Supramolecular Metal Complexes

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“Induced Fit” in Chiral Recognition: Epimerization upon Dimerization in the Hierarchical Self-Assembly of Helicate-type Titanium(IV) Complexes[**]

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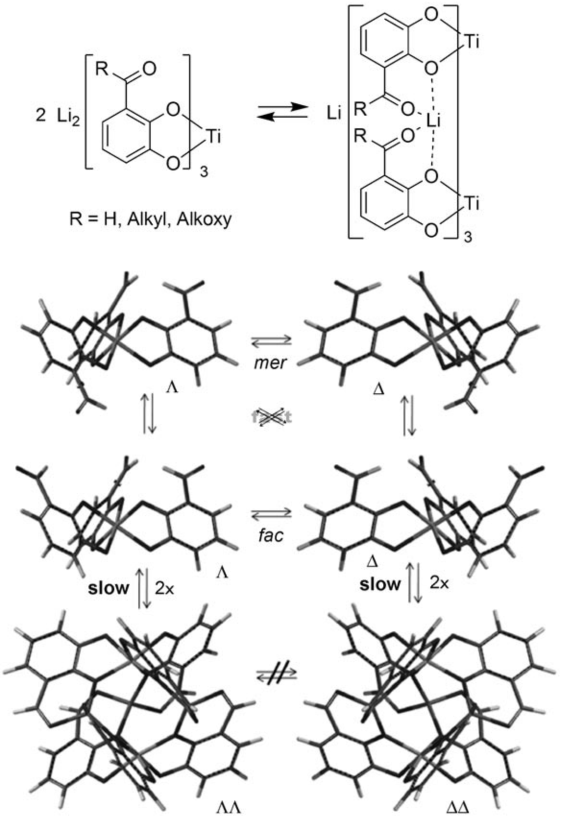
Dedicated to Professor Dieter Enders on the occasion of his 65th birthday

The processing and transfer of stereochemical information is based on communication between two chiral units or between a chiral and a prochiral unit. Stereoselective processes often rely on chirality transfer from a chiral ligand to a catalytically active (metal) center.[1,2] In supramolecular chemistry,[3] the interaction of a substrate with a receptor (which might be a catalyst) follows the lock and key principle,[4] and an “induced fit” between the components enables optimized interaction.[5] Thus, stereoselection (for example, in catalysis) is often based on supramolecular chiral recognition processes.

In helicates,[6] the transfer of stereochemcial information between two units has been investigated thoroughly.[7] The introduction of enantiomerically pure ligands can afford diastereomerically and enantiomerically pure helicates.[8] Recently, hierarchically formed[9] helicates with bridging lithium cations were described,[10] in which three Li$^+$ ions connect two mononuclear complex moieties. In this case, the interlocking of the two propeller-type complexes, which allows effective coordination of the lithium ions, is only possible if the two propellers possess the same twist.

The distorted octahedral mononuclear complex exists in solution as four fast equilibrating isomers. The ligands can have a *fac* or a *mer* orientation (sometimes referred to as *syn* and *anti*) and the complexes a Λ or Δ configuration (Scheme 1). A slow reversible Li$^+$-mediated dimerization occurs only between homochiral units of the *fac* isomers, and in the dimers the stereochemistry (“the helical twist”) is locked. Racemization of the helicates proceeds by slow dissociation, but not by direct interconversion. Although the tetrahedrally coordinated lithium cations are extremely labile, the cooperative binding of three cations slows down the dissociation of the dimer.



Scheme 1. Hierarchically assembled triple lithium-bridged bistitanium(IV) complexes. The isomers of the monomeric unit are in fast equilibrium with each other, while the ΛΛ and ΔΔ dimers are formed slowly. The latter species are able to racemize by slow dissociation, but not by direct interconversion.[10]

Monomers and dimers are easily distinguished by NMR spectroscopy because of the anisotropic shift as well as the diastereotopicity in the dimer.[10] The monomer–dimer equilibrium is influenced by different factors. For example, the dimer is more stable in less-coordinating solvents such as methanol, while the monomer is the major species in strongly coordinating solvents (for example, DMSO).[10]

In the racemic system, all the equilibria between enantiomers are equivalent (Scheme 1). The introduction of chiral information results in the formation of diastereomers, and epimerization at the metal complex will favor one of the diastereomeric chiral species. Therefore, the chiral esters **1**-H_2

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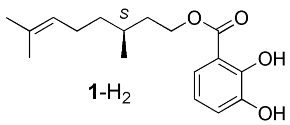
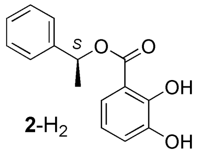


1-H_2



2-H_2

and **2**-H_2 of 2,3-dihydroxybenzoic acid were prepared starting from (*S*)-citronellol and (*S*)-phenylethanol.[11]

1-H_2 and **2**-H_2 form titanium(IV) triscatecholates[12] on reaction (3 equiv) with [$TiO(acac)_2$] (1 equiv) and Li_2CO_3 (1 equiv) in methanol. ^{1}H NMR spectroscopy reveals that in the case of $Li_2[(\mathbf{1})_3Ti]$, the dimer $Li[Li_3\{(\mathbf{1})_3Ti\}_2]$ is the only observable species in [D_4]MeOH. Both the monomer and dimer are observed in [D_6]DMSO, and a dimerization constant of $K_{dim} = 2400\,M^{-1}$ has been determined. The dimer is identified by two multiplets of diastereotopic O-CH_2 protons at $\delta = 3.54$ and 2.94 ppm, while the monomer shows only one signal ($\delta = 4.10$ ppm). The fast isomerization at the monomer (for example, by a Bailar twist or Ray–Dutt rearrangement) prevents the stereoisomeric complexes ($S\Lambda$ and $S\Delta$) from being observed separately. Thus, the γ-methyl group of the monomer appears only as one doublet at $\delta = 0.88$ ppm, while in the dimer this methyl group splits into two doublets in a ratio of 40:60 at $\delta = 0.77$ and 0.73 ppm. This is a measure of the stereochemical induction of the γ stereocenter on the complex units that results in 20% *de*. CD spectroscopic investigations of the complex $Li_2[(\mathbf{1})_3Ti]/Li[Li_3\{(\mathbf{1})_3Ti\}_2]$ either in methanol or DMSO indicate that the Λ configuration dominates in the complex.

In the case of ligand **2**-H_2, the stereocenter of the ester is much closer to the metal ion and stronger stereochemical induction occurs. In fact, only one "enantiomerically pure" diastereoisomer is found in the NMR spectrum of the dinuclear complex $Li[Li_3\{(\mathbf{2})_3Ti\}_2]$. No diastereotopic NMR probes are present in the case of ligand **2**; however, the dimeric titanium(IV) complex shows the characteristic high-field shift of the α proton or of the methyl resonance. The dimer ($\delta_{CH\text{-}\alpha} = 4.47$, q) is the dominant species in [D_4]MeOH. Only traces of the monomer ($\delta_{CH\text{-}\alpha} = 5.04$, q) are observed ($K_{dim} = 4600\,M^{-1}$). The situation is reversed in [D_6]DMSO: The monomer $Li_2[(\mathbf{2})_3Ti]$ ($\delta_{CH\text{-}\alpha} = 5.89$, q) is the major species, while only traces of dimer $Li[Li_3\{(\mathbf{2})_3Ti\}_2]$ ($\delta_{CH\text{-}\alpha} = 4.91$, q) are found ($K_{dim} = 16\,M^{-1}$).

The CD spectra of $Li_2[(\mathbf{2})_3Ti]/Li[Li_3\{(\mathbf{2})_3Ti\}_2]$ in methanol and DMSO are roughly mirror images (Figure 1). A positive Cotton effect is observed around 340 nm and a negative Cotton effect around 405 nm in methanol, while a negative Cotton effect is found around 360 nm and a positive one at 420 nm in DMSO. The free ligand does not show significant CD signals, and so the detected transitions can be attributed to the titanium(IV) triscatecholate. According to earlier assignments[13] and recent computational studies (see the Supporting Information), the configuration of the complexes with ligand **2** depends on the solvent: Δ in methanol and Λ in DMSO. This effect could be due to the dominating presence of the monomer in DMSO and of the dimer in methanol.

Crystals suitable for X-ray structure analysis were obtained,[14] but an accidental cation exchange during the recrystallization resulted in the potassium salt of $[Li_3\{(\mathbf{2})_3Ti\}_2]^-$ being obtained. Figure 2 depicts one of the two independent structures of the anion in the crystal, with the interlocking of the complex units and the bridging by three lithium cations (all Λ configuration). The complex has the right-handed helical form (ΔΔ).

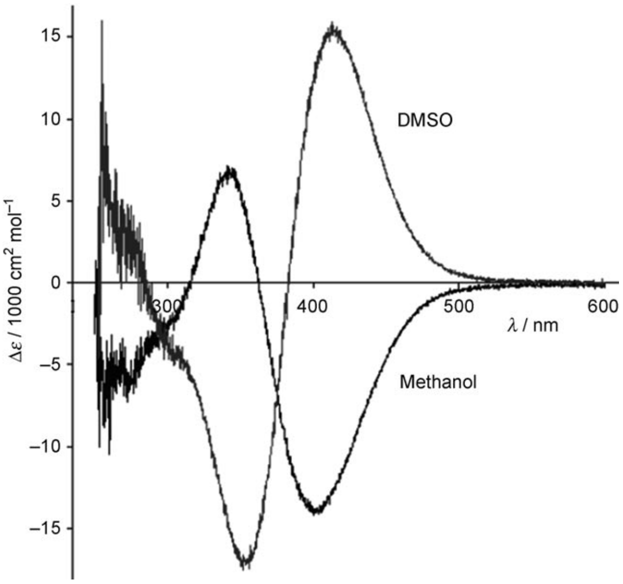


Figure 1. CD spectra of $Li_2[(\mathbf{2})_3Ti]/Li[Li_3\{(\mathbf{2})_3Ti\}_2]$ in methanol and DMSO.

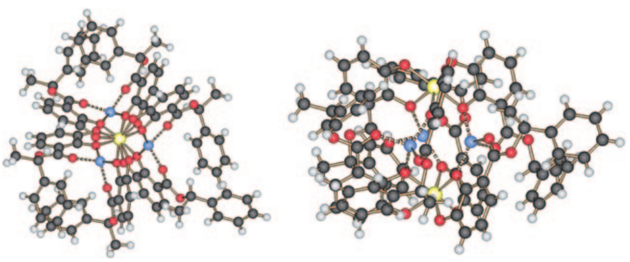


Figure 2. Molecular structure of the anion $[Li_3\{(\mathbf{2})_3Ti\}_2]^-$ in the crystal (only one of the two inequivalent units in the lattice is shown). C black, H white, O red, Li blue, Ti yellow.

Figure 3 summarizes the rationalization of the stereochemical inversion of the complex units upon dimerization. Esters of secondary alcohols are known to adopt a conformation in which the proton at the α position is oriented in the same direction as the carbonyl oxygen atom, which results in a dihedral angle $C_{carbonyl}$-O-C-H of close to 0°.[15] This orientation remains in monomeric $Li_2[(\mathbf{2})_3Ti]$. Both the carbonyl group as well as the α hydrogen atom point away from the complex unit ("outwards"). This fixes the substituents at the chiral unit relative to the coordination site. The higher steric pressure of the phenyl compared to the methyl group controls the tilting of the propeller-type complex, thereby resulting in a preferred Λ configuration (Figure 3 b, top).

In the dimer, the carbonyl oxygen atom binds "inwards" on coordinating to a lithium cation, and therefore rotation of

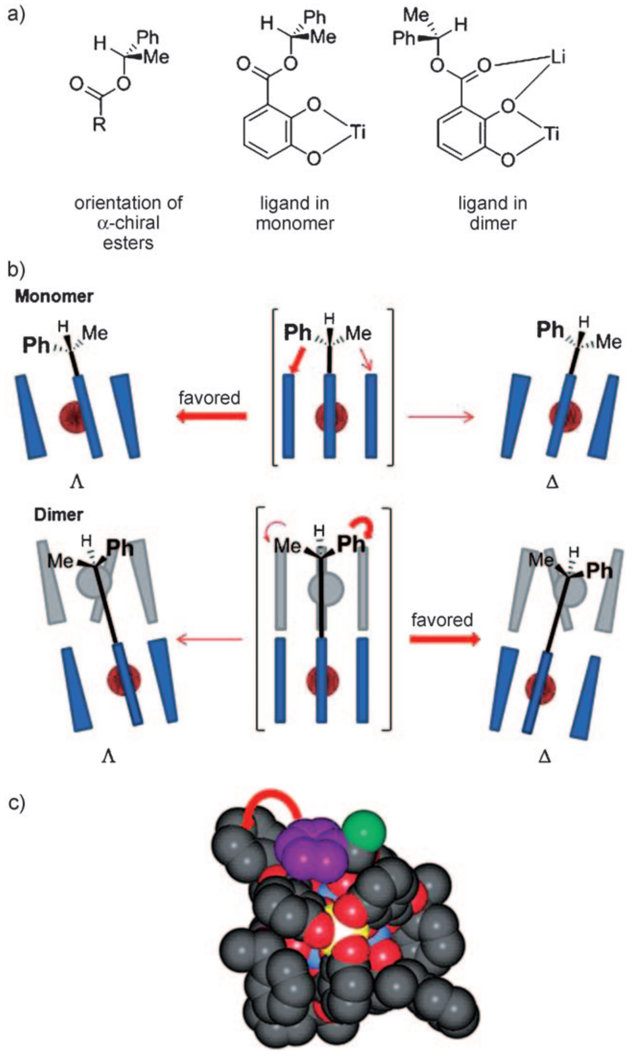


Figure 3. a–c) Rationalization of the preferred stereochemistry of the monomer and dimer based on the result of the X-ray structure analysis (c; view down the Ti–Ti axis, groups of one of the chiral substituents are shown in magenta (phenyl) and green (methyl)). b) The structure of the ester group is fixed by the preferred orientation of the small hydrogen atom towards the carbonyl oxygen atom.[15] The formation of the favored stereoisomers is explained on the basis of the steric interaction in the hypothetic nontwisted "trigonal prismatic" species (shown in parenthesis). Red arrows indicate steric interactions.

the ester groups occurs upon dimerization. Now, the steric pressure from the large phenyl group on the trischelate of the second complex moiety (Figure 3b, bottom) results in the opposite twist compared to the monomer. Embedding the chiral ester substituent in the groove of the helical complex enforces some twisting of the dihedral angle C_{carbonyl}-O-C-H to 20–55°. This is stabilized by attractive CH–π interactions between the secondary α proton and a neighboring catechol unit at the second coordination site (Figure 3c). Solvent effects on the CD spectra were observed previously, and it was pointed out that the simple interpretation of CD spectra might lead to mistakes.[16] However, in our study different characterization techniques combined with computational studies (see the Supporting Information) lead to a clear picture of the situation.

The reduced steric bulk of the ester of ligand **1** and the chiral information in the γ position results in the complex $\mathrm{Li_2[(\mathbf{1})_3Ti]/Li[Li_3\{(\mathbf{1})_3Ti\}_2]}$ being present mainly as a dimer. Even in DMSO, the monomer becomes only dominating at concentrations as low as approximately $10^{-7}\,\mathrm{mol\,L^{-1}}$. The dimer is the major species in methanol as well as in DMSO under the conditions used for the NMR ($c \approx 0.003\,\mathrm{mol\,L^{-1}}$) as well as CD ($c \approx 0.001\,\mathrm{mol\,L^{-1}}$) experiments. Thus, as expected, the CD spectra are similar in both solvents.

In summary, a unique example of stereoinduction is presented, in which the stereochemistry at a labile metal complex unit is inverted and locked upon lithium-mediated dimerization. The stereocontrol can be explained by different conformations at the ester in the monomer and the dimer. This result is impressive in the context of dynamic chiral resolution in a supramolecular system following "induced fit" based on stereorecognition.

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[14] X-ray crystal structure analysis of $K[Li_3\{(\mathbf{2})_3Ti\}_2]$: $Li_3K(\{C_{15}H_{12}O_{14}\}_3Ti)_2\cdot{}^1/_2\,C_4H_{10}O\cdot C_2H_6O\cdot 2\,H_2O$, $M_r = 1812.36$, orange crystal $0.35\times0.20\times0.10\ mm^3$, $a = 24.1223(2)$, $b = 28.7844(2)$, $c = 29.0182(5)$ Å, $V = 20148.7(4)$ Å^3, $\rho_{calcd} = 1.195\ g\,cm^{-3}$, $\mu = 0.270\ mm^{-1}$, empirical absorption correction ($0.911 \leq T \leq 0.974$), $Z = 8$, orthorhombic, space group $P2_12_12_1$ (no. 19), $\lambda = 0.71073$ Å, $T = 223(2)$ K, ω and ϕ scans, 136005 reflections collected ($\pm h$, $\pm k$, $\pm l$), $[(\sin\theta)/\lambda] = 0.59$ Å^{-1}, 35058 independent ($R_{int} = 0.095$) and 27748 observed reflections $[I \geq 2\sigma(I)]$, 2164 refined parameters, $R = 0.097$, $wR^2 = 0.286$, Flack parameter 0.10(3), max. (min.) residual electron density 1.00 (−0.35) e Å^{-3}, hydrogen atoms calculated and refined as riding atoms, hydrogen atoms at water molecules could not be located, disordered solvents in voids could not be assigned in a chemically meaningful way. Data sets were collected with a Nonius Kappa CCD diffractometer. Programs used: data collection COLLECT (Nonius B.V., 1998) data reduction Denzo-SMN (Z. Otwinowski, W. Minor, *Methods Enzymol.* **1997**, *276*, 307), absorption correction Denzo (Z. Otwinowski, D. Borek, W. Majewski, W. Minor, *Acta Crystallogr. Sect. A* **2003**, *59*, 228), structure solution SHELXS-97 (G. M. Sheldrick, *Acta Crystallogr. Sect. A* **1990**, *46*, 467), structure refinement SHELXL-97 (G. M. Sheldrick, *Acta Crystallogr. Sect. A* **2008**, *64*, 112), graphics SCHAKAL (E. Keller, Univ. Freiburg, **1997**). CCDC 794290 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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