the preceding cases, the *meso*-structures of the complexes show a greater preference for the tetrahedral form than do the optically active complexes, the difference in the free energies of transition amounting to 0.3–0.4 kcal mole^{-1}. The considerable difference in the equilibrium positions is apparent in enhanced extinction and enhanced magnetic susceptibility of a solution of the complexes obtained from the racemic ligand in comparison with a solution of the optically active complex[153].



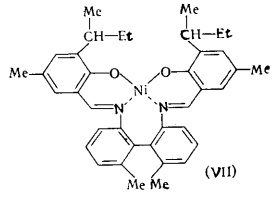
(IV) (V) (R = MeCHCH$_2$Me, MeCHCH$_2$Ph)

This difference is still larger in nickel complexes of γ-imino-thiols (IV).[154,155] When R = $C_6H_5CH_2CH(CH_3)$, the magnetic moments determined for complexes of the racemic and optically active ligands are respectively 2.40 and 2.08 β, whence the magnetic moment of the pure *meso*-form was calculated as 2.68 ± 0.12 β. The difference in

the free energies of interconversion of planar square into tetrahedron for *meso*-structure and optically active complex is 0.7 kcal mole^{-1}, so that the equilibrium proportions of the corresponding tetrahedral form are respectively 77% and 54%.[155] Considerably smaller effects are observed in *N*-substituted 2-acetiminodimedonato-complexes (V), where square planar forms predominate with both *meso*-structures and optically active bis-complexes[156]. The opposite situation is found in nickel complexes of *N*-alkylated aminomethylenecamphors (VI), where the equilibrium for the optically active complexes—but not for the *meso*-structures—is displaced further towards the tetrahedral form[157,158]. Thus, in a large number of bis-complexes of Schiff bases with nickel ions, enantioselectivity is apparent in a difference in stability ratios of square planar and tetrahedral forms between *meso*-complexes and the two optically active complexes.



(VI)



(VII)

An interesting case of the enantioselective solvation of complexes of quadridentate Schiff bases (VII) has been described by Ernst et al. In such complexes the Δ or Λ configuration at the metal atom is determined unambiguously by the configuration of the atropoisomeric ligand, and equilibrium between planar and tetrahedral structures is established without racemisation of the complex[159]. In non-chiral solvents the n.m.r. spectrum contains signals from three pairs of diastereomers, but signals from all the enantiomers—Δ(*ll*) and Λ(*dd*), Δ(*dd*) and Λ(*ll*)—can also be distinguished in chiral solvents. If, however, the solvent used is not 100% optically pure, the splitting of the signals observed initially from these diastereomeric pairs gradually disappears (with pinene of optical purity 90% in about 1 h). This unusual pattern was explained[160] by selective solvation of the Δ(or Λ)-isomers of the complex by *d*(or *l*)-pinene, with the formation now of the enantiomeric, n.m.r.-equivalent pairs Δ*d* and Λ*l*. Initially both Δ- and Λ-isomers are more strongly solvated by the solvent enantiomer present in excess, but the spectrum contains signals of the two pairs of enantiomers. With the establishment of equilibrium Δ- and Λ-enantiomers undergo enantioselective solvation, and the splitting of their signals disappears.

Complexes of Schiff bases obtained from pyridoxal and α-amino-acids have aroused considerable research interest in connection with their important role in biological transaminations. Complexes of zinc and aluminium with alanine derivatives[161] and of aluminium with derivatives of serine[162,163], alanine, leucine, threonine, α-aminobutyric acid, and norvaline[163] have been studied by n.m.r. spectroscopy. Octahedral complexes containing two planar terdentate ligands exist as three diastereomeric pairs. The homogeneous diastereomers of the optically active L-serine derivative differ by about 0.9 kcal mole^{-1} in energy; the *meso*-complex occupies an intermediate position with respect to stability[162]. Appreciable enantioselectivity has not been observed in complexes of the Schiff base of alanine: the quantities of the *meso*-structure and of optically active complexes in the equilibrium solution are roughly the same[161].

Nevertheless, Holm[152] reported the presence of enantioselectivity in the zinc and nickel complexes of the Schiff bases obtained from esters of alanine and phenylalanine with salicylaldehyde. Different properties have also been found[164] in copper complexes of *N*-salicylidene derivatives of aspartic acid. The greater stability of the homogeneous structure than of the *meso*-structure was shown by polarimetric titration for the copper complexes of Schiff bases of salicylaldehyde and α-methylbenzylamine[165].

When a chiral ketone (*S*-2-hydroxy-6,6′-dimethyl-2′-nitro-5-nitrosodiphenyl) is used to catalyse the racemisation of D- and L-alanine in the presence of copper ions, some difference (3–5%) is observed in the rates of racemisation of the enantiomers. Racemisation probably takes place in a complex of the resulting Schiff base[166].

VI. COMPLEXES WITH OTHER LIGANDS

The first communication on enantioselectivity in complexes probably appeared as early as 1900, when copper complexes of *dl*-tartaric acid were found[167] to be more stable than those of the optically active acid. It has been observed also that the solution obtained by mixing equal quantities of complexes of *l*- and *d*-tartaric acids absorbs light 19% more strongly than does either of the initial solutions[168–171]. In acid medium only monotartratocopper was detected, its formation constant being the same for *l*- and *dl*-tartaric acids[172,173]. More detailed investigations of this system showed that differences arise in alkaline solution, where polynuclear complexes are formed[171], whose composition is different with *l*- and with *dl*-tartaric acids. Electron spin resonance data[174] and X-ray diffraction[175] also indicate that the complexes are dinuclear.

The vanadyl ion also forms more stable complexes with *dl*-tartaric acid than with the optically active acid[171,176]. Both e.s.r. data[176] and X-ray examination[177] show that the complex is dinuclear and that steric interactions are smaller if the ligands differ in configuration[177]. The absorption spectra of complexes of VO^{2+} with *dl*- and *l*-tartaric acids also differ sharply[176], the former being red–brown in colour, and the latter violet. A difference is apparent also in resistance to oxidation[178], although the oxidation products are the same with the two complexes. A detailed survey has been made of the stereochemistry of dinuclear complexes of tartaric acid[179]. Stereoselectivity of formation of tartaric-acid complexes has been observed also with nickel[180] and antimony(III),[181] structures containing two ligands of the same configuration being the more stable here.

In the case of eight-coordinated zirconium(IV) and hafnium(IV) complexes, *dl*-hydroxy-acids (mandelic, lactic) ensure better formation of hydrogen bonds than do optically active ligands, whose complexes are less stable[182].

Different equilibrium positions and different activation energies of the transition between planar square and tetrahedron have been found for bis-complexes of nickel and cobalt(II) with racemic and optically active phosphines[183]. Considerable enantioselectivity develops in bis-complexes of nickel with penicillamine (ββ-dimethylcysteine), where the optically active structures are more stable than the *meso*-structure by 0.55 kcal mole^{-1}. These diamagnetic complexes probably have a square planar structure with a paired *cis*-arrangement of β-thiol and α-amine donors[30,37].

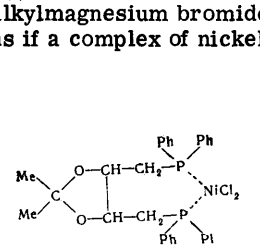
Selective photochemical decomposition by circularly polarised light of cobalt(III) and chromium(III) trioxalates[184–187] and of chromium(III) trisacetylacetonate[188]

leads merely to a slight enrichment of the mixture with one of the enantiomers. Measurement of the relative viscosity of solutions of optically active and racemic [$CrAcac_3$] in the presence of di-isopentyl *d*-tartrate has been used to study enantioselective effects of solvation of the complex[189]. Considerable Pfeiffer effects have been observed in complexes of tin(IV) and titanium(IV) with acetylacetone and dibenzoylmethane[190], as well as on aluminium tris-acetylacetonate, cobalt(III) and chromium(III) trioxalates, and zinc bisbenzoylacetonate[134].

The occurrence of kinetic enantioselective effects in labile complexes enables stereoselective polymerisation to be accomplished by means of coordination catalysts, which ensure selection, and addition to the growing polymer chain, of monomers of only one steric configuration. As a result, optically active polymer chains are formed from a racemic monomer mixture. For example, the complex of diethylzinc with methanol effects stereoselective polymerisation of racemic methyloxiran, which is proved by the possibility of separating the final polymer into two fractions of opposite optical activity[191-193]. Enantioselectivity with respect to monomers is due to the presence in the complex of a chiral terminal unit of the growing chain. The configuration of the whole chain is obviously determined by the chance configuration of the first monomer unit which entered the coordination sphere of the complex. If, however, the initial catalytic complex contains a chiral ligand, it already exerts control at the stage of reaction with the first monomer molecule. The whole of the polymer formed is then optically active, while the unchanged monomer is enriched with the second enantiomer. Such stereoselective polymerisation of *dl*-methyloxiran is catalysed by complexes of diethylzinc with optically alcohols (e.g. borneol)[194-198], amines[199], glutamic ester[200], amino-acids[201], complexes of iron(III) chloride with bornyl ethyl ether[202] and of triethylaluminium with the *N*-carboxy-anhydride of L-alanine[203], and also by magnesium *d*-tartrate[204,205].

Analogous processes of stereoselective and stereo-elective polymerisation by means of coordination catalysts have been reported for racemic alk-1-enes[206-210], α-amino-acid *N*-carboxyanhydrides[211,212], and also mixtures of methyloxiran and such anhydrides[213,214]. The possibility exists for using this process for the partial resolution of racemic compounds[215], e.g. methylthi-iran, where the effects of kinetic enantioselectivity are especially considerable.

The ability of an asymmetric complex catalyst to effect the selection of substrate enantiomers explains such reactions as the enantioselective oxidation of catechol in the presence of (+)-[$CoClNH_3en_2$]Br_2[76,213] and the reduction of racemic methylmethoxynaphth-1-ylphenylsilane by means of lithium tetrahydroaluminate in the presence of (+)-quinidine to optically active methylnaphth-1-ylphenyl-silane[217]. Similarly, the reaction of halogenated alkenes with a racemic s-alkylmagnesium bromide yields optically active hydrocarbons if a complex of nickel with an optically active diphosphine



is used as catalyst[218].

VII. USE OF ENANTIOSELECTIVE EFFECTS IN COMPLEXES FOR THE RESOLUTION OF RACEMATES

All methods for the resolution of racemates (in contrast to the separation of diastereomers) are inevitably based in some way on enantioselective processes. Resolution of a racemate entails either selective chemical modification of one of the enantiomers or its transfer to a separate phase. Kinetic enantioselective effects correspond to the first condition. The use of thermodynamic enantioselectivity in labile complexes for the practical separation of enantiomers is possible only in two-phase systems.

The first attempts to use enantioselective effects in complex formation for the resolution of racemates were undertaken by Bailar[106] as early as 1939. Only considerably later was partial resolution of tartaric acid accomplished by reaction with [$CoCO_3(l\text{-pn})_2$]$^+$.[110,111] The optical purity of *l*-tartaric acid, which showed less tendency to replace the carbonate ligand in the complex, reached 80%. A similar effect was observed with lactic and α-chloropropionic acids, where 30% resolution was achieved[110]. Considerable enrichment of the solution with *l*-propylenediamine occurs in the reaction of the *dl*-diamine with Λ(+)-[CoEDTA]$^-$.[128] Complete resolution of the diamine is possible when Λ(−)-[CoPDTA]$^-$ is used[129]. Similarly, *dl*-cyclohexanediamine can be successfully resolved by means of [$CoCO_3(l\text{-pn})_3$]$^+$,[219] and the resolution of (±)-[CoEDTA]$^-$ effected by means of *l*-propylenediamine[129].

The propylenediamine which distils from a solution containing the copper or nickel complex of *d*-tartaric acid and excess of the *dl*-diamine exhibits weak negative rotation[220] (optical purity 2–3%). On the other hand, distilling the diamine over [Cu_2(L-Glu)$_2H_2O$] gives 4% enrichment with *d*-propylenediamine. If excess of DL-alanine is added to a solution containing the copper complex of *d*-tartaric acid or L-glutamic acid, [$CuAla_2$] precipitates out enriched 3.8% with D-alanine or 3.3% with L-alanine[220]. Harada has reported[221-223] the resolution of DL-aspartic acid on its addition to a solution of the copper complex of L-glutamic acid, L-proline, or L-alanine. In all cases the complex [Cu(D-Asp)$_2$] is precipitated, in the last case in 40% yield of optical purity 95%. Detailed study of this process showed[224] that the presence of L-alanine in solution considerably accelerates crystallisation of the copper complex of D-aspartic acid in comparison with that of the L-aspartic-acid complex only in the pH range 2.7–5.3, while the proportions of copper and aspartic acid in the precipitate vary in the range 1 : 1.2–1.3. After deposition of the D-aspartic-acid complex, its enantiomer begins to crystallise with equally high optical purity. Similarly, D-lysine tungstophosphate crystallises preferentially[225] on the addition of dodecatungstophosphoric acid to a solution containing DL-lysine hydrochloride and $\Delta(-)_{5461}$-[CoEDTA] (or the complex cobalt(III) cyclohexanediamine-tetra-acetate). The true nature of the enantioselective processes leading to acceleration of the crystallisation of one enantiomer of a racemate from a solution containing an optically active component or a solid[226] is still not clear.

The enrichment with D-alanine (by 13.8%) of the complex [$CoAla_3$], formed when [Co(L-Asp)$_2$]$^-$ is treated with excess of DL-alanine at pH 9.5–10 in the presence of activated carbon, is probably due to kinetically controlled enantioselective exchange of ligands. The additional presence of powdered cellulose raises the optical purity

of D-alanine in the precipitated complex to 30–35%.[227] A still greater effect is produced by chitosan and its derivatives[228]. Accompanying this process by the action of DL-alanine and L-aspartic acid on $\Delta\Lambda$-$[Co(CO_3)_3]^{3-}$ showed[229] that ligand exchange involved the intermediate formation of (–)-$[CoCO_3(L\text{-}Asp)_2]^{3-}$, after which (–)-$[Co(D\text{-}Ala)_2L\text{-}Ala]$ was precipitated.

The possibility of using stereoelective polymerisation tion[215] or enantioselective hydrogenation[217] to resolve racemates has been mentioned in preceding Sections. Gillard[230] indicates that micro-organisms may be used to resolve $[CoGly_3]$.

A very large number of publications have appeared on the separation of enantiomers of stable complexes by chromatographic methods using dissymmetric stationary phases. The peculiarities of the chromatographic method in practice enable even very slight enantioselective effects of ligand exchange in the outer coordination sphere of these complexes to be exploited. Thus the different degrees of association of the enantiomers of $[M\,en_3]^{3+}$ (M = Co^{II}, Cr^{III}, Rh^{III}) with *d*-tartaric acid[231] or with aluminium(III) *d*-tartrate[232,233] permit complete separation of these enantiomers by thin-layer chromatography or electrophoresis. Trisacetylacetonates of these metals are partly resolved during extraction with di-isopentyl-*d*-tartrate[234] or with a solution of (+)-$[Co\,en_3]^{3+}$.[235]

Selective sorption on optically active quartz was proposed[236,237] for the separation of enantiomers of $[CoClNH_3en_2]^{2+}$ and $[CoClNH_3DMG]^{+}$ (where DMG = dimethylglyoximato). This method proved acceptable also for separating enantiomers of $[CoCO_3(NH_3)_2en]^{+}$,[238] $[CoDMG_3]$,[239] disalicylidenetriethylenetetraminecobalt(III),[240] and several others[241]. Chromatography on columns of optically active quartz has effected the resolution of several cobalt and chromium complexes[241–244] (some of these results have not been confirmed[245,246]), $[CoEDTA]^{-}$,[247] bisbenzoylacetonatoberyllium(II),[248] tetrahedral nickel complexes of formazans[249,250], oxalate[244] and acetylacetonate[251] complexes of cobalt(III) and chromium(III), and the complex of platinum(II) with *N*-ethyl-*N*-methylglycine[252]) which contains an asymmetric nitrogen atom). The enantiomers of trishexafluoroacetylacetonatochromium(III) have been separated by gas chromatography[253,254]. Sodium perchlorate crystals have been reported[255,256] as possessing a similar ability to resolve racemates of complex compounds.

The largest effects in the separation of enantiomers are usually observed in chromatography on carbohydrates (Table 4). The hydroxy-groups of these sorbents obviously play an active part in forming the outer coordination sphere of the complexes. In some cases the efficiency of the chromatographic process can be considerably enhanced (up to complete separation of the enantiomers) if an optically active eluant, e.g. sodium *d*-tartrate solution, is used[284,285].

Significantly more modest successes have been achieved in the separation of enantiomeric complexes by means of synthetic dissymmetric ion-exchange resins containing optically active groups—quinine[286], tartrate or antimonyltartrate anions, and also Λ-$[Co\,en_3]^{3+}$ anions[287].

Rogozhin and Davankov's proposed[288–292] ligand-exchange chromatography[43] of racemates—a new principle for the separation of enantiomers capable of complex formation—is based on enantioselective effects of inner-sphere ligand exchange. Chromatography is conducted on a sorbent having chiral complexing groups, in the presence of metal ions (copper, nickel, zinc, etc.) giving kinetically labile complexes. Thermodynamic enantioselective effects develop in the formation of a mixed sorption complex incorporating in the chiral stationary ligand, the metal ion, and the mobile ligand (the racemate molecule). These workers synthesised a wide range of dissymmetric sorbents based on a cross-linked macro-network polystyrene framework with bidentate[293–295] and terdentate[296–300] stationary ligands like α-amino-carboxylic and α-amino-phosphonic[301] acids. Racemates of many compounds capable of complex formation—amino-acids, amino-alcohols, diamines, heterocycles, etc.—have been resolved on these sorbents[44,47,48]. The high enantioselectivity of complex formation in these systems ($\delta\Delta G^{\circ}$ may exceed 1 kcal $mole^{-1}$ [50,56–58]) ensures exceptionally high selectivity of sorption of enantiomers, which can be exploited for their separation not only on an analytical but also on a preparative scale. Better separations are observed when the total denticity of stationary and separable ligands coincides with the coordination number of the metal atom[44]. The efficiency of separation is influenced by the degree of saturation of the sorbent with metal ions[45,46], temperature, eluant concentration, and several other factors[302].

Table 4. Resolution of racemates of coordination compounds by chromatography on carbohydrates.

Sorbent	Resolvable complex	Ref.
D-Lactose	Cr^{III} trisacetylacetonate	189,257,260
	Co^{III} trisacetylacetonate	257-262
	Rh^{III} trisacetylacetonate	259-261
	Ru^{III} trisacetylacetonate	259
	Y^{III}, Gd^{III} trisacetylacetonates	263
	Co^{III} trisbenzoylacetonate	259
	Cr^{III} trisbenzoylacetonate	264
	Ni^{II}, Cu^{II} bis-β-keto-imines	265
	bisacetylacetonatopropylenediaminevanadyl	266
	tris-5-methylhexane-2,4-dionatocobalt(III)	267
Starch	trisethylenediamine-cobalt(III), -chromium(III)	268,269
	trisglycinatocobalt(III)	268-271
	Co^{III} trisdithiocarbamate	268,269
	Co^{III} trisdithiocarbaminate	269
	Co^{III}, Cr^{III} trioxalates	269
	bisglycylglycinatocobalt(III)	271
	bisethylenediaminecobalt(III)	272
	tris-L-α-aminoisobutyratocobalt(III)	273
	hexamethyl-1,4,8,11-tetra-azacyclotetradeca-1,7-dienatonickel(II)	274
Cellulose	Co^{III} trioxalate	272,275
	tris-α-amino-carboxylatocobalt(III)	275
	trisalkylene-1,2-diaminecobalt(III)	276,277
	tribenzo[*b*, *f*, *j*]-1,5,9-triazacylododecenato-nickel(II)	278
Carboxymethylcellulose	hexakis-2-aminoethylthiolatotricobalt(III)	279
	Co^{III} bisiminodiacetate	280
	Co^{III} trimethylenediaminetetra-acetate	280
	dichlorobisphenanthrolinerhodium(III)	281
Diethylaminoethylcellulose	Co^{III} ethylenediaminetetra-acetate	282
Phosphorylated cellulose	trisethylenediaminecobalt(III)	282
	Co^{III} bisiminodiacetate	282
	bisdiethylenetriaminecobalt(III)	282
SE-Sephadex	bisdiethylenetriaminecobalt(III)	283

Similarly, a sorbent based on a styrene—divinylbenzene copolymer with *N*-carboxymethyl-L-valine—a stationary terdentate ligand—has been synthesised by Angelici et al.[303,304]. In the presence of copper ions racemates of isoleucine—and rather less effectively those of valine and alanine—are partly resolved on this sorbent.

Bernauer [60,61,305,306] proposed a somewhat modified method of ligand-exchange chromatography: a stationary chiral complex of iron(III) with 2'-hydroxyethyl-D-propylenediaminetriacetic acid L-[Fe(D-HEPTA)]$^-$ was bound by an ionic bond—not a covalent bond—to a polymeric carrier (Dowex 1 × 2 anion-exchange resin). Only acid racemates, which preserve the overall negative charge of the complex when one of its acetate ligand groups is replaced, can be resolved on such a solvent. This condition is satisfied by acetyl and benzoyl derivatives of leucine, alanine, phenylalanine, and methionine, which were in fact partly resolved by ligand chromatography. In all cases the more stable mixed complexes formed derivatives of D-amino-acids, the ratio of sorbed D- and L-ligands falling in the above sequence of amino-acids from 1.08 to 1.03 ($\delta\Delta G^\circ$ = 0.10–0.02 kcal mole^{-1}). Bernauer [61] has used a chiral stationary complex of copper, nickel, or zinc with D(−)-propylenediaminetetra-acetic acid of total charge 2- to strengthen the bonding of the complex to the anion-exchange resin carrier. On such a sorbent 60% separation of α-methylbenzylamine isomers is observed ($\delta\Delta G^\circ$ = 0.3 kcal mole^{-1}).

It is interesting that Bruschtein [307], in an earlier study of the interaction of polymers of *N*-acryloyl and *N*-methylacryloyl derivatives of L-amino-acids (glutamic and aspartic acids, glycine, asparagine) with copper complexes of propylenediamine and of tyrosinamide, detected no enantioselective effects.

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Thus a fairly large number of processes, in which thermodynamic or kinetic enantioselective effects develop in one form or another, are already known in the chemistry of coordination compounds. These effects are observed both in the coordination of chiral ligands and in processes involving only the outer coordination sphere of the complex. The literature on enantiospecific effects is equally vast, but could not be considered within the scope of the present Review.

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