STEREOSELECTIVITY IN COORDINATION COMPOUNDS

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I. Introduction

Biological aspects of inorganic chemistry are becoming increasingly important. Many of the most striking effects observed require an understanding of the subtle details of some inorganic stereochemistry not previously reviewed. Further, in classical coordination chemistry, it has become increasingly clear that a good deal of valuable information is to be obtained from the interplay of optical configuration and spectroscopy. For example, it is possible to characterize spectroscopic levels from measurements of circular dichroism if the absolute optical configuration of the compound is known.

The time is therefore ripe for an exposition of the ways in which stereospecific effects arise from the interaction in transition metal complexes of several sources of asymmetry.

The behavior of molecular diastereoisomers has been known as stereospecificity or stereoselectivity in organic chemistry for some years, and this is the sense in which we use the term stereoselectivity. Unfortunately, in coordination chemistry as in organic chemistry, the term has also been applied to other types of behavior, such as retention of geometrical configuration, e.g.,

$$cis\text{-}[\mathrm{Coen_2Cl_2}]^+ \rightarrow cis\text{-}[\mathrm{Coen_2(H_2O)Cl}]^{2+}$$

and retention of optical configuration, e.g.,

$$\text{D}(+)\text{-}[\text{Coen}_2\text{Cl}_2]^+ \rightarrow \text{D}(+)\text{-}[\text{Coen}_2\text{CO}_3]^+$$

We use the term "stereoselectivity" to refer only to the behavior of molecular diastereoisomers, i.e., asymmetric metal complexes containing further centers of asymmetry. This definition covers the transition state of many reactions of optically active complexes with optically active ligands, such as the reaction of (+)$[\text{Coen}_2\text{CO}_3]^+$ with (+)tartaric acid; such reactions have usually been called stereospecific in the past.

There is a rapidly growing tendency among organic chemists for reactions of the type formerly called stereospecific to be called stereoselective ("stereospecific" being reserved for reactions which are 100% stereoselective). Although this usage does not represent a fixed state of affairs (today's stereospecific reaction may be tomorrow's 99% stereoselective reaction, as experimental methods improve), we have revised the common inorganic usage whereby stereospecificity refers to one molecular diastereoisomer having different properties from another, and call such effects stereoselective, in accordance with modern organic practice.

A. NOMENCLATURE

Although no description of basic principles of optical activity is given in this review, a few points of nomenclature are necessary. First, the absolute optical configuration of complexes: it is now known by the Bijvoet method (*11*) of anomalous diffraction of X-rays that the Fischer convention for D-glyceraldehyde corresponds to reality. It has further been shown (*78*) in a similar way that the enantiomer of the trisethylenediaminecobalt(III) cation, which is dextrorotatory at the sodium D line ($[\alpha]_D = +90°$), has the absolute configuration shown in Fig. 1a. This configuration may be called D (*43*), Λ (*82*), or $S(C_3)R(C_2)$ (*19*, *21*). Second, a positive Cotton effect for an isolated electronic transition is shown in Fig. 1b. Curves are given for both the more commonly measured optical rotatory dispersion, and the rather more informative circular dichroism. Both phenomena, the inverse rotatory dispersion curve and the circular dichroism band, are included under the name Cotton effect. The intimate connection between configuration and Cotton effect will be clear from Fig. 1.

In naming complexes, we adopt the following rules:

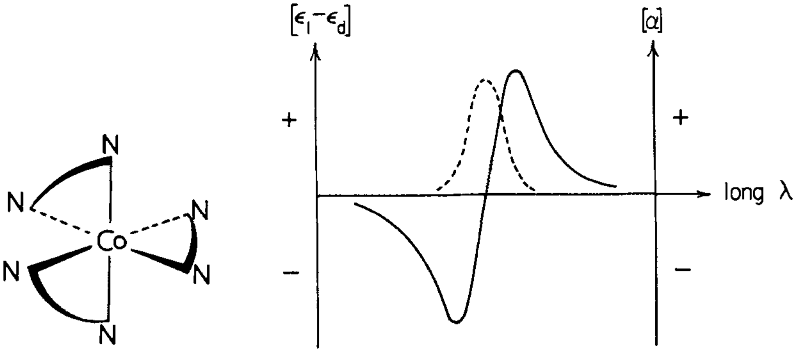
(a) Any sign of rotation given, whether for complex or for ligand, refers to sodium yellow light (589 mμ) unless otherwise specified, e.g., (+)$[\text{Coen}_2(\text{NCS})(\text{H}_2\text{O})]^{2+}$, $(+)_{5461}[\text{Coen}_2(\text{NCS})\text{Cl}]^+$, (+)$[\text{Coen}_2(+\text{tartrate})]^{2+}$.

(b) Absolute configurations for complex or ligand are given where known in an accepted nomenclature, e.g., D(+)-$[\text{Co}(+\text{pn})_3]^{3+}$, (+)$[\text{Co}(\text{L}(+)\text{-alaninate})_3]$.

(c) Abbreviations for ligands are as in a recent book (*58*), except as follows: diamines are abbreviated as in (*37*), EDTA denotes the ethylenediaminetetraacetate ion, PDTA the propylenediaminetetraacetate ion, CHXTA the *trans*-1,2-cyclohexanediaminetetraacetate ion, Ala the alaninate anion, and hmc the hydroxymethylenecamphorate anion.

B. STEREOSELECTIVITY

Optical enantiomers react at exactly equal rates with symmetric reagents to form exactly similar products, distinguishable only by some measurement with an asymmetric technique. Rephrasing this statement, symmetrical properties of enantiomers are exactly equal. Thus, the electronic and infrared spectra of the enantiomers of tartaric acid or of trisethylenediaminecobalt(III) chloride are superposable.



(a) (b)

FIG. 1(a) The D configuration, as in $(+)[\mathrm{Coen}_3]^{3+}$. This has left-handed helicity about the C_3 axis, right-handed about any C_2 axis, i.e., $\mathrm{D} \equiv \mathrm{S}(C_3)\mathrm{R}(C_2)$. (b) A positive Cotton effect: —— optical rotatory dispersion; - - - - - circular dichroism $(\epsilon_l - \epsilon_d)$.

Molecules with more than one (say *n*) element of asymmetry may obviously form enantiomers, where all *n* elements of asymmetry differ in optical configuration from one enantiomer to the other. However, such molecules may also form diastereoisomers, in which at least one and at most $(n - 1)$ elements of asymmetry have the same optical configurations. Examples of such diastereoisomers are common in coordination chemistry; an illustrative series is D-$[\mathrm{Co}(-\mathrm{pn})_3]^{3+}$, D-$[\mathrm{Co}(-\mathrm{pn})_2(+\mathrm{pn})]^{3+}$, D-$[\mathrm{Co}(-\mathrm{pn})(+\mathrm{pn})_2]^{3+}$, and D-$[\mathrm{Co}(+\mathrm{pn})_3]^{3+}$. These are diastereoisomers; their respective enantiomers are, of course, L-$[\mathrm{Co}(+\mathrm{pn})_3]^{3+}$, L-$[\mathrm{Co}(+\mathrm{pn})_2(-\mathrm{pn})]^{3+}$, L-$[\mathrm{Co}(+\mathrm{pn})(-\mathrm{pn})_2]^{3+}$, and L-$[\mathrm{Co}(-\mathrm{pn})_3]^{3+}$. In the case of diastereoisomers, there is no reason to suppose that symmetrical properties will be similar. This is, of course, the basis of the well-known method of resolution by means of forming diastereoisomeric salts, in which a racemic cation, ±C, is caused to form a salt with an asymmetric anion, say (+)A. The possible salts (+)C(+)A and (−)C(+)A are diastereoisomers, and not enantiomers (the enantiomer of (+)C(+)A is (−)C(−)A, and there is no (−)A in the system). The properties of the diastereoisomers will differ in many respects. Because there will be differences in interaction between cation and anion in the solid state, lattice energies and hence solubilities will differ. Crystallization of the mixture of (+)C(+)A and (−)C(+)A will therefore lead to the less soluble diastereoisomer crystallizing first.

In cases where the separate elements of asymmetry are contained within the same molecule or ion, the diastereoisomers may show surprising differences in properties. For example, the mixture obtained (*57*) from the reaction of (+)tartaric acid with DL-carbonatobisethylenediaminecobalt(III) cation contains both possible diastereoisomers. These react at strikingly different rates with nitrite ion, to such effect that the nitrite-containing product is optically pure:

$$(+)[\mathrm{Coen_2}(+\mathrm{T})]^+ \rightarrow \mathrm{D}(+)\text{-}[\mathrm{Coen_2(NO_2)_2}]^+$$

$$(-)[\mathrm{Coen_2}(+\mathrm{T})]^+ \rightarrow \text{no reaction}$$

The remainder of this review is concerned with individual types of system in which stereoselective differences have been observed between diastereoisomeric molecules. No attempt has been made to include all the work which has appeared, although relevant literature has been searched to May 1965. The aim has been to set out the areas of agreement, and to point out the paucity of data in places where information would be of the utmost value. In particular, the lack of quantitative data is emphasized.

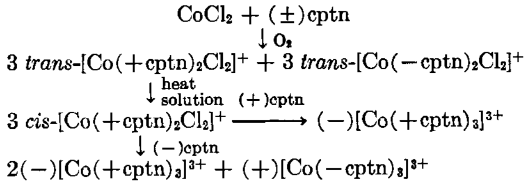
II. Complexes of Diamines

A. HISTORICAL

It has been recognized for many years that, in the complexes of transition metals with optically active diamines, there are marked stereoselective effects. The earliest demonstrations of this matter rested on the isolation from reaction mixtures of less diastereoisomers than the predicted number. Indeed, it was for many years thought that, in tris complexes of optically active diamines, this stereospecificity was complete, and that, using a diamine such as (+)propylenediamine, only one complex cation, say $(+)[\mathrm{M}(+\mathrm{pn})_3]^{n+}$, was formed. For example, the following reaction was discovered (*94*) very early, and confirmed (*8*) more recently.

$$3[\mathrm{Co}(-\mathrm{pn})_2\mathrm{Cl_2}]^+ + 3(+\mathrm{pn}) \rightarrow 2(-)[\mathrm{Co}(-\mathrm{pn})_3]^{3+} + (+)[\mathrm{Co}(+\mathrm{pn})_3]^{3+}$$

Similarly, Smirnoff (*92*) was able to isolate only two series of salts from the oxidation of cobalt(II) chloride in the presence of racemic propylenediamine. These contained $(-)[Co(-pn)_3]^{3+}$ and $(+)[Co(+pn)_3]^{3+}$. It was clear that one of the possible diastereoisomers, said by Jaeger (*53*) to be the most symmetrical, is the most stable, although whether this stability was kinetic or thermodynamic was not known. Similar work has been performed on complexes of other diamines. Jaeger and Blumendal found (*56*) that, using racemic *trans*-cyclopentanediamine, the reactions observed were:



$$\begin{tikzcd}
CoCl_2 + (\pm)cptn \arrow[d, "O_2"] & \\
3\ trans\text{-}[Co(+cptn)_2Cl_2]^+ + 3\ trans\text{-}[Co(-cptn)_2Cl_2]^+ \arrow[d, "\text{heat}\ \text{solution}"] & \\
3\ cis\text{-}[Co(+cptn)_2Cl_2]^+ \arrow[r, "(+)cptn"] \arrow[d, "(-)cptn"] & (-)[Co(+cptn)_3]^{3+} \\
2(-)[Co(+cptn)_3]^{3+} + (+)[Co(-cptn)_3]^{3+} &
\end{tikzcd}$$

Similar results were found for the complexes of rhodium(III), and later the work was extended (*55*) to complexes of *trans*-1,2-cyclohexanediamine, which gave rise to exactly similar stereospecific formation of favored isomers.

Although all this early work relied on isolation of complexes, and more recent work, discussed in subsequent sections, shows that the stereoselective effects are not nearly so absolute as was earlier thought, there is a great deal of evidence that one diastereoisomer, usually the most symmetrical, is a good deal more stable than the others. This has been explained (*15*) as a thermodynamic effect in terms of conformational analysis, although it appears likely that many of the stereoselective effects observed in complexes of ligands other than diamines may have a kinetic origin.

B. CONFORMATIONAL THEORY

1. *Conformation of a Five-Membered Chelate Ring*

As pointed out by earlier workers (*38*), chelation of a 1,2-diamine results in a nonplanar structure. In their remarkable paper (*15*) on the conformational analysis of chelate rings, Corey and Bailar calculated the preferred conformation of a chelate ring formed by ethylenediamine, using the best values for bond lengths available. The resulting carbon-carbon backbone is very similar to the side of a cyclohexane ring. There is now a great deal of evidence (*38*) that chelate rings formed by 1,2-diamines have, to a very good approximation, just this preferred conformation. For example, in the crystal structures of D(+)-$2[Coen_3]Cl_3 \cdot NaCl \cdot 6H_2O$ (*78*), D(+)-$[Coen_3]Br_3 \cdot H_2O$ (*77*), L(−)-$[Co(-pn)_3]Br_3$ (*86*), and *trans*-

$[\mathrm{Co(-pn)_2Cl_2}](\mathrm{H_5O_2})\mathrm{Cl_2}$ (*52*) the chelate rings are always *gauche*, and the detailed stereochemistry is, within a small amount, that calculated by conformational analysis.

2. Interaction of Three Chelate Rings

It was early realized (*85*) that a 1,2-disubstituted ethane in the *gauche* form is, in principle, a resolvable compound, since it has no center, plane, or alternating axis of symmetry. Although the only attempt (*91*) to resolve a monoethylenediamine compound—$[\mathrm{Coen(NH_3)_4}]^{3+}$—failed, this can be attributed to rapid inversion of the chelate ring. It is clear from Fig. 2 that a chelated diamine molecule is asymmetric. The forms shown, which might be called *d* and *l*, or (+) and (−), were in fact called (*15*) *k* and *k′* by Corey and Bailar, the *k* form being part of a right-handed helix, and the *k′* form part of a left-handed helix. One might expect these right-handed helices to pack better around a left-handed helix than around a right-handed one. Corey and Bailar were able to show (*15*) that three *k*- form diamine ligands would exhibit less H—H repulsion when packed into a complex of D configuration, which of course has a left-handed principal threefold axis, $\mathrm{S(C_3)}$, than when packed around a right-handed helix as in the L complexes. The result of packing three *k*-form diamine ligands is shown in Fig. 3; this complex was named "lel" because its threefold axis is parallel with the C-C bonds in the ligands. The diastereoisomeric complex, with *k′*-form ligands, was called "ob," because the threefold axis was obverse to the C-C bond direction (see Fig. 3).

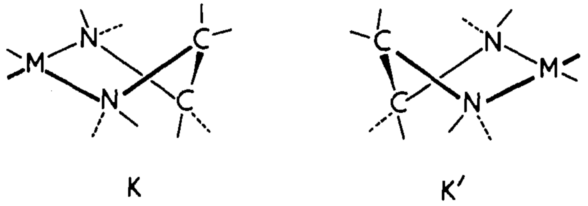


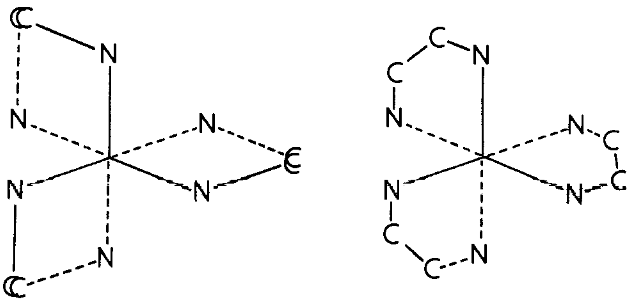
FIG. 2. Mirror image conformations of a diamine chelate ring.

This prediction (*15*) of a stable form with three *k*-form ligands in a complex of D configuration is valid for ethylenediamine itself; the energy difference calculated between the D(*kkk*) (lel) form and the D(*k′k′k′*) (ob) form was ca. 1.8 kcal/mole. This difference represents the stabilization of D(*kkk*)-$[\mathrm{Coen_3}]^{2+}$ relative to its diastereoisomer D(*k′k′k′*)-$[\mathrm{Coen_3}]^{3+}$, or of L(*k′k′k′*)-$[\mathrm{Coen_3}]^{3+}$ relative to L(*kkk*)-$[\mathrm{Coen_3}]^{3+}$. It is certainly true that in all the crystal structures so far reported* of trisdiamine metal complexes,

* These are $2[\mathrm{Coen_3}]\mathrm{Cl_3 \cdot NaCl \cdot 6H_2O}$ (*78*), $[\mathrm{Coen_3}]\mathrm{Br_3 \cdot H_2O}$ (*77*), L(−)-$[\mathrm{Co(-pn)_3}]\mathrm{Br_3}$ (*86*), and $[\mathrm{Nien_3}](\mathrm{NO_3})_2$ (*93*).

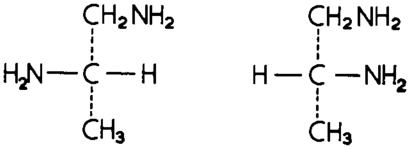
there has been a genuine threefold axis of rotation through the metal atom, in keeping with the conformational prediction that all three chelate rings will be equivalent.

In complexes of optically active diamines, the *k* and *k′* forms of ethylenediamine now correspond to the (+) and (−) enantiomers of the diamine. The absolute configurations of (+)- and (−)propylenediamine are shown in Fig. 4. Now, in addition to the hydrogen repulsions of the N-H groups in nonbonded *cis* positions, there is the additional factor, stabilizing the *k* form for (+)pn or the *k′* form for (−)pn, that the methyl group will be much more stable as an equatorial substituent. Here is the explanation of the observed stereospecificity in complexes of optically active diamines—it is only in the D-$[M(+pn)_3]^{n+}$ complex diastereoisomer that the methyl groups can be equatorial. Similar arguments may be used for other optically active diamines, and those, say (+)AA, with the optical configuration related to that of (+)pn will give as the most stable diastereoisomer D-$[M(+AA)_3]^{n+}$. This offers a method of deducing optical configurations of ligands or metal complexes, and examples of such deductions are discussed later.



"lel" "ob"

FIG. 3. The "ob" and "lel" isomers.



$$H_2N-\overset{\displaystyle CH_2NH_2}{\underset{\displaystyle CH_3}{C}}-H \qquad H-\overset{\displaystyle CH_2NH_2}{\underset{\displaystyle CH_3}{C}}-NH_2$$

(+) (−)

FIG. 4. The absolute configurations of (+)- and (−)propylenediamine.

C. RECENT WORK

Since the appearance of the conformational theory outlined above, a good deal of careful work has been performed by Dwyer and his students on stereoselectivity in trisdiamine systems. They found (*25*) more isomers than had previous workers. Trispropylenediaminecobalt(III) cation was obtained (*25*) as a mixture of the L(− − −), D(− − −), D(+ + +), and L(+ + +) forms. Using a charcoal catalyst to establish equilibrium rapidly, the reaction,

$$\mathrm{D}(-\ -\ -) \rightleftharpoons \mathrm{L}(-\ -\ -)$$

was shown to have an equilibrium constant, $K = 5.75$. The free energy is thus -1.02 ± 0.05 kcal/mole, which is the order of magnitude expected for conversion from the *kkk* form to a less conformationally stable form.

An early explanation for the nonisolation of the less stable diastereoisomers in systems involving cobalt(III) was that disproportionation occurred. On the ground that such an explanation would not be reasonable for the inert complexes of rhodium(III), where stereoselective effects also occur, Dwyer argued (*25*) that the difficulties in cobalt(III) systems could arise from intermediates of coordination number higher than 6, and the presence of labilizing cobalt(II) compounds. Such complications are less likely to arise in complexes of platinum, and some quantitative work (*23*) on the diastereoisomeric trispropylenediamine complexes of platinum(IV) has been done:

$$[\mathrm{PtCl_6}]^{2-} + 3(+)\mathrm{pn} \rightarrow (+)[\mathrm{Pt}(+\mathrm{pn})_3]^{4+} + (-)[\mathrm{Pt}(+\mathrm{pn})_3]^{4+}$$

$$[\mathrm{PtCl_6}]^{2-} + 3(-)\mathrm{pn} \rightarrow \underset{85\%}{(-)[\mathrm{Pt}(-\mathrm{pn})_3]^{4+}} + \underset{15\%}{(+)[\mathrm{Pt}(-\mathrm{pn})_3]^{4+}}$$

The pairs of diastereoisomeric cations formed in each reaction were separated by means of the fractional crystallization of their oxalates, which are sparingly soluble in water. The relative amounts of stable and unstable diastereoisomers show that the energy difference between them is about that predicted for a conformational *kkk* → *k'k'k'* change.

Dwyer also made a careful study of the mixed products obtained from reactions of propylenediamine and ethylenediamine with cobalt(III). The results (*28*) are collected in Table I. It is clear that the results may readily be rationalized on the basis that D(*kkk*) isomers are more stable than D(*k'k'k'*).

The complexes of cobalt(III) with resolved *trans*-1,2-cyclopentanediamine have very recently been re-examined (*31*), and several corrections were made to the early work. However, although the ion previously formulated as trisdiaminecobalt(III) was in fact shown to contain a polynuclear species, the stereoselectivity of the formation of the complex was confirmed.

1. Applications

Configurations: From the conformational theory of stereospecificity, it is clear that a given hand of an optically active 1,2-diamine gives a most stable diastereoisomeric tris complex with any metal which has the same optical configuration. This was first demonstrated experimentally by Jaeger, who showed (*54*) that the stable diastereoisomers $[M(-\text{chxn})_3]^{3+}$, where M = Co, Rh, and Cr, had related optical configurations, since they formed mixed crystals of the same space group as their optically active parents, rather than partial racemates. He also showed that the dissymmetries of spots were similar on a Laue picture taken with X-radiation directed from $000\bar{1}$ to 0001 for the three isomorphous nitrates.

TABLE I
COMPOSITION OF "MIXED" TRISDIAMINE SPECIES[a]

	Products (%)			
			Direct synthesis	
Product	From $[\text{Coen}_2\text{Cl}_2]\text{Cl}$	From $[\text{Coen}_2(\text{NO}_2)_2]\text{Cl}$	(−)pn/en = 1:2	(−)pn/en = 2:1
$(-)[\text{Coen}_2(-\text{pn})]^{3+}$	27	28	27	15
$(-)[\text{Coen}(-\text{pn})_2]^{3+}$	10	17	18	37
$(-)[\text{Co}(-\text{pn})_3]^{3+}$	13	4	6	30
$(+)[\text{Coen}_2(-\text{pn})]^{3+}$	17.5	15.5	13	7
$(+)[\text{Coen}(-\text{pn})_2]^{3+}$	1	3.5	3	5
$(+)[\text{Co}(-\text{pn})_3]^{3+}$	1	1	1	2

[a] From reference (*22*).

Several applications are possible of this stereospecific induction of configuration by optically active diamines. Knowing the absolute configuration of the diamine, it is obviously possible to predict which diastereoisomer of the trisdiamine complex will be the more stable. A prerequisite is the knowledge of the configurations of 1,2-diamines. These may be related by comparing the Cotton effects of their metal complexes, such as the blue (or yellow) Lifschitz salts, $[\text{Ni}(\text{diamine})_2]X_2$, X being an anion. A self-consistent correlation on these lines has been obtained (*37*) for all the diamines which have been used in stereospecific studies. Those having the optical configuration related to that of (+)propylenediamine (itself related to L(+)alanine) are (*37*) (+)pn, (+)bn, (+)cptn, (+)chxn, (+)phenen, and (−)stien. The more stable diastereoisomer of complexes containing three of any of these diamines will have the D configuration.

A good deal of use has been made of this principle. The general method has been to decide which diastereoisomer is the more stable, e.g., D(+)-[Co(+pn)$_3$]$^{3+}$. The nature of the Cotton effects of this diastereoisomer is then determined, and compared with those of resolved complexes of inactive diamines, such as (+)[Coen$_3$]$^{3+}$. Since the spectroscopic levels in the ligand field region are extremely similar for such closely related compounds, a direct comparison of optical configuration is possible. For example (*21*, *43*), the more stable diastereoisomer, D(+)-[Co(+pn)$_3$]$^{3+}$, has Cotton effects exactly similar to those of (+)[Coen$_3$]$^{3+}$, which is known to have the D configuration by Bijvoet analysis. The optical configuration of the more stable diastereoisomer has recently been confirmed directly by a full Bijvoet method analysis (*86*) of the stable diastereoisomer (−)[Co(−pn)$_3$]$^{3+}$, which was found to have the L configuration. In another example (*21*), the more stable diastereoisomer of [Rh(−pn)$_3$]$^{3+}$, which must have the L configuration, shows a circular dichroism spectrum very similar to that of the cation (+)[Rhen$_3$]$^{3+}$, which therefore also has the L configuration. Work of this kind has been performed for complexes of cobalt(III) (*21*, *43*), chromium(III) (*19*), rhodium(III) (*43*), and platinum(IV) (*20*) and the results are summarized in Table II. Results obtained by such classical methods (*16a*) as partial racemate formation are confirmed by this stereospecific method.

TABLE II
CONFIGURATIONS OF TRISDIAMINE COMPLEXES

Cation	D configuration[a]	Circular dichroism		(+)T[b]	A.R.[c]
		mμ	$\epsilon_l - \epsilon_d$		
[Coen$_3$]$^{3+}$	(+)	493	+1.9	(+)	(+)
[Rhen$_3$]$^{3+}$	(−)	310	+1.4	(−)	(−)
[Iren$_3$]$^{3+}$	(−)	315	+0.4	—	—
[Cren$_3$]$^{3+}$	(+)	460	+1.7	—	—

[a] From stereoselectivity (*21*).
[b] Relative configurations from less soluble diastereoisomers.
[c] Relative configurations from the method of active racemates (*16a*).

2. Spectroscopy

A brief summary of the spectroscopy of dihedral complexes is necessary. For d^6 spin-paired complexes, such as those of cobalt(III), with pure octahedral symmetry, O_h, the ground state is $^1A_{1g}$, $(e_g)^6$, from which triply degenerate spin-allowed transitions may occur within the *d-d* manifold to

${}^1T_{1g}$ (Band I) at lower energy, and ${}^1T_{2g}$ (Band II) at higher energy, the excited states arising from $(e_g)^5(t_{2g})^1$. Band I is magnetic-dipole-allowed, and therefore gives rise to a much larger rotational strength than Band II, which is magnetic-dipole-forbidden. In a trischelate complex, the highest element of symmetry is the threefold axis; complexes of ligands such as 1,2-diamines also have three twofold axes, so that such complex ions as $[\mathrm{Coen_3}]^{3+}$ belong to the point group D_3. This is equivalent to the statement that there is a trigonal distortion about the cobalt atom. The threefold degeneracy of the excited states is lifted, and both Bands I and II become split into an A and an E state. Under Band I for such complexes, two transitions therefore occur, each giving rise to a Cotton effect (${}^1A_1 \rightarrow {}^1E_a + {}^1A_2$). It may be predicted that these will be of opposite signs. For D(+)-$[\mathrm{Coen_3}]^{3+}$ it has been shown (*9*) that the E_a transition has a positive rotational strength. This leads to the rule that if the E_a transition gives a positive Cotton effect, the complex has the D configuration. Conversely, absolute configurations may be used to deduce spectroscopic information, since, if the complex has the D configuration, then the positive Cotton effect under Band I arises from ${}^1A_1 \rightarrow {}^1E_a$. This offers a method of assessing small spectroscopic splittings, and it has been shown (*19*) in this way that the splittings of Band I in trisdiamine complexes of cobalt(III), rhodium(III), and chromium(III) are all in the same sense, the $A \rightarrow E$ component falling at lower energy than the $A \rightarrow A$ component.

A number of studies have appeared on the spectroscopic splittings in trisdiamine complexes; it has been suggested (*97*) that the two components observed under Band I are not in fact due to ${}^1A_1 \rightarrow {}^1A_2$ and ${}^1A_1 \rightarrow {}^1E_a$ of a trigonal complex, but to the "lel" and "ob" conformations of the complex. However, the more stable diastereoisomer D(+)-$[\mathrm{Co(+pn)_3}]^{3+}$, which exists purely in the "lel" conformation by virtue of the equatorial requirement of the methyl groups, shows (*21*) two bands, in the same way as (+)$[\mathrm{Coen_3}]^{3+}$. A similar pair of Cotton effects of opposed signs is observed for the stable diastereoisomers of $[\mathrm{Rh(-pn)_3}]^{3+}$ (*21*) and of $[\mathrm{Co(-chxn)_3}]^{3+}$ (*83*). It has recently been suggested (*67*) that the sign of the Cotton effect which arises from the charge transfer absorption at ca. 220 mμ is related to the k or k' configuration of the ligand.

Configurational relationships based on the effect of forming ion pairs with polarizable anions are in agreement with the earlier work using stereospecificity. In particular, the similar behavior with phosphate ions of D(+)-$[\mathrm{Coen_3}]^{3+}$ and D(+)-$[\mathrm{Co(+pn)_3}]^{3+}$ may be attributed (*71*) to the possibility of stabilizing the "lel" conformation in both by hydrogen bonding. L(−)-$[\mathrm{Co(+pn)_3}]^{3+}$, the less stable diastereoisomer, behaves in a totally different manner.

3. Two Asymmetric Diamines

When two asymmetric ligand molecules combine with a metal salt to produce a *cis* complex with an asymmetric metal atom, then the six possible optical isomers that can be produced, arranged in pairs of enantiomers, are:

D(++) and L(−−)
D(+−) and L(+−)
D(−−) and L(++)

If only one enantiomer of the ligand has been used in the reaction, say the (−) form, then the possible products are limited to the D(−−) and the L(−−) isomers, which are not enantiomers but diastereoisomers. The diastereoisomers should be separable by fractional crystallization or by chromatographic techniques. If the metal complex which results from the combination of the racemic ligand with the metal is planar or tetragonal, e.g., $[Pt(diamine)_2]Cl_2$ or *trans*-$[Co(diamine)_2Cl_2]Cl$, then the possible products are (++), (−−), and (+−). The first two isomers are enantiomeric and have no center of symmetry. The (+−) isomer has a center of symmetry and should therefore be physically different from the pair of enantiomers. However, it has been pointed out (*95*) that this difference in symmetry, and hence in "allowedness" of the electronic transitions, will be too small to be observed experimentally, and a similar observation is that the electronic spectra of solutions of racemic copper(II) alaninate and of optically active copper(II) alaninate are identical (*39*), despite an earlier report (*17*) of differences.

4. Evidence for Stereoselectivity

Tetragonal complexes: There is a good deal of evidence that the equatorial preference of substituents on 1,2-diamine chelate rings gives rise to considerable effects on stabilities. For example, complexes of *meso*- and *dl*-1,2-diamines, such as stilbenediamine, differ in thermodynamic stability (*38*) because the *meso* complexes have at least one substituent which is axial on the *gauche* chelate ring. A similar explanation applies to the greater preparative stability (*31*) of copper complexes of the 1,2-amino-alcohol, ψ-ephedrine, than for ephedrine itself. Unfortunately, there is no thermodynamic information whatsoever on the relative stabilities of such complexes as *trans*-$[M(+AA)_2]^{n+}$ and *trans*-$[M(+AA)(-AA)]^{n+}$. The theory (*15*) of Corey and Bailar predicts that the complexes containing two molecules of diamine of the same hand (*kk*) will be more stable than the mixed *meso* complex containing one ligand of each optical hand (*kk'*). There are some early preparative studies which suggest that this is true.

Jaeger and Blumendal (*56*) found no mixed isomers in the reaction products of cobalt(II) chloride and trans-1,2-cyclopentanediamine. Optically inactive *trans*-dichloro-1,2-cyclopentanediaminecobalt(III) chloride was prepared (1) by mixing equimolar amounts of *trans*-$[Co(-cptn)_2Cl_2]Cl$ and *trans*-$[Co(+cptn)_2Cl_2]Cl$, and (2) from the racemic base.

The compounds produced by the two methods were identical in physical properties. In the first reaction there was no reason to expect that equilibration had occurred. Therefore they concluded that no mixed isomers had been formed. However, it appears (*81*) that the *trans*-1,2-cyclopentanediamine used by Jaeger was impure. When the pure diamine was used (*81*), several of Jaeger's reactions could not be repeated.

Corey and Bailar showed (*15*) that in planar and tetragonal complexes only the hydrogen-hydrogen interactions of the neighboring amine groups were significantly different between the *kk* and the *kk'* forms, i.e., between the optically active and the *meso* forms. Calculations showed that the *kk* form was more stable than the *kk'* form by about 1 kcal/mole. Therefore the *kk* form will predominate at equilibrium by a factor of about 5. The early failure to find the mixed isomer, which must form only a small percentage of the total reaction product, may be because the complete reaction product was not examined. It has been suggested (*79*) that Hurlimann's work (*48*) on the *cis*-dinitrobispropylenediaminecobalt(III) ion actually referred to the *trans* isomer. However, he found no mixed isomers, whatever the complex he studied.

Cis-bisdiamine complexes: It is clear from the treatment of conformations by Corey and Bailar (*15*) that the hydrogen-hydrogen repulsions and the equatorial preference of substituents in the chelate rings, which dictate the details of stereochemistry in the trisdiamine complexes, will also be present in *cis*-bisdiamine complexes, although the effect is expected to be smaller in the bis complexes. There is a good deal of evidence that this is so, and that there is a more stable diastereoisomer of the pair D-$[M(+AA)_2XY]^{n+}$ and L-$[M(+AA)_2XY]^{n+}$. Mere occurrence of a Cotton effect for the *d-d* transitions of the equilibrium mixture does not prove this, since there is no reason why the rotatory powers of the two diastereoisomers should be equal. Even a 1:1 mixture will therefore give a net Cotton effect. The preferred method of procedure is to isolate both diastereoisomers pure, as salts of inactive anions, and to use their rotatory properties to analyze the equilibrium mixture (which may be the original synthetic product or, more commonly, the product of equilibrating either diastereoisomer.)

Unfortunately a good deal of the early work is severely qualitative in nature. For example, when a solution of *trans*-dichlorobis(+)cyclopentanediaminecobalt(III) chloride was heated, the product is (−)*cis*-dichlorobis(+)cyclopentanediaminecobalt(III) chloride. This reacted (*56*) with a further mole of (+)base to give the favored tris(+)base complex. However, this does not prove that the *cis*-bis complex contained an excess of one diastereoisomer.

Hurlimann (*48*) could isolate only two isomers from a compound which he regarded as a *cis*-dinitrobispropylenediaminecobalt(III) salt. These isomers were designated D(− −) and L(+ +). However, optical rotatory dispersion (*79*) showed that his compound was largely the *trans* isomer. Similarly, Jaeger and Blumendal (*56*) could not find mixed isomers in *cis*-dichlorobispropylenediaminecobalt(III) chloride, or in *cis*-dichlorobiscyclopentanediaminecobalt(III) chloride.

Since the work (*15*) of Corey and Bailar on the conformation of chelate rings, greater care has been taken in the examination of products of reactions of metal ions with asymmetrical ligands. It was suggested (*15*) that, in many such reactions, especially those where there were labile intermediates, thermodynamic equilibria would be found, so that "mixed isomers," which had previously been overlooked, should be detectable by careful examination of the products.

Dwyer and Sargeson (*30*) reacted (−)propylenediamine with tetrachloroethylenediamineplatinum(IV) in dimethylformamide. In this solvent the product is precipitated as soon as it is formed. The product will therefore be kinetically controlled. As the complexes of platinum(II) are not labile, platinum(II) impurities would not produce the thermodynamically controlled product. The product was resolved, and it was shown (*30*) that the ratio of the (+) and (−) forms of ethylenediaminebis(−)propylenediamineplatinum(IV) chloride was 55:45 in favor of the (+) form. Dwyer *et al.* (*28*) prepared bis(−)propylenediamine-ethylenediaminecobalt(III) chloride in the presence of charcoal, and separated the products by paper chromatography. They found that the ratio of the D(− −) to the L(− −) isomer was 13.4:86.6. From the equilibrium constant, the free energy difference between the isomers was 1.2 kcal/mole, the value expected from the conformational theory. As the reaction started from a cobalt(II) salt in the presence of activated charcoal, the ratio of the products was not determined kinetically, but by the relative thermodynamic stabilities of the products.

The oxalatobis(−)propylenediaminecobalt(III) ion was prepared and separated into its diastereoisomers by the same workers (*27*). The equilibrium constant $K = \text{D}(--)/\text{L}(--)$ was calculated from the rotation of the mixture. This showed (*27*) that there was 42 ± 2% of the L(− −) form at equilibrium; the difference in free energy between the diastereoisomers is 200 cal/mole. The ratio of the amounts of the diastereoisomers obtained from the equilibrium studies was the ratio obtained from the recovery of the reaction products. The reaction product was therefore at thermodynamic equilibrium.

A preparation which is absolutely stereospecific has been reported by Dwyer and McDermott (*26*). The reaction of cobalt(II) chloride, (−)propylenediamine, and carbon dioxide in the presence of lithium carbonate gave optically pure L-carbonatobis(−)propylenediaminecobalt(III) chloride on crystallization from aqueous acetone. The lower solubility of the L diastereoisomer and the equilibrium, which must exist between the D and the L diastereoisomers, are the cause of the absolute stereospecificity in this preparation. This "second order asymmetric synthesis" shows how dangerous it is to argue from the isolated solid products back to the nature of the equilibria in solution. Martinette and Bailar (*70*) had previously attempted to separate the diastereoisomers by fractional crystallization. This was only partially successful, but they did show that the impure diastereoisomers differed markedly in optical rotatory dispersion, although their electronic absorption spectra and conductivities were the same.

5. *Applications to Absolute Configuration*

Iwasaki and Saito have determined (*52*) the absolute configuration of *trans*-dichlorobis(−)propylenediaminecobalt(III) chloride by the Bijvoet method. The (−)propylenediamine chelate rings were found to be in the *kk* conformation, as predicted (*15*) by Corey and Bailar. However, work by Saito and his co-workers shows that in *trans*-dichlorobisethylenediaminecobalt(III) chloride (*76*) and in *trans*-dichlorobis(+−)propylenediaminecobalt(III) chloride (*52a*) the chelate rings are in the *kk′* conformation. Results on solids are not a completely reliable guide to the nature of solutions. The equilibrium studies of other types of system in solution by Dwyer and his co-workers agree well with the predictions of Corey and Bailar.

The conformational theory can therefore be used (*43*) to assign the absolute configuration of bisdiamine complexes in the same way as it has been used for the trisdiamine complexes.

If the conditions of a reaction are such that a thermodynamic equilibrium is achieved, then conformational analysis will show which isomer is the more stable and will thus predict the predominant isomer in the reaction product. Table III shows the ratio of the diastereoisomers calculated from the free energy values.

In trisdiamine complexes and in bisdiamine complexes, the more stable isomer predominates by a considerable margin. However, in complexes with only one diamine this predominance is reduced because the physical difference between the diastereoisomers is much less. There is therefore a greater degree of uncertainty. There have been no assignments of the absolute configuration of complexes with only one asymmetric diamine ligand. Indeed, in contrast to the increasing use of stereoselectivity in

TABLE III
FREE ENERGY DIFFERENCES AND RATIOS OF DIASTEREOISOMERS

ΔG (cal/mole)	%D(+++)	%L(+++)	K = D(+++)/L(+++)
1800	95.2	4.8	18.94
1200	88	12	7.33
600	73	27	2.70

complexes with three asymmetric diamine ligands, there has been only one report (*43*) on the use of stereoselectivity to assign the absolute configuration of complexes of bisdiamines. The argument is essentially similar to that for the trisdiamine complexes; the stable diastereoisomer $(-)[Co(-pn)_2CO_3]^+$, from the conformational theory, has the L configuration. This diastereoisomeric cation has a rotatory dispersion curve essentially enantiomorphous with that of resolved (+)carbonatobisethylenediaminecobalt(III) cation, which may therefore be assigned (*43*) the D configuration.

Qualitative work on $[Co(AA)_2X_2]^{n+}$ complexes by Mathieu (*73*) showed that the more stable diastereoisomers of nine complexes of the type $(+)[Co(+pn)_2(NO_2)_2]^+$ had positive rotatory dispersion curves. Since these complexes have the D configuration induced by the equatorial requirement of the methyl groups, their Cotton effects serve as a reference for determining the absolute configurations of the analogous complexes of ethylenediamine, which are (*43*) D(+)-$[Coen_2(NO_2)_2]^+$ and D(+)-$[Coen_2(H_2O)_2]^{3+}$. These last complexes have since been related chemically, together with all the intermediate complexes (*34*).

6. *Reactions*

Bailar and McReynolds prepared (*7*) *cis*-dichlorobis(−)propylenediaminecobalt(III) chloride and the corresponding carbonato complex. The two diastereoisomers of the carbonato complex were not of equal stability. The conversion between these diastereoisomers has been extensively studied, with various experimental conditions (*69, 70*).

Several workers (*8, 56*) have tried to prepare mixed trisdiamine complexes by the reaction of the bis active diamine complex with either the racemic diamine, or the other enantiomer of the base. They failed to isolate any mixed isomers. This failure is explained by later work which showed (*33*) that trisdiaminecobalt(III) complexes would be racemized in basic solutions. Therefore any excess of the diamine will cause the mixed isomers that might have been formed initially to rearrange into the equilibrium mixture which is the result of the conformational interactions of the puckered diamine rings. The mixed isomers form a very small percentage of this mixture and considerable experimental dexterity is required to isolate and identify them.

Active carbonato complexes have been used (*44*) for the partial resolution of several organic acids. Carbonatobis(−)propylenediaminecobalt(III) chloride reacts at a different rate with the (+) form of the organic acid than with the (−) form. Excess of the racemic acid was used and the unreacted acid was found to be partially resolved. The amount of resolution, which in the most successful experiment was only 30%, should be considerably increased if optically pure L-$[Co(-pn)_2CO_3]Cl$ were used. A similar reaction between racemic alanine and *trans*-dichlorobis(−)propylenediaminecobalt(III) chloride was unsuccessful. There was no preferential coordination of one enantiomer of the alanine in the metal complex formed. Tartratobisdiaminecobalt(III) complexes also show a difference in the stability and reactivity between the diastereoisomers. This difference has been used (*45*, *57*) to obtain partial resolutions of racemic tartaric acid and racemic propylenediamine.

During some interesting work (*75*) on the asymmetric synthesis of threonine, glycinatobis(−)propylenediaminecobalt(III) iodide (probably a mixture of diastereoisomers) was caused to react with acetaldehyde at controlled pH at room temperature. A very small amount of threonine was obtained with an asymmetric yield of 8%. When (−)glycinatobisethylenediaminecobalt(III) iodide was used, the asymmetric yield dropped to 1%. (−)Threonine was formed in preference to the (+) enantiomer. Reactions of this Knoevenagel type, between acetaldehyde and a methylene group in an amino acid chelate ring, also occur readily (*40*) in complexes of cobalt(III) with peptides.

Only one reaction of a trisdiamine complex has been reported (*8*). (+)Trisethylenediaminechromium(III) bromide, or tris(−)propylenediaminechromium(III) chloride, was allowed to react with an excess of racemic phenylalanine for several hours. A polynuclear complex of phenylalanine with chromium(III) was obtained, and the unreacted phenylalanine showed no optical activity.

7. *One Asymmetric Ligand*

The predominance of one optical isomer in the equilibrium mixture of the products of a reaction which could produce several diastereoisomers is less marked when there is only one asymmetric ligand per metal atom than when there are two or more asymmetric ligands. Werner (*96*) claimed to have isolated the eight possible isomers of the *cis*-dinitroethylenediaminepropylenediaminecobalt(III) cation. Bailar confirmed this work, but found that there was no stereoselectivity. However, Sargeson (*87*) has cast some doubt on the chemical isomerism of all the products of the reaction used to form this complex, which is allegedly:

$$\mathrm{Coen(NH_3)(NO_2)_3 + pn \rightarrow [Coenpn(NO_2)_2]^+}$$

The "isomers," separated by chromatography, do not all have optical rotatory dispersion spectra similar to those of $\mathrm{[Co(AA)_2(NO_2)_2](NO_2)}$, where AA = en or pn.

It has also been pointed out (*38*, *87*) that the compound (+)bisethylenediamine-1,2-cyclopentanediaminecobalt(III) chloride, which Jaeger (*56*) claimed to have made, is likely to be a mixture of (+)trisethylenediaminecobalt(III) chloride and (+)tris-1,2-cyclopentanediaminecobalt(III) chloride, because the reaction of *cis*-dichlorobisethylenediaminecobalt(III) chloride with (+)propylenediamine gives (*87*) a product whose stoichiometry is $\mathrm{[Coen_2pn]Cl_3H_2O}$ and which remains unchanged after several recrystallizations. This "isomer" is a solid solution of D-$\mathrm{[Coen_3]Cl_3H_2O}$ and D-$\mathrm{[Copn_3]Cl_3H_2O}$. The components cannot be separated by crystallization of the product of this reaction in methanol. However, 1% of the product was made up of cobalt(II) compounds. The presence of cobalt in this kinetically labile state may explain the failure of the attempts to isolate the mixed isomers. Dwyer *et al.* (*28*) reacted cobalt(II) chloride, (−)propylenediamine, ethylenediamine, and hydrochloric acid at 25° in the presence of charcoal while air was bubbled through the mixture. The composition of the products depended on the ratio of ethylenediamine to propylenediamine in the reaction mixture. The ratio of the products was that given by a statistical treatment assuming that the two bases are equivalent. The products of the reaction were separated by chromatography and then resolved. In the equilibrium mixture, the ratio of the (+) to the (−) diastereoisomer of bisethylenediamine(−)propylenediaminecobalt(III) chloride was 1 to 2.1. The free energy difference between the isomers is 450 cal/mole. From the conformational theory, one might expect about 600 cal/mole.

The only other case where one diastereoisomer has been shown to predominate at equilibrium was reported (*27*) by the same authors. They found stereoselectivity in the formation of potassium bisoxalato(−)propylenediaminecobaltate(III) from cobalt(II) acetate. The diastereoisomers were separated and separately equilibrated with activated charcoal. At equilibrium there was 38 + 2% of the (−)[(−)] diasterereoisomer. This was also the percentage found in the initial reaction product. The free energy difference between the (−)[(−)] and the (+)[(−)] diastereoisomers was 270 cal/mole.

In mixed diamine complexes of platinum(IV) in dimethylformamide solution, where the ratio of the products is determined by the kinetics of the reaction, the two diastereoisomers of the bisethylenediamine(−)propylenediamineplatinum(IV) chloride were formed (*30*) in equal amounts. Bailar and his co-workers (*14*) prepared and resolved *cis*-dinitroethylenediamine-(+)2,3-butanediaminecobalt(III) chloride as the bromocamphorsulfonate; the rates of racemization of the two diastereoisomers were different.

The experimental work on the diamine complexes of metals, discussed here, suggests that the initial products of a reaction involving asymmetric molecules are determined kinetically. The ratio of these products will be given by the statistical chance of their formation, and they will be found in this ratio if they are immediately isolated, or if there is no means by which the thermodynamically unstable isomers may rearrange to the more stable isomers. The work of Dwyer and his associates has shown that the mixed isomers in the case of cobalt(III) are kinetically stable and will not rearrange to the thermodynamically favored ratio of isomers unless they are treated with activated charcoal, which will racemize (*18*, *88*) trisdiamine complexes of cobalt. The mechanism involved is probably reduction to labile cobalt(II) complexes, which will rearrange. Reoxidation will reform cobalt(III) complexes but with a different ratio of isomers. Popplewell has observed (*84*) that the rate of exchange of C^{14}-ethylenediamine with coordinated ethylenediamine in the $[Coen_3]^{3+}$ ion on charcoal is slower than the rate of racemization of $(+)[Coen_3]^{3+}$ under the same conditions. The racemization must therefore proceed, at least in part, by an intramolecular process. In basic solution, trisethylenediaminecobalt(III) ions are in equilibrium (*33*) with *cis*- and *trans*-bisethylenediaminecobalt(III) ions. $(+)[Coen_3]^{3+}$ will therefore be racemized in such solutions. The use of excess diamine in the preparation of diamine complexes of cobalt(III) will ensure that the products will be isolated in the thermodynamically favored ratios. Further, the presence (*29*) of cobalt(II) compounds in a reaction mixture apparently involving only cobalt(III) compounds is evidence of equilibration via a redox mechanism.

8. 1,2-Diaminetetraacetic Acids as Ligands

One of the very few cases where absolute stereospecificity has been observed is in complexes of substituted ethylenediaminetetraacetate ions. Two of these have been studied to date, those derived from propylenediamine (PDTA) and from *trans*-cyclohexanediamine (CHXTA). The stability constants (*51*) of (−)- and of (±)PDTA with such metals as magnesium and calcium are equal. When (+)PDTA forms a complex with a metal, for the methyl substituent on the *N*,*N'*-chelate ring to be equatorial, only one diastereoisomer is possible. It is found (*12*) that $(-)_{5461}[Co(+PDTA)]^-$ forms with complete stereospecificity; there is no evidence whatsoever for the other diastereoisomer (where the methyl group would be axial). A similar situation occurs (*24*) in the complexes of CHXTA. The absolute configuration of (+)PDTA is known from its relationship with (+)pn, and so the absolute configuration of the $(-)_{5461}[\mathrm{Co}(+\mathrm{PDTA})]^-$ may be deduced (*35*) as that in Fig. 5. By comparison of the observed circular dichroism curves, as in Table IV, the absolute configuration of $(-)_{5461}[\mathrm{Co}(\mathrm{EDTA})]^-$ is shown (*35*) to be that derived from Fig. 5, by replacing the methyl group with a hydrogen atom. Similar deductions have been made (*36*) for the absolute configurations of rhodium(III) complexes of EDTA, using the stereospecifically formed $[\mathrm{Rh}(+\mathrm{PDTA})(\mathrm{H_2O})]$ as a reference point. It was also possible to show in this way that the analogous energy levels in the analogous complexes of chromium(III) and cobalt(III) did not occur in the same order (*36*).

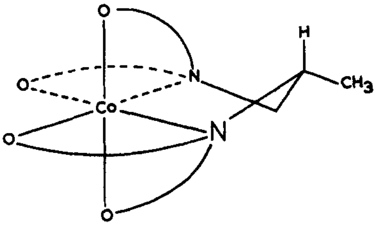


FIG. 5. The absolute configuration of $(-)_{5461}[\mathrm{Co}(+\mathrm{PDTA})]^-$.

Two stereoselective reactions of $[\mathrm{Co}(+\mathrm{PDTA})]^-$ were discovered by Irving and Gillard; these were

$$(-)_{5461}[\mathrm{Co}(+\mathrm{PDTA})]^- + (\pm)\mathrm{pn} \rightarrow \mathrm{D}(+)\text{-}[\mathrm{Co}(+\mathrm{pn})_3]^{3+} \qquad (49)$$

and

$$(-)_{5461}[\mathrm{Co}(+\mathrm{PDTA})]^- + \mathrm{en} \rightarrow \mathrm{D}(+)\text{-}[\mathrm{Coen}_3]^{3+} \qquad (50)$$

Some analogous reactions of the analogous complex of EDTA are also known:

$$(+)_{5461}[\mathrm{Co}(\mathrm{EDTA})]^- + \mathrm{en} \rightarrow (+)[\mathrm{Coen}_3]^{3+} + \mathrm{EDTA} \qquad (25a)$$

$$(+)_{5461}[\mathrm{Co}(\mathrm{EDTA})]^- + (\pm)\mathrm{pn} \rightarrow (+)[\mathrm{Co}(+\mathrm{pn})_3]^{3+} + \mathrm{EDTA} \qquad (6)$$

Mechanistic studies (*12*) of reactions of this type have not so far led to full steric details of transition states, but the results so far available are encouraging.

III. Complexes of Amino Acids

A. INTRODUCTION

The ring formed by an α-amino acid chelated to a transition metal is more nearly planar than that formed by a 1,2-diamine. Any stereo-

TABLE IV
CIRCULAR DICHROISMS OF DIAMINOTETRACARBOXYLATOCOBALTATES(III)[a]

Compound	Band I				Band II			
	ν_{max}	Sign	ν_{max}	Sign	ν_{max}	Sign	ν_{max}	Sign
$(-)_{546.1}[Co(EDTA)]^-$	17,010	+ve	19,420	−ve	23,801	+ve	27,470	+ve
$(-)_{546.1}[Co(+PDTA)]^-$	17,040	+ve	19,420	−ve	23,870	+ve	27,550	+ve

[a] From reference (*35*).

selectivity that occurred in complex compounds with α-amino acid ligands might be expected to be smaller than that in complexes of diamines. The easy separation of three of the four possible geometrical-optical isomers of tris-α-L-alaninatocobalt(III) by Lifschitz was considered to be the result either of a smaller free energy difference between the diastereoisomers than in trisdiamine complexes, or of a greater difference in solubility of the diastereoisomers. Others have suggested (*2*) that the high stability of the α-amino acid chelate ring will prevent the rearrangement of the isomers once formed. This argument is reasonable for the complexes of cobalt(III) but will not hold for the much more labile complexes of α-amino acids with nickel(II) and copper(II). It is with these labile complexes that the quantitative work has been done (*10, 39, 46, 47, 68*).

It is impossible to study equilibria in the trisamino-acidate complexes of cobalt(III) and rhodium(III) for several reasons (*20*). The principal hindrance is the extreme insolubility of one of the isomers in the alanine cobalt system, which prevents (*20*) the attainment of true equilibrium between the isomers. The very great solubility (*20*) of the trisaspartate and the trisglutamate complexes has so far prevented the complete separation of the isomers. The stability of the α-amino acid chelate rings is the other obstacle to equilibration studies. The optical rotation is unaffected by dissolution of the complexes in 50% sulfuric acid. The optical activity of $Co(L\text{-alaninate})_3$ is also unaffected (*20*) by boiling with a trace of cobalt(II) chloride or by warming with activated charcoal at 80°. If the α-isomers, that is, the (1,2,6)-isomers, are boiled with activated charcoal they are quantitatively converted (*20*) to the very insoluble β(+)-isomer. Therefore no equilibrium can be detected between the α- and β-isomers.

Certain tartrate complexes have been discussed in this section because the conformations of complexes of α-hydroxy acids bear some resemblance to those of α-amino acids.

B. ONE AMINO ACID

When only one amino acid is present in a complex, little stereoselectivity is expected. For example, Lifschitz (*64*) made compounds of the type $[Coen_2(\alpha\text{-amino-acidate})]Cl_2$, with glycine, D-alanine, and L-leucine. They were "resolved"* with (+)bromocamphorsulfonic acid and with (+)tartaric acid. Lifschitz showed that no dissymmetric synthesis had occurred, i.e., that the amounts of D and L $[Coen_2(L\text{-amino-acidate}]^{2+}$ were equal within experimental error. Similar results were obtained by Mathieu (*72*). The circular dichroisms of these complexes have recently been reported

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* This is not in fact a resolution, but a fractional crystallization; the resolving agent is *not* essential in separating the diastereoisomers, whose salts with inactive anions often have different solubilities.

(*13*) over an extended range. The optical rotatory dispersion of "racemic" (synthetic) $[\text{Coen}_2(\text{L-ala})]\text{I}_2$ changes (*20*) when fractional crystallization is carried out in aqueous ethanol, one diastereoisomer being less soluble than the other. This illustrates one of the difficulties of studies of stereoselectivity—the product from the reaction mixture, after recrystallization, is not representative of the reaction mixture.

A compound (*57*) which should be very similar to the monoamino acid complex is $[\text{Coen}_2(+)\text{tartrate}]\text{Cl}$. The two diastereoisomers were not completely separated but it was shown that the partially separated compounds had different reactivities, solubilities, and stabilities. For example, the difference in reactivity of the diastereoisomers was used (*57*) to give partially resolved complexes:

$$\begin{array}{llll} \text{DL-}[\text{Coen}_2(+\text{tartrate})]\text{Cl} & +\ \text{en} & \rightarrow & \text{D-}[\text{Coen}_3]\text{Cl}_3 \\ & & & (70\%\ \textit{resolved}) \\ & +\ \text{Ca(NO}_2)_2 & \rightarrow & \text{D}(+)\text{-}[\text{Coen}_2(\text{NO}_2)_2]\text{Cl} \\ & & & (\textit{good resolution}) \\ & +\ \text{HCl} & \rightarrow & \text{D}(+)\text{-}[\text{Coen}_2\text{Cl}_2]\text{Cl} \\ & & & (\textit{good resolution}) \end{array}$$

The high stereoselectivity of these reactions arose because only one of the diastereoisomers underwent reaction at room temperature. The more stable diastereoisomer, L(+), was more abundant and therefore more stable than the D(+) isomer. This means that there were stereoselective influences in the preparation of the complex, which is not unexpected from a polydentate ligand such as the tartrate anion. The asymmetric reactions (*75*) of $[\text{Co}(-)\text{pn}_2\text{glycinate}]\text{I}_2$ and $(-)[\text{Coen}_2\text{glycinate}]\text{I}_2$ have been discussed (Section II). The salt, $\text{D}(+)[\text{Coen}_2(\text{L-glutamate})]\text{ClO}_4$, is formed stereoselectively from $\text{DL-}[\text{Coen}_2\text{CO}_3]\text{ClO}_4$ and L-glutamic acid (20).

C. Two Amino Acids

There has been a good deal of quantitative work on bis-α-amino acid metal chelates. The compounds, Cu(α-amino acid)$_2$, are easily prepared. They are planar and could exist as either *cis* or *trans* geometrical isomers. All the structural evidence* shows that the complexes of asymmetric amino acids have the *trans* configuration. The planar M(*dl*-amino-acidate)$_2$ will be centrosymmetric and should therefore differ from the M(*d*-amino-acidate)$_2$ which is not centrosymmetric. Dijkgraaf (*17*) claimed to have observed this difference manifested as a difference in the oscillator strength in the electronic absorption band at 620 mμ. In fact, this difference is spurious, and arises because the molecular formulas of the two diastereo-

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* Although a recent X-ray analysis (*32*) of Cu(glycinate)$_2$ shows it to be a *cis* complex, and two crystalline forms of Cu(L-alaninate)$_2$ and of its enantiomer have been obtained (*42*).

isomers are different (*39*). On mixing equimolar solutions of the two enantiomers, Cu(D-alanine)$_2$ and Cu(L-alanine)$_2$, the electronic spectrum does not change. It has also been shown (*39*) that the stability constants, K_2, for the equilibria

$$\mathrm{Cu(L\text{-}ala)} + \mathrm{L\text{-}ala} \rightleftharpoons \mathrm{Cu(L\text{-}ala)_2}$$

and

$$\mathrm{Cu(L\text{-}ala)} + \mathrm{D\text{-}ala} \rightleftharpoons \mathrm{Cu(L\text{-}ala)(D\text{-}ala)}$$

are equal. Bennett had previously shown (*10*) that the optically pure diastereoisomers were favored in an apparently similar system. He obtained the formation constants for the mixed and the optically pure diastereoisomers of copper(II) with asparagine by potentiometric titration. The values he obtained were:

Nonmixed complex (*dd* or *ll*) $K_2 = 2.82 \times 10^6$
Mixed complex (*dl*) $K_2 = 7 \times 10^5$

Using the contact shifts of protons in the ligands, all the isomers in certain equilibrium mixtures have been detected. By studying the systems over a temperature range, thermodynamic constants for all the species present could be obtained. This technique, of course, depends on the complex being paramagnetic and is therefore not applicable to cobalt(III) complexes. McDonald and Philips (*68*) studied the proton contact shifts of the cobalt(II) bishistidine complex in deuterium oxide. They found that the DD and the LL complexes had identical contact shifts. If the optically pure complexes are mixed, then new peaks appear which have larger contact shifts. Equilibrium studies showed that in this system the mixed complex is the more stable, since it is in greater concentration at equilibrium than the DD or the LL isomers. The difference (*68*) in free energies for the 2:1 octahedral histidine cobalt(II) complexes is 0.7 kcal/mole. Holm and his co-workers (*47*) studied the bis(5-methyl-*N*-*sec*-butylsalicylaldimine)-nickel(II) complex. For this complex containing a Schiff base the proton contact shifts for the (++) and (−−) isomers were again the same, but when the optically pure complexes were mixed a new set of peaks appeared at once. These were identified as being due to the (+−) complex. The spectrum was measured from −40° to 100°, giving thermodynamic constants for the equilibrium, planar ⇌ tetrahedral, as shown in Table V.

The bis-L-aspartic acid complex of cobalt(III) has been used to obtain partly resolved alanine from the racemic amino acid (*89*). Sodium bis-L-aspartatocobaltate(III) was mixed with an excess of DL-alanine at pH 9.5–10 at 20°–40°. Activated charcoal was added to the reaction mixture. The excess alanine was removed from the precipitated tris-L-α-alaninatocobalt(III). The alanine was 13% resolved, the D enantiomer having been preferentially coordinated. If cellulose powder was also added to the reaction mixture, then the resolution was increased to 30%.

There is obviously a contradiction between the results (*39*) in the copper α-alanine system, where the stabilities of the mixed isomer and the optically active isomer are equal, and the asparagine (*10*) or histidine (*68*) system. A possible clue to the reason for this arises from the study of stereoselective effects in the copper(II) tartrate system. It was noticed by Cotton (*16*) that alkaline solutions of copper(II) mono(+)tartrate and copper(II) mono(±)tartrate were of differing blue colors. It has recently been shown (*20*) that this is due to polymerization, the equilibrium constant for

$$n[\mathrm{Cu}(+\mathrm{T})] \rightleftharpoons [\mathrm{Cu}_n(+\mathrm{T})_n]$$

differing from that for

$$n/2[\mathrm{Cu}(+\mathrm{T})] + n/2[\mathrm{Cu}(-\mathrm{T})] \rightleftharpoons [\mathrm{Cu}_n(+\mathrm{T})_{n/2}(-\mathrm{T})_{n/2}]$$

TABLE V
THERMODYNAMIC DATA[a] FOR A SCHIFF BASE COMPLEX

	Complex	
	(++) or (−−)	(+−)
ΔH	1,240 cal/mole	1,590 cal/mole
ΔS	1.58 e.u.	2.41 e.u.
ΔG	709 cal/mole	789 cal/mole

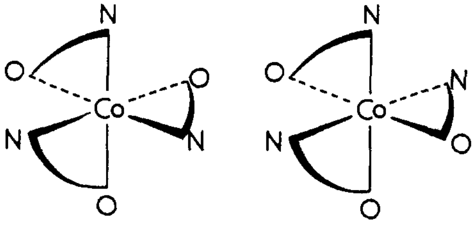
[a] From reference (*47*).

Similar stereoselective effects are found (*20*) for vanadyl tartrate species; the common assumption that asymmetric syntheses occur in the formation of such complexes as tris(+)tartratochromium(III) is probably warranted. The stereoselective effects described above for complexes of the tridentate ligands histidine and asparagine may also possibly arise from the presence of polymeric complexes.

D. THREE AMINO ACIDS

Three molecules of bidentate α-amino acid may be coordinated to a transition metal atom in two ways to give an octahedral complex. These two geometrical isomers designated α and β (see Fig. 6) could in principle give a maximum of eight optical isomers for each geometrical isomer. However, if an optically active amino acid is used the number of isomers is limited to four, α-D(LLL), α-L(LLL), β-D(LLL), and β-L(LLL). Lifschitz (*62*) claimed to have isolated the two α-isomers and one β-isomer of tris-L-α-alaninatocobalt(III). The single β-isomer was so insoluble that he could not tell whether it was a mixture of diastereoisomers or an optically pure compound. He also reported (*63*) the rotatory dispersion spectra of all four isomers of the tris-L-glutamatocobaltate(III) anion. The salts of these are, unfortunately, very soluble, and the compounds have not so far been obtained in crystalline form. However, Lifschitz found (*63*) that by varying the preparative method he obtained either the two D isomers (α and β) or the two L isomers. Presumably, then, the nature of the product is kinetically determined (although there is doubt (*20*) about the optical purity of Lifschitz' isomers, this suggestion about kinetic control is not affected). In the same way, the ratio of the amounts of α-isomers to β-isomers in the tris-L-alaninatocobalt(III) system depends (*60, 74*) on the preparative method.

No crystalline derivatives of the tris-L-aspartatocobaltate(III) were isolated (*66*), and isomerism was not discussed fully. Ley found (*59*) that in the tris-*N*-methylalanine cobalt(III) system, solubility difficulties hindered the work on isomerism.



β α

FIG. 6. The geometrical isomers of Co(amino-acidate)$_3$.

The difference in free energy between the two diastereoisomers of one geometrical isomer will depend only on the interactions between the substituents on the α-carbon atom in the amino acid, because of the planarity of the carboxylate part of the chelate ring. This interaction will be greater in the optically pure (1,2,3)-isomers than in the optically pure (1,2,6)-isomers, because in the former all three substituent groups are pointing in the same direction along the threefold rotation axis (C_3 axis), while in the (1,2,6)-isomer one substituent points away from the other two and steric interference will be reduced. The steric interaction will depend on the size of the substituent on the α-carbon atom. In alanine complexes this substituent is a methyl group, in aspartic acid complexes it is a —CH_2—CO_2H group, and in glutamic acid complexes it is a —CH_2—CH_2—CO_2H group.

The stereoselectivity of a reaction depends on the size of the free energy difference between the diastereoisomers, which the reaction produces. If the stereoselectivity arises from the interaction of substituents on the α-carbon atom of the ligand, then it will be least in the α-Co(L-alaninate)$_3$

complex and greatest on the β-[Co(L-glutamate)$_3$]$^{3-}$ ion of the complexes so far studied. We have shown that there is little stereoselectivity in the first complex. Lifschitz claimed (*63*) that there is considerable stereoselectivity in the glutamic acid complexes, but that the predominating isomer depends on the method of preparation. This is rather surprising. In our work on the Co(L-alaninate)$_3$ complexes we obtained (*20*) the optical rotatory dispersion curves of all four isomers (+)α, (−)α, (+)β, and (−)β. These isomers were optically pure. The optical rotatory dispersion of the (+)α-isomer was approximately the mirror image of that of the (−)α-isomer. The same was true of the β-isomers. The optical rotatory dispersion curves reported (*66*) for the (+)α and the (−)α complexes with the L-aspartic acid were also enantiomorphous. However, the optical rotatory dispersion curves, which Lifschitz reported (*63*) for the L isomers of the [Co(L-glutamate)$_3$]$^{3-}$ complexes, appear to be very similar to the curves for the D isomers. From a comparison of the optical rotatory curves (*63*), which Lifschitz obtained for the glutamate complexes, with the curves obtained (*20*) for the Co(L-alaninate)$_3$ complexes, it appears that [Co(L-glutamate)$_3$]$^{3-}$ isomers with the D configuration were the principal products obtained by Lifschitz in his study of this system. Stereoselectivity is therefore considerable in the glutamate complexes. A study is currently being made (*42*) on the corresponding complexes with valine and leucine, which also have large substituents on the α-carbon atom in the chelate ring, to see if this trend is continued.

IV. Other Ligands

Very little work has been done on stereospecific effects in complexes of ligands other than diamines or amino acids. The possible effects in complexes of such ligands as amino-alcohols or diols have been overlooked. However, some data are available (*20, 65*) on complexes of (+)hydroxymethylenecamphor, which acts as a β-diketone. It is certainly true that an apparently stereospecific reaction occurs with cobalt(III). The circular dichroism of a typical product shows (*71a*) 710 mμ, $\epsilon_l - \epsilon_d = -0.50$; 603 mμ, $\epsilon_l - \epsilon_d = +6.20$. From the relative sizes of these Cotton effects and those in fully resolved cobalt(III) complexes, it seems likely that a stereospecific synthesis has taken place, and that the product is not the 1:1 mixture of the diastereoisomers D-Co(+hmc)$_3$ and L-Co(+hmc)$_3$ that would arise in the absence of stereospecific interactions, but one or the other of them almost pure. From chromatographic work (*20*) it is clear that one diastereoisomer is present as ca. 95% of the mixture, so that the formation of tris(+)hydroxymethylenecamphoratocobalt(III) occurs with very marked stereoselectivity. This is extremely interesting, in view of the fact that the chelate rings in these β-diketonato complexes are virtually planar, and interactions of the type discussed by Corey and Bailar (*15*) for puckered rings are not present. In the case of the trishydroxymethylenecamphor complexes (*20*) of cobalt(III) and rhodium(III), it appears that one diastereoisomer is a good deal more stable than the other. In the case (*65*) of Cr(+hmc)$_3$, both diastereoisomers are formed, with the (+) isomer in large excess. These may be separated, but, on allowing a methanol solution of either pure diastereoisomer to stand for a day, the equilibrium mixture is again obtained.

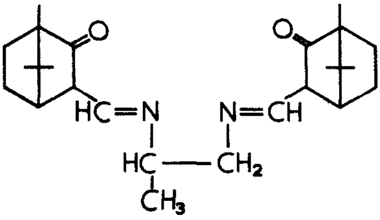


FIG. 7. Bishydroxymethylenecamphorpropylenediimine.

When hydroxymethylenecamphor condenses with propylenediamine to form the Schiff base, shown in Fig. 7, there are several diastereoisomers possible (*42a, 80*); calling the ligand HPH, those of interest are (+)H(+)P(+)H, (+)H(+)P(−)H, and (+)H(−)P(−)H. The complexes of these three individual tetradentate ligands are of different colors. This may be explained by differing steric requirements of the different ligands.

The only other optically active ligand which has been used at all extensively is (+)tartaric acid. For example, it is often said that when an aqueous solution of a chromium(III) salt reacts with three equivalents of (+)tartaric acid, a stereospecific synthesis occurs. It may well be true that a stereoselective process occurs, in view of the rather large Cotton effects observed for the reaction product, but it is not necessarily true. Tartrate systems are difficult to elucidate because of the presence of polynuclear complexes. This dominates (*1*) the tartratocopper(II) and tartratovanadyl systems, and renders dubious the stability constants measured in such systems. It is significant that solutions of the so-called "chromitartrate" ion do not obey the Beer-Lambert law, and show a strong absorption at ca. 350 mμ, suggesting the intervention of polynuclear species.

V. Conclusion

A great deal of new experimental work is required in this fascinating field. A large number of stereoselective effects is already known, but the number of these which have been explained is small. The detailed results on amino acid and peptide complexes of cobalt(III) are only beginning to appear, and studies of metals other than cobalt are generally conspicuous by their absence. A most interesting observation (*61*) is that the stabilities of the complexes of cobalt(II) with L-alanyl-D-alanine differ from those with L-alanyl-L-alanine. The remarkable biochemical stereospecific effects observed include the differential action of enantiomers of complexes with living systems, and the foundations for further work on such effects are only partially laid. It has recently been shown (*41*) that in the nonheme iron protein isolated from clostridia and other bacteria, ferredoxin, chemical reduction by sodium dithionite in the presence of α,α'-bipyridyl gives optically inactive tris-α,α'-bipyridyliron(II) salts whereas, when the protein is treated with 8 M urea in the presence of bipyridyl, $(-)[Fe(bipy)_3]^{2+}$ is formed stereospecifically.

It is said (*90*) that when such racemic substrates as catechin or 3,4-dihydroxyphenylalanine are allowed to react with oxygen in the presence of optically active cobalt(III) complexes, such as the (−)bromoamminebisethylenediaminecobalt(III) cation, one hand of the substrate is oxidized very much faster than the other. The similarity of the stereoselective effects in these comparatively simple systems to those observed in enzymatic processes suggests that the behavior of optically active diastereoisomeric complexes may provide convenient models for much more complex biological systems.

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