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Coordination Chemistry Reviews
178–180 (1998) 1183–1192

COORDINATION CHEMISTRY REVIEWS

Enantioselective creation of helical chirality in octahedral (OC-6) complexes. Recent advances

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Received 4 June 1997; accepted 16 July 1997

Contents

Abstract

The enantioselective creation of helical chirality (Δ/Λ in octahedral complexes is of crucial importance for applications in organic syntheses (enantioselective transition metal catalysts) as well as in bioinorganic chemistry (Δ/Λ biological recognition). This paper presents some selected examples depicting the controlled enantioselective formation of OC-6 complexes involving helical chirality © 1998 Elsevier Science S.A. All rights reserved.

Keywords: Asymmetric inorganic synthesis; Chiral ligands; Helical chirality

1. Introduction

Asymmetric synthesis has been, and remains, an essential goal in organic chemistry. Asymmetric inorganic synthesis is far from the state of development exhibited in organic chemistry, despite the importance of the chirality in transition metal complexes. For instance, the fundamental role of the absolute configuration at the

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PII S0010-8545(98)00085-X

metal center has been demonstrated in the recognition of iron(III)-siderophores by the membrane receptor proteins [1–6]. It is patent that the sense of the metal chirality is of the same importance in bioinorganic chemistry than the sense of the carbon chirality in bioorganic chemistry.

A plethora of chiral transition metal catalysts are used for enantioselective organic syntheses [7]. These catalysts are prepared by using chiral (and enantiopure) organic ligands and, in many cases, the metal is an inherent chiral element of the so-built catalyst. The configuration at the metal is usually occulted and the enantioselectivity of the catalyzed reaction is attributed to the chiral organic ligand in the catalyst. Of course, this is true but may be regarded as a "mental by-pass"! It is patent that the chiral organic ligand has induced a stereoselective creation of the chiral metal center during the preparation of the metal catalyst. Then, the enantioselectivity of the catalyzed reaction, which most often takes place within the coordination sphere of the metal complex, is also, and even primarily, due to the chirality of the metal center.

Synthetic organic chemists claim that stereochemical control is the most important aspect of the synthesis of molecules that contain one or more stereogenic elements. This control is an essential goal for a good synthetic design. Obviously, the same is true in the field of inorganic synthesis. Moreover, starting from such a control, a more rational design of enantioselective metal catalysts for organic syntheses may be considered. Despite the fact that helical chirality (see below) has been known for a long time, the stereochemical control for the enantioselective syntheses of coordination compounds may be considered, to date, as an emerging challenge.

This paper tries to present some recent and selected examples of enantioselective inorganic syntheses.

2. Chirality of coordination compounds

An exhaustive and excellent presentation of the stereochemistry of coordination compounds has been published by Von Zelewsky [8]. We will just underline some features here. In coordination chemistry, most chiral structures are devoid of chiral centers and most often helical chirality occurs. Helical chirality in OC-6 complexes requires at least two bidentate ligands leaving two ligand position in a *cis* configuration occupied by other ligands Fig. 1

The skew line reference system can be used for this kind of chirality [9]. The absolute configuration is related to the handness of the helix formed by the ligands. The chirality descriptors Δ (right rotation) or Λ (left rotation) are used. The oriented line reference system may be used in cases where the skew line system is ambiguous [10].

Chiral coordination compounds have been known for a long time: the first representation of an enantiomeric pair for an octahedral complex was given by Werner in 1899 [11]. $[Co(en)_2(NO_2)_2]Br$ which leads to a spontaneous resolution of the racemic form upon crystallization is probably the first example of obtention of enantiomerically pure synthetic octahedral complexes. The first resolution of a chiral octahedral complex in its enantiomers was achieved by Werner in 1911 [12]. The

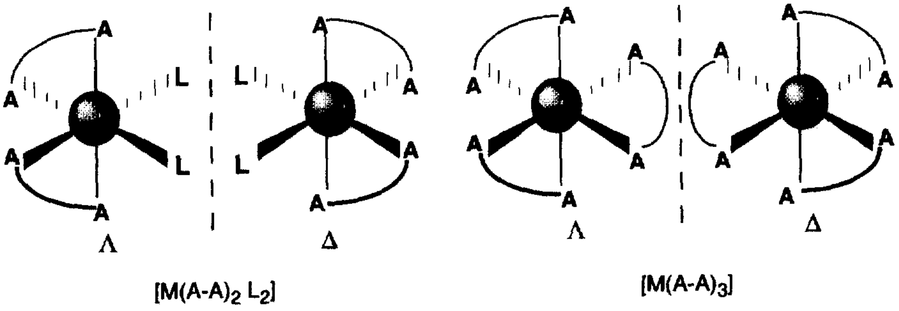

Fig. 1. Helical chirality.

absolute configuration of the two enantiomers of $[Co(en)_3]^{3+}$, was elucidated in 1955 by Saito et al. [13] using the Bijvoet method. An exhaustive review of the methods available to determine the absolute configuration of transition metal complexes appeared in 1970 [14].

To date, numerous enantiomers (especially for the OC-6 $[M(A–A)_3]$ complexes) have been purified from the racemic mixtures, most often by formation of diastereomeric salts with enantiomerically pure counter ions. Few examples of asymmetric inorganic syntheses involving the controlled creation of a chiral octahedral metal center are known. After a brief overview concerning the primitive approaches, we will present herein some recent and selected examples. Contrary to a widely held idea, optically stable complexes can be obtained (see below) from metals which do not involve ligand field stabilization, and in some cases structural effects inhibit the expected lability of the complex.

3. The first approaches of enantioselective inorganic syntheses

Several decades ago, numerous papers described the coordination of transition metal ions (most often Co^{3+}) by enantiopure chiral bidentate ligands (most often amino acids or 1,2-diamine derivatives) leading to mixtures of optically active diastereoisomers in unequal amounts (see [8], chap. 5, Section 5.5). Usually, the ligand corresponds to the A–B (and not the A–A) type, leading to four stereoisomers upon octaedral complexation (Fig. 2).

Only the Δ versus Λ selectivity and not the *fac* versus *mer* selectivity is the subject of this paper. It arises from the diastereoselectivity between *RRR*-Δ and *RRR*-Λ forms for the *fac* and the *mer* isomers, respectively.

The stereoselectivity of the complex formation has been attributed to conformational effects and this selectivity varies from one example to another. As an example, upon complexation of Co(III), the optically active (+)-hydroxymethylenecamphor yields to a thermodynamically controlled mixture of the diastereoisomeric tris complexes in which the Δ configuration seems to be the only observed [15]. With rhodium(III), Λ and Δ isomers are isolated resulting from a kinetic control of the

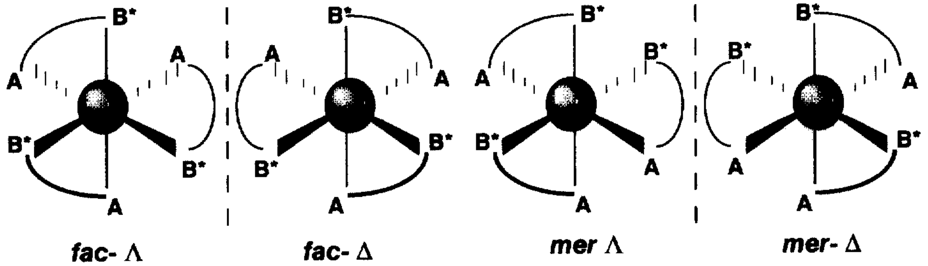

Fig. 2. The four stereoisomers (two enantiomeric pairs) of *R,R,R*-[M(A-B*)$_3$] from *R*-(A-B*).

reaction [15]. The authors emphasized the fact that the ligand "is capable of dictating an optical configuration at the metal ion even where the complex is kinetically labile". As a matter of fact, this point is the basis of this paper.

The importance of intramolecular interligand non-covalent interactions in stereoselectivity has been pointed out by Okawa [16]. This approach has allowed chemists to rationalize the stereoselectivities observed in the formation of 1:3 complexes of the trivalent Sc, Y, La, Al, Ga and In salts with 4-(1-menthyloxy)-1-phenyl-1,3-butanedione and 4-(1-menthyloxy)-1-*p*-tolyl-1,3-butanedione [17].

4. Enantioselectivity with natural and abiotic siderophores

As pointed out at the beginning of this paper, the recognition of iron(III)-siderophores by the membrane receptor proteins is related to the absolute configuration at the metal center. Raymond et al. have shown from CD spectra, that the ferric complex [as well as the Cr(III) and the Rh(III) complexes] of natural enterobactin (a chiral triscatecholate siderophore from *Escherichia coli*, based on three L-serine units) [1] assumes only the Δ-configuration [18,19]. The enantioenterobactine, built with D-serine units, gives the Λ iron complex which is not as efficient in growth promotion as the native enantiomer. The first structural characterization of a metal–enterobactin complex has been established by Raymond [for vanadium (III)] and reveals the Δ-configuration [20,21] (Fig. 3).

The geometry is intermediate between trigonal prismatic and octahedral with a twist angle of 28°. Shanzer et al. have suggested that the source of the preference for the Δ-configuration in enterobactin complexes arised from hydrogen bonding between the amide protons and the ester oxygens of the serine backbone, occuring in the free ligand before complexation [22]. Nevertheless, Raymond attributes the stereospecificity to conformational constraints in the triserine backbone, and molecular modelling calculations correctly predict the chiral preference [20,21]. Parabactine, another catecholate siderophore, forms a Λ gallium(III) chelate exclusively [23]. Stereospecificity of octahedral complexation has also been evidenced for hydroxamate siderophores. For example, the ferric siderophore, ferrichrome, from the smut fungus, *Ustilago sphaerogena*, assumes the Λ-*fac* absolute configuration in the crystalline state and in solution [24].

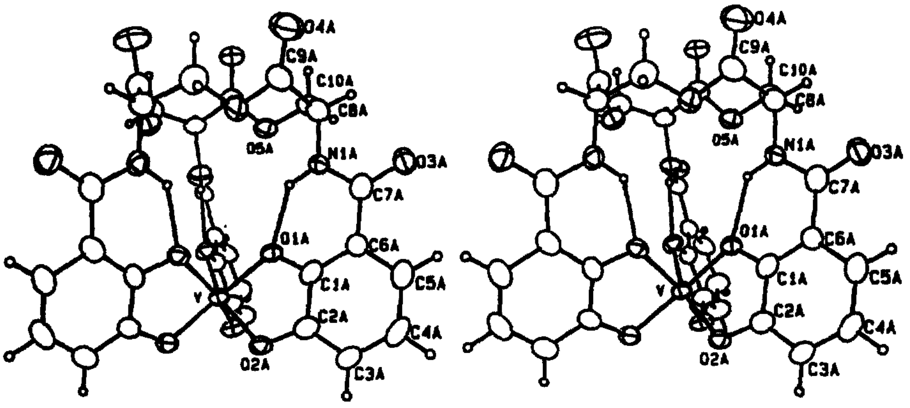

Fig. 3. Stereoview of $[V(ent)]^{2-}$ from Ref. [20].

Elegant biomimetic studies involving synthetic siderophores are typical examples of asymmetric inorganic syntheses. Chiral analogues of enterobactin [25] and desferrichrome [26] (Fig. 4) give respectively, the Δ-*fac* and the Λ-*fac* complexes. The control of Δ/Λ configuration has been also evidenced with artificial ferrichrome [27].

The control of the absolute configuration of the iron(III) octahedral center by the chirality of alanine residues introduced in a cyclophane with three catecholic arms (enterobactin model), has been evidenced [28]: the L-alanine residue prefers to give out the Λ-configuration, while the D-residue stabilizes the Δ-configuration. The first demonstration of a bidentate chiral ligand (Fig. 5) that results in 100% stereoselectivity in the formation of tris-chelate complexes with labile metal ions [Fe(III), Ga(III)] in aqueous solution, has been established in the work of Raymond et al. [29].

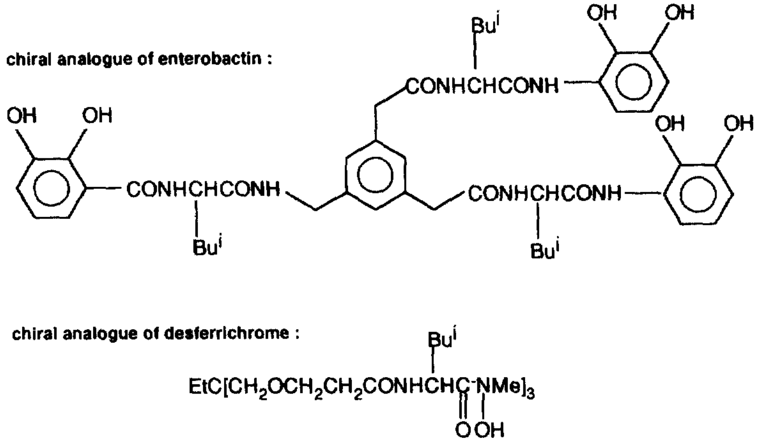

Fig. 4. Abiotic siderophores (synthesized from L-amino acids).

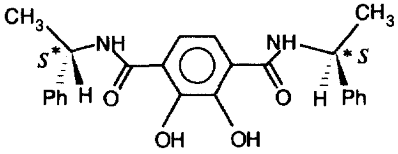

Fig. 5. A chiral bidentate ligand LH_2, which gives 100% of Λ complexes $[L_3Ga]^{3-}$ or $[L_3Fe]^{3-}$.

Weakly polar aryl/aryl and alkyl/aryl interactions (identified in the crystal structure) are responsible the selectivity.

5. A highly enantioselective series of ligands: the Von Zelewsky's "chiragens"

In a recent series of papers, Von Zelewsky et al. have evidenced the high potentialities of a new family of ligands (chiragens) for stereoselective syntheses of octahedral complexes with predetermined helical chirality [30–33]. Chiragens are enantiopure bis bidentate ligands involving two identical bipyridine subunits incorporating stereogenic centers derived from (−)-myrtenal (Fig. 6).

Chiragens are C_2 symmetric, each half containing three stereogenic centers, two from the natural precursor and one at the bridgehead. Chiragens can occupy four non planar coordination sites in an OC-6 complex, leaving two equivalent *cis* positions and the chirality of the rigid ligand predetermines unambiguously the chirality Δ or Λ of the complex. The absolute configuration of chiragens can be inverted by using (+)-myrtenal as starting material. As an example, the chiragen with $n=6$, leads enantiospecifically to the complex Δ-[Ru((+)-chiragen)(4,4′-dimethylbipyridine)]$(CF_3SO_3)_2$. The absolute configuration has been determined by X-ray crystallography and by circular dichroism (CD) in solution. This result confirms the configuration easily predicted from models: the Λ-configured product is not possible for sterical reasons (and consequently the Δ isomer cannot isomerize). All the chiragens described by Von Zelewsky exhibit enantiospecific OC-6 complexation, with the expected configuration. The complexes of the type Δ or Λ-[Ru(chiragen)Cl_2] can be used as chiral building blocks for the synthesis of

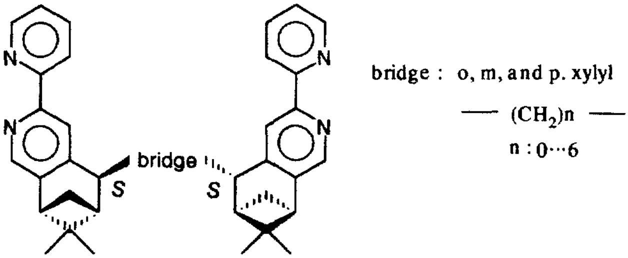

Fig. 6. The chiragens ligands.

stereochemically well-defined polynuclear species [32]. An enantiopure osmium complex of chiragen has also been described [33].

6. Ligands with axial chirality

The direct control of the Δ or Λ coordination by intrinsically chiral bidentate moieties with axial chirality has been evidenced for tris(binaphtolate) complexes of tungsten(VI) [34]: the chiral *aR* binaphtol reacting with WCl_6 leads to the *aR*, *aR* *aR*-Λ tris chelate.

The use of enantiopure binaphtol-derived ligand has led to the spectacular example of a stereospecific Δ/Λ control by the chiral macrobicyclic cavity $\mathbf{LH_6}$ (Fig. 7)[35]. The two enantiomers (*aR,aR,aR*) and (*aS,aS,aS*) of the bicapped tris (binaphtol) have been synthesized.

This hexadentate ligand is built with three identical bidentate subunits (three binaphtol moieties of the same axial chirality (*aR* or *aS*). It has been established that tripodate complexes were forced to the *fac* isomer [36]. This is a fortiori true for $\mathbf{LH_6}$ which may be regarded as a tripodate with its three feet connected by the second TREN moiety: only a *cis* (*fac*) arrangement of each set of three hydroxyl groups (top and bottom set in the figure) can be built. Only the Δ and Λ isomers have to be taken into account for a given ligand: only Δ-*aR,aR,aR* and Λ-*aR,aR,aR* could be formed from the *aR,aR,aR* ligand and only Δ-*aS,aS,aS* and Λ-*aS,aS,aS* could be formed from the *aS,aS,aS* enantiomer of $\mathbf{LH_6}$. From each enantiomer of the ligand, exclusive formation of one octahedral configuration for a gallium(III), a chromium(III) and an iron(III) centre in the chiral macrobicyclic cavity has been evidenced. The two enantiomers (*aR,aR,aR*) and (*aS,aS,aS*) lead, respectively, to the Λ and Δ isomers for the complexes (shown by CD spectroscopy for chromium and iron centers and molecular modeling). Only one isomer has been detected in both cases and the unique complexes, respectively obtained from the *aR,aR,aR* and *aS,aS,aS* enantiomers of $\mathbf{LH_6}$, are enantiomers. It appears that the chirality of the ligand leads to the formation of only one of the two possible diastereomeric metal complexes: the configuration (Δ or Λ) of the created chiral octahedral centre is

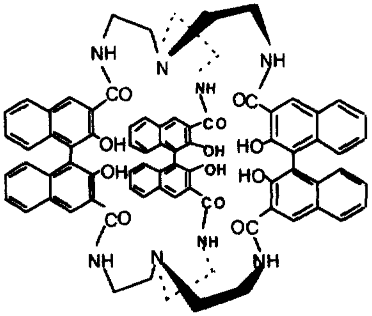

Fig. 7. A chiral macrobicyclic cavity $\mathbf{LH_6}$, possessing six convergent hydroxyl groups.

entirely controlled by the chirality of the ligand. The constrained bicapped structure does not allow inversion of the octahedral centre, contrary to simple tris-bidentate complexes. It has to be emphasized that octahedral inversion would lead to diastereoisomeric material since the ligand is unracemizable under the experimental conditions. Chromic ions induce kinetic inertness leading to stable optical isomers. No exchange has been observed for the gallium and the iron complexes (kinetic lability resulting of the absence of ligand field stabilization would favor the release of the metal and, then, the exchange between free and complexed ions). This exchange has been observed for the simple tris (bidentate) complexes [36].

Molecular modeling studies show that the Δ-*aS*,*aS*,*aS* complex has a lower energy than the Λ-*aS*,*aS*,*aS* complex. The former complex retains its original configuration during the minimization process; it adopts a structure substantially flattened along the C_3 principal axis. In a further step, the iron atom has been removed from the preceding structures leading to the two conformers of the ligand, respectively preorganized for Δ and Λ complexation. The lower-energy conformer ($\Delta E=$ 107.7 kcal/mol) corresponds to the Δ-*aS*,*aS*,*aS* configuration. The noticeable energy difference between the two conformers arises from van der Waals terms and from the stacking of the aromatic rings (possible only for the flattened Λ-*aS*,*aS*,*aS* isomer); the electrostatic interactions are not stabilizing. It has to be emphasized that the trend in the energy values, and not their absolute magnitude, should be considered.

7. Conclusion and prospective

To date, the only envisaged way to asymmetric inorganic syntheses is the use of chiral ligands. The chirality of the ligand predetermines the metal chirality. Some spectacular results have already been obtained. In particular, the chiragen ligands family allows the controlled obtention of unracemisable enantiopure helical complexes with predetermined absolute configuration at the metal center.

In a prospective view, two possibilities seem to be an easy application of the preceding features.

7.1. *Polynuclear complexes*

The combination of several octahedral centers involving helical chirality in one molecular unit can lead to a plethora of stereoisomers ("fuzzy stereochemistry"). To our knowledge, the only approach to develop a strategy for the synthesis of stereochemically well-defined polynuclear species is that of Von Zelewsky [32], which implies the assembly of enantiomerically pure building blocks. Possible true asymmetric inorganic syntheses would be, for instance, the direct preparation of μ-oxo bimetallic complexes by using a chiragen ligand in each coordination site.

7.2. Asymmetric inorganic syntheses with immolation of the inductor group

In organic chemistry, a true asymmetric synthesis does not lead to a diastereoisomeric mixture of isomers in unequal amounts, but to a mixture of enantiomers involving an enantiomeric excess of one of the two. In indirect asymetric syntheses, the chiral inductor group is removed from the final product of the reaction. It seems a priori easy to envisage a similar pathway for inorganic asymmetric syntheses, if the chiral inductor group is connected to the ligand via a removable bond. A possibility may be illustrated by the hydrolysis of the amide bonds of the ligand depicted in Fig. 5, after the enantiospecific helical complexation.

Direct asymmetric inorganic syntheses seems, to date, a futuristic challenge. It would be interesting to study, for instance, helical complexation reactions using achiral bidentate ligands, in chiral media (solvents, micelles, supramolecules...).

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