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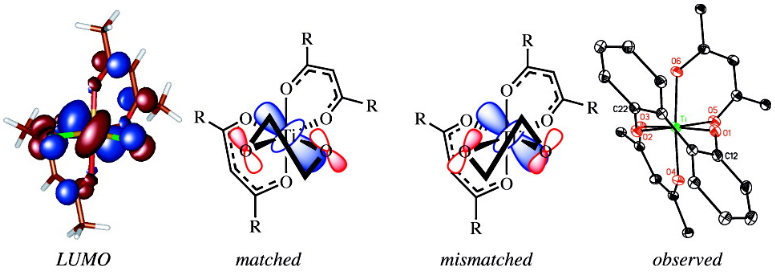

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Electronic Dissymmetry in Chiral Recognition

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Enormously diverse chemical structures, ranging from antibodies to organometallic complexes, have been used to achieve chiral recognition. Despite this structural diversity, the basic mechanism by which chiral recognition is achieved is nearly universal. To discriminate between the enantiomers of a substrate, a receptor must have a chiral three-dimensional shape that positions its functional groups in such a way that its *nonbonding* interactions, whether repulsive (steric effects) or attractive (electrostatic, van der Waals, hydrogen bonding, or hydro- or solvophobic interactions), are significantly different in the two diastereomeric complexes formed with the substrate.[1] Even when covalent bonds are used to anchor the substrate to the receptor, the actual chiral discrimination is generally accepted to require dissymmetric nonbonding interactions.[2] Here we describe a fundamentally different approach to chiral recognition: the use of a dissymmetric electronic structure to discriminate between enantiomers on the basis of chiral bonding interactions.

Bis(β-diketonato)titanium(IV) alkoxides, (dike)$_2$Ti(OR)$_2$, are readily prepared and are invariably chiral, with a C_2-symmetric, *cis* geometry.[3] While the σ-bonding in an octahedral (dike)$_2$TiX$_2$ complex is essentially achiral (pseudo-C_{2v} symmetry), the π-bonding is intrinsically chiral. Each diketonate has only one effective π-donor orbital, the π-nonbonding HOMO, to engage in π-donation to the d^0 titanium fragment, resulting in one *A*- and one *B*-symmetry combination of ligand π-donor orbitals. In particular, the *A*-symmetry ligand combination splits the two *A*-symmetry dπ orbitals, such that one dπ orbital is antibonding with respect to the diketonate ligands and one is nonbonding. This latter orbital is thus the complex's LUMO, and resembles a "tipped" d_{z^2} orbital, with the direction in which it tips determined by the configuration at titanium.[4] Hybrid DFT calculations (B3LYP, 6-31G* basis)[5] on (acac)$_2$TiCl$_2$ support this qualitative picture (Figure 1a) and indicate that the LUMO is significantly below both of the other Ti dπ orbitals (0.32 eV below the b orbital and 0.39 eV below the other a orbital).[6]

By itself, there is nothing intrinsically chiral about a d_{z^2} orbital. However, if a substrate experiences two-point binding to the (dike)$_2$Ti fragment, then the tipping of the LUMO with respect to the TiX$_2$ plane does engender dissymmetry. If the substrate is capable of π-donation, then one enantiomer of the substrate can potentially interact more strongly with the LUMO than the other, as illustrated for the two enantiomeric conformations of an ethylene glycolate in Figure 1b. For a Ti center of Λ configuration, the δ ligand conformation tilts the oxygen π-donor p orbitals to improve alignment with the LUMO and hence the strength of the O-to-Ti π-donation, while the λ conformation tilts them the opposite way and should be less favorable. Note that this argument is based entirely on bonding considerations rather than the steric effects classically adduced to justify the different stabilities of the conformations in, for example, Co(en)$_3^{3+}$.[7] Indeed, the sterically svelte nature of the diketonates, with their monosubstituted oxygen donors and substituents pulled back by the chelate geometry, makes this an ideal system to observe electronic effects since steric effects are expected to be small.

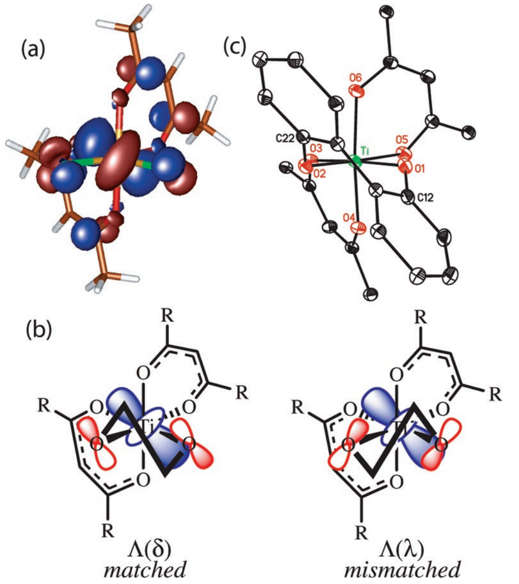

Figure 1. Manifestations of electronic dissymmetry. (a) Calculated LUMO of (acac)$_2$TiCl$_2$ (B3LYP, 6-31G*). (b) Differential overlap of *A*-symmetry π-donor orbitals of ethylene glycolate to Λ-(dike)$_2$Ti in δ (left) and λ (right) conformations. (c) Core of (dbm)$_2$Ti(BINOL) (phenyl and BINOL rings abridged for clarity), illustrating the diastereomer observed in the solid; (tmhd)$_2$Ti(BINOL) (see Supporting Information) is similar.

The efficacy of this electronic effect has been probed in complexes of 1,1′-bi-2-naphtholate (BINOL), which adopts a characteristic zigzag conformation[8] with substantial tilting of the Ti−O−C plane out of the O−Ti−O plane, with O−Ti−O−C dihedral angles averaging 42° in monometallic complexes.[9] (RCOCHCOR)$_2$Ti(BINOL) complexes (R = CH$_3$, acac; R = Ph, dbm; R = ^{t}Bu, tmhd) are prepared by treating Ti(O^{i}Pr)$_4$ with 2 equiv of the diketone and 1 equiv of H$_2$BINOL.[10] At room temperature, the complexes are fluxional, exchanging axial and equatorial substituents on the diketonate ligands. Titanium diketonates are known to undergo facile trigonal twists,[11] which not only interconvert equatorial and axial substituents but also epimerize the titanium center and thus allow the diastereomeric BINOL complexes to equilibrate. When CD$_2$Cl$_2$ solutions of the (dike)$_2$Ti(BINOL) complexes are cooled sufficiently to freeze out the fluxional process, in each case only a single diastereomer is observed by NMR within the limits of detection (Table 1).[12,13] The identity of the diastereomer formed has been determined in the solid state by X-ray crystallography of the dbm and tmhd complexes to be the Λ-*S*/Δ-*R* isomer (Figures 1c and 2a), in agreement with the electronic predictions based on overlap of the BINOL lone pairs with the titanium LUMO.

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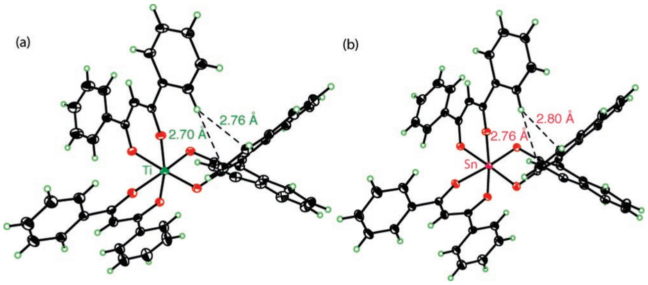

Figure 2. Thermal ellipsoid plots of (a) $(dbm)_2Ti(BINOL)$ and (b) $(dbm)_2Sn(BINOL)$ (40% ellipsoids).

Table 1. Stereoselectivity of Complexation of BINOL to $(dike)_2M$

complex	observed dr (*T* of NMR observation)
$(acac)_2Ti(BINOL)$	>20:1 (below −50 °C)
$(dbm)_2Ti(BINOL)$	>40:1 (below −20 °C)
$(tmhd)_2Ti(BINOL)$	>100:1 (below 5 °C)
$(acac)_2Sn(BINOL)$	5.4:1 (35 °C) 6.7:1 (−15 °C)
$(dbm)_2Sn(BINOL)$	3.6:1 (35 °C) 3.0:1 (−15 °C)
$(tmhd)_2Sn(BINOL)$	3.4:1 (35 °C) 4.6:1 (−15 °C)

Attribution of the high diastereoselectivities to steric or van der Waals interactions between the $(dike)_2Ti$ and BINOL fragments seems unlikely on the basis of the small steric profile of the diketonate ligands and the uniformly high selectivities seen as the diketonate substituent size is varied. To provide further evidence against some subtle structural effect, the preparation of the corresponding tin diketonate complexes $(RCOCHCOR)_2Sn(BINOL)$ was undertaken. Structurally, the tin and titanium complexes should be close analogues, as seen in the structures of the two $(dbm)_2M$-(BINOL) complexes (Figure 2). While the Sn−O bonds are ∼0.1 Å longer than the Ti−O bonds, the nonbonding contacts are extremely similar, with the shortest dbm carbon to naphthalene plane distances of 3.56 (Ti) and 3.48 Å (Sn), and closest dbm hydrogen to BINOL carbon contacts of 2.70 (Ti) and 2.76 Å (Sn). Thus, if nonbonding interactions set the relative configurations of the metal and BINOL stereocenters, the tin and titanium complexes should show similar diastereoselectivities. In contrast, if binding stereoselectivity has a principally electronic origin, the much weaker π-bonding and minimal d orbital participation expected in main group compounds[14] should result in markedly lower diastereoselectivities in the tin complexes. In fact, stereodiscrimination is uniformly modest in the tin compounds (Table 1). Both diastereomers are observed in solution for all three complexes, in ratios that range from about 3:1 to 6:1 and are rather insensitive to temperature.

The electronic influence of an *un*symmetrical coordination sphere has previously been used to transfer stereochemical information,[15] and such electronic asymmetries have often been proposed to modulate enantioselectivities in catalytic reactions in the presence of steric contributions to a chiral environment.[16] Here we show that a chiral electronic structure can exist even in the symmetrical bis(diketonato)titanium(IV) fragment, and that the electronic dissymmetry in these complexes can have sufficient energetic consequences to give rise to useful levels of chiral recognition. Efforts are in progress both to prepare enantiomerically pure $(dike)_2Ti$ complexes and to use their electronic dissymmetry to provide chiral induction in chemical reactions.

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Supporting Information Available: Details of DFT calculations, preparation and characterization of new compounds, and crystallography (in tabular and CIF format). This material is available free of charge via the Internet at http://pubs.acs.org.

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(4) A qualitative argument that establishes the nature of the LUMO involves replacing the two X groups of $(dike)_2TiX_2$ by another diketonate to form D_3-symmetric $[Ti(dike)_3]^+$. The three dike π-donor orbitals transform as $A_2 + E$, so the d_{z^2} orbital aligned along the 3-fold axis (of A_1 symmetry in D_3) must be strictly nonbonding with respect to the diketonates.
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(6) At least some of the splitting in the dπ manifold may be due to interactions with the acac LUMOs, which are calculated to be much closer in energy to the dπ orbitals than the acac HOMOs ($\Delta E \approx 1.3$ and 4 eV, respectively). Since the nodal pattern of the acac LUMO is reversed relative to the HOMO, the effects are synergistic in the *A* manifold, with the higher dπ orbital interacting only with the filled acac orbital and the lower-energy dπ orbital interacting only with the empty acac orbital. More details on the calculations are given in the Supporting Information.
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(12) For the rather soluble $(tmhd)_2Ti(BINOL)$, all stray peaks in the methine region of the ^1H NMR spectrum are smaller than either of the ^{13}C satellites of the major compound, so 100:1 is a conservative estimate of the preponderance of the major diastereomer. More modest lower limits on the dr must be given for the progressively less soluble dbm and acac complexes; the latter also exists in a monomer/dimer equilibrium.
(13) There are two nondegenerate trigonal twists of $(dike)_2Ti(chel)$ complexes, a Ray-Dûtt twist, which scrambles equatorial and axial groups, and a Bailar twist, which specifically interconverts the axial groups of one diastereomer only with the equatorial groups of the other diastereomer. If the latter were much faster than the former, it would give rise to the appearance of a single species by NMR regardless of the true dr. However, this is not a likely explanation for the observed spectra because (1) spectra are unchanged in appearance down to −90 °C, which would require an unprecedentedly fast Bailar twist in the BINOL complex;[11] (2) the two processes typically occur at similar rates;[11] and (3) EXSY spectroscopy on $(acac)_2Sn(BINOL)$ (where both diastereomers can be observed) confirms that the methyl groups in the minor diastereomer exchange with the axial and equatorial methyl groups in the major diastereomer at comparable rates.
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