

Conservation of Helicity and Helical Character Matching in Chiral Interactions

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ABSTRACT An electronic theory for molecular chirality and chiral interactions has recently been published that suggests that underlying chiral interactions is the conservation of molecular electronic helicity and that enantioselectivity in a reaction can be maximized when the interacting chiral components are helically matched. Herein are presented proofs for these principles, and their connections with other theories and implications for the design of chiral catalysts are discussed. *Chirality* 17:S177–S182, 2005. © 2005 Wiley-Liss, Inc.

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Molecular chirality is usually thought to be a solely geometrical property, and accordingly, the interactions of chiral molecules are often analyzed by considering steric effects. We recently described a helix theory for chirality and chiral interaction that suggests the possibility that electronic effects may also be significant, and possibly dominant.^{1–4} It reduces all types of molecular chiralities, including point, axial, planar, helical chirality, and others, into helicities. Any chiral molecule can therefore be assigned as either right- or left-handed. The diastereomeric interactions between two chiral molecules are thus either homohelical (when the interacting helices have the same handedness) or heterohelical (when they do not). The theory suggests that the principle underlying chiral interactions is the conservation of molecular electronic helicity: a chiral catalyst will prefer forming its product enantiomer, and a chiral host will prefer recognizing its guest enantiomer, that allows the catalyst or host to preserve its helicity—or handedness—at the transition states. Numerous experiments support the theory. The theory further suggests that the energetic difference between homohelical and heterohelical interactions can be maximized, so the enantiomeric excess (ee) can be ca. 100%, when the interacting helices are matched in their helical characters. Herein we present proof for the helicity conservation and helical character matching principles and discuss the connections between these principles and other theories and implications for the design of chiral catalysts.

RESULTS AND DISCUSSION

Electron-on-a-Helix Model

A conceptual tool directly related to the theory is the electron-on-a-helix model of Tinoco and Woody, in which the states and eigenvalues of an electron constrained to move on a helix can be solved exactly.⁵ The model is the simplest for a chiral molecule and has proven to be theoretically appealing and analytically effective when ap-

plied to a variety of real systems.^{6–9} A helix can generally be characterized by the following parameters: radius, pitch, length, and, in the case of a molecular helix, mass of electrons on the helix. Although a molecular helix may be not a regular helix with the uniform parameters upon which the original treatments were based, this simple model captures the essence of more complex chiral systems that can be viewed as linear combinations of regular helices. The energy of an electron of mass m constrained on a k -turn helix of a radius a and a pitch $2\pi b$ is:

$$E_n = \hbar^2 n^2 / 8mk^2 (a^2 + b^2), \text{ where } n = 1, 2, 3, \dots \quad (1)$$

Not surprisingly, as helicity weakens, this result can eventually be reduced formally to that of an achiral linear (when $a = 0$) or circular (when $b = 0$) system, but note that a chirality (optical activity) condition automatically demands that the values of a and b both be non-zero.⁵ A chiral molecular interaction can therefore be modeled by a pair of helices interacting with each other, and the different energetic consequences of enantiomeric helices on the same helix with which they interact are only electronically distinguished by their handedness. This is generally illustrated in Scheme 1 by the homohelical and heterohelical diastereomeric interactions between an optically pure helix **I** and oppositely handed helices **II**.

Now suppose in a chiral interaction that the catalyst- or host-helix has a turn k , radius a , and pitch $2\pi b$. Because

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Scheme 1. Homohelical and heterohelical electronic interactions between helices (+)-I and (\pm)-II. The black ball represents an interaction that couples the helices together.

a homohelical interaction extends the helix, it can be viewed as adding an additional turn k' , radius a' , and pitch $2\pi b'$, to the original k , a , and $2\pi b$, respectively. The system energy would therefore be:

$$E_{\text{homo}} = \hbar^2 n^2 / 8m_{\text{eff}} (k + k')^2 [(a + a')^2 + (b + b')^2], \quad (2)$$

where m_{eff} represents the mass of electron densities that are effectively movable on the helix. In contrast, a diastereomeric heterohelical interaction compresses the helix, it can similarly be viewed as subtracting an additional turn k' , radius a' , and pitch $2\pi b'$. The system energy would then be

$$E_{\text{hetero}} = \hbar^2 n^2 / 8m_{\text{eff}} (k - k')^2 [(a - a')^2 + (b - b')^2]. \quad (3)$$

It follows that E_{homo} is always less than E_{hetero} .

It can also be seen that the difference between the free energy changes for homohelical and heterohelical transition states, $\Delta\Delta G^\ddagger = E_{\text{homo}} - E_{\text{hetero}}$, has a maximum when $k' = k$, $a' = a$, and $b' = b$. This suggests that for a reaction to be highly enantioselective, the characteristics of the interacting helices must be similar. They must be helically, therefore energetically, matched.

It is not yet feasible to calculate this helical character-matching effect accurately. However, one could estimate, very approximately, its energetic significance. For example, in a highly enantioselective reaction effected by a chiral BINAP ligand, the $\Delta\Delta G^\ddagger$ under a perfect helical character matching condition may be obtained as:

$$\Delta\Delta G^\ddagger = E_{\text{homo}} \approx 2E_{\text{BINAP}},$$

where E_{BINAP} denotes the energy of electrons movable along the local BINAP ligand ring helix $-P-C^1=C^2-C^3=C^4-P-$ (Scheme 2).

The corresponding helix radius and pitch may be derived from an X-ray crystal structure¹⁰ of the (*R*)-BINAP-Rh complex: $a = 1.5 \text{ \AA}$, and $b = 1.5/2\pi = 0.24 \text{ \AA}$ (note that, due to this $1/2\pi$ factor, the effect on the system energy is usually much smaller for the pitch than the radius; see calculation below). We choose $k = 1$, a maximum value for most molecular helices of interest. It is difficult to assign $m_{\text{eff}} = n \times m_e$, where n is not nec-

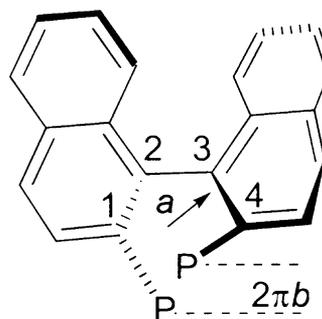
essarily an integer and represents a small fraction of the electrons that actually move along the helix. Herein we tentatively assign $n = 2$ on the basis of the more polarizable π electrons at $C^1=C^2$ and $C^3=C^4$ bonds. Therefore at 1 mol scale we have:

$$\begin{aligned} \Delta\Delta G^\ddagger &= E_{\text{homo}} \approx 2E_{\text{BINAP}} \\ &= 2N_A \hbar^2 \times 10^{-3} / 8nm_e k^2 (a^2 + b^2) \times 4.2 \times 10^{-20} \\ &= 43.7/nk^2 (a^2 + b^2) = 43.7/2(1.5^2 + 0.24^2) \\ &= 9.5 \text{ (kcal/mol)}. \end{aligned}$$

Note that even with $m_{\text{eff}} = 12m_e$, which is the total mass of all bonding electrons along the helix $-P-C^1=C^2-C^3=C^4-P-$, $\Delta\Delta G^\ddagger$ still is 1.6 kcal/mol.

Clearly these values are sufficient to bring about high ee values. The helical character matching conclusion offers a useful way to investigate catalyst/substrate structure-ee relationships. An example is the asymmetric hydrogenation of (*Z*)-methyl acetamidocinnamate. A variety of chiral diphosphine-Rh catalysts were developed for this reaction. These catalysts differ considerably in sizes yet all induce nearly perfect enantioselectivities ($\sim 99.9\%$ ee) in this reaction.³ Applying a lock-and-key principle, it makes sense to ask what properties these "keys" have in common that allow them to open the same "lock" equally well.

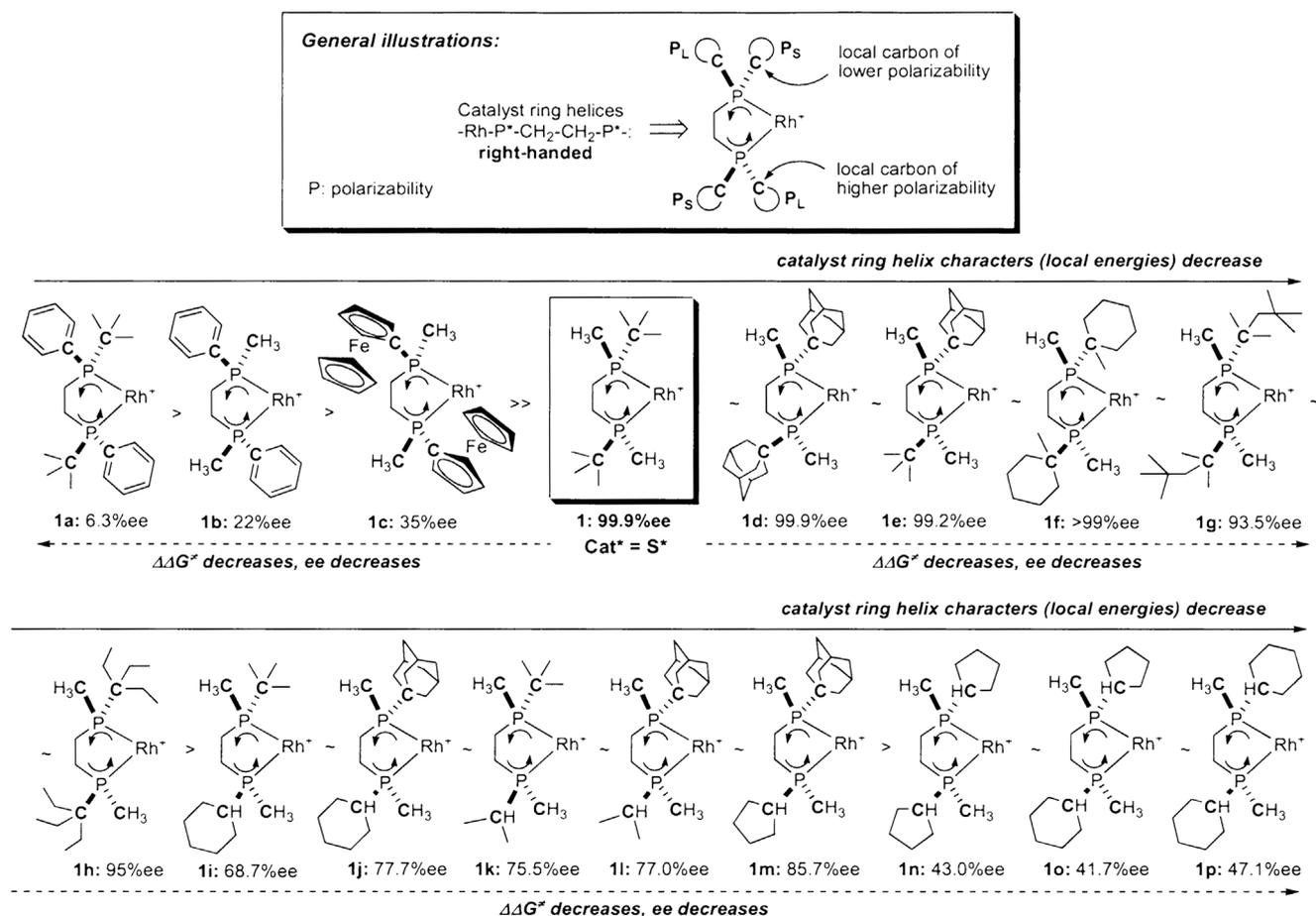
According to a previous analysis,³ while the helix parameters of each of these ligand ring helices differ, the different parameters compensate. This means that *the local*



Scheme 2. Helix parameters of the (*R*)-BINAP ligand ring helix in a transition-metal complex.

energies of electrons on the ligand–Rh ring helices may be the same and equal to the local energy of electrons on the substrate–Rh ring helix. It follows that other catalysts, whose helical characters (local energies) are either higher or lower than the perfect values suggested by these extremely enantioselective catalysts, will induce lower ee values in the same reaction because in all of these cases the catalyst–substrate energetic mismatching should result in decreased $\Delta\Delta G^\ddagger$ (it should be noted here that the identity of the coupling means between the interacting helices, which is represented by a black ball in Scheme 1, and may in reality be a metal, a hydrogen bond, or π – π stacking etc., may also significantly influence the efficiency of such catalyst–substrate helical character matching thus the values of $\Delta\Delta G^\ddagger$ and ee, although it usually does not change the direction of asymmetric induction in a reaction under a given mechanistic framework). This is indeed in accord with experiments. The BisP*–Rh-type catalysts of generic ligand structure $R_1R_2P^*-\text{CH}_2\text{CH}_2-\text{P}^*R_1R_2$,^{11–19} which are among other catalysts analyzed previously,³ serve as attractive platforms for visualizing this relationship because they constitute a series of structurally simi-

lar complexes and because they have been evaluated under similar—or identical—catalysis conditions, which enables facile helical character ranking and ee comparisons of the catalysts. The helix lengths of the five-membered chelate rings are essentially the same. The helical characters of these catalysts are therefore determined by the differences between the local polarizabilities of the R_1 and R_2 substituents because they deform the $-\text{CH}_2-\text{P}^*-\text{Rh}-$ bonds, thus regulating both the radius and the pitch of the corresponding catalyst ring helices in $-\text{Rh}-\text{P}^*-\text{CH}_2-\text{CH}_2-\text{P}^*-\text{CH}_2-\text{CH}_2-\text{P}^*-\text{Rh}-$. Therefore, with a fixed helical length, a greater polarizability difference would result in a greater catalyst ring helix pitch and, concomitantly, a smaller radius. These in turn lead to a net result of a higher local energy because, as noted above, it depends on the value of the radius much more than that of the pitch. In Scheme 3, these catalysts are listed in order of decreasing local polarizability distinction between the R_1 and R_2 substituents, i.e., phenyl sp^2 carbon-versus- 3° sp^3 carbon > phenyl sp^2 carbon-versus- 1° sp^3 carbon > ferrocenyl sp^2 carbon-versus- 1° sp^3 carbon > 1° sp^3 carbon-versus- 3° sp^3 carbon > 1° sp^3 carbon-versus- 2° sp^3 carbon.²



Scheme 3. Dependence of magnitude of enantioselection on the catalyst–substrate helical character matching in asymmetric hydrogenation of (*Z*)-PhCH=C(CO₂Me)NHAc catalyzed by BisP*–Rh complexes. Cat*, catalyst ring helical character; S*, substrate ring helical character. Catalyst ring helices are all right-handed, as indicated by arrows, thus all lead to (*R*)-product in various ee. The local polarizability sequences of P substituents in each catalyst are indicated by the general illustrations shown at the top.

These catalysts all have right-handed catalyst ring helices, i.e., $-\text{Rh}-\text{P}^*-\text{CH}_2-\text{CH}_2-\text{P}^*-\text{}$, thus all lead to the same product enantiomer.² Catalyst **1** with $\text{R}_1 = \text{}^t\text{Bu}$ and $\text{R}_2 = \text{Me}$, highlighted in the box, is the most enantioselective, implying the most perfect catalyst–substrate helical character matching. Catalysts whose helical characters are higher than **1**, such as **1a–c**, and catalysts whose helical characters are lower than **1**, such as **1d–p**, are expected to be energetically mismatched with the substrate to different extents and are indeed experimentally found to give reduced ee values that are in accord with their deviations from **1**. Also, independent of the size variations of R_1 and R_2 , catalysts of comparable helical characters, such as **1d–h**, **1i–m**, and **1n–p**, give comparable ee values, further highlighting the control of catalyst–substrate helical character matching on the magnitude of enantioselectivity. By contrast, application of conventional steric theories, such as the diene twist rule¹⁸ or the quadrant rule,¹⁹ to these systems seem not to lead to correct predictions either of the senses of asymmetric induction or of the variations in ee. That certain catalyst structural properties can be related to the magnitudes of the ee they induce should have practical utility. With some catalyst–ee information in hand, it helps to identify the structure of a more promising catalyst that should be tried next in the pursuit of high ee for a given substrate.³

The discussion above considers many catalysts and one fixed substrate. Alternatively, for a given catalyst that can achieve very high ee on a substrate, other helically similar substrates should give ee values that are comparably high. This, in fact, agrees with common practices.^{20,21} Overall, the most important lesson seems to be that, to design a good catalyst (the key), rather than focusing on the rigidity, bulkiness, or C_2 symmetry of the catalyst, one should focus more on the helical character, which can be analyzed from polarizability considerations in a reaction mechanism, of the substrate (the lock) with which the catalyst should interact. It is obvious that in general it is easier to discover, by either design or serendipity, a highly enantioselective catalyst for a substrate of a large helical character than for a substrate of a small helical character.^{1–4,20,21} However, if helical character matching issues could be addressed quantitatively,

it would be possible to design highly enantioselective systems more widely.

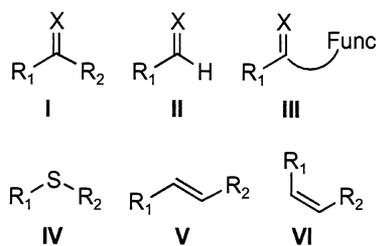
Helical Electronic Effects Versus Steric Effects in Asymmetric Catalysis

Although asymmetric induction is usually a consequence of many factors that intimately interplay in a reaction, our results^{1–4} suggest that electronic effects may be more important than is generally considered. Common substrates employed in asymmetric catalysis are summarized in Scheme 4. Their asymmetric reactions can be categorized as follows on the basis of simple polarizability property considerations.

Facilitated by strong helical electronic effects, class **A** reactions have significant potential in achieving high ee. This is particularly true when the catalysts are structurally modular, therefore, helically flexible in matching with a broad spectrum of substrates and when helical electronic effects and steric effects function synergistically, meaning, for example, that reactions of substrates **I**, **IV**, and **VI** where R_1 is both more polarizable and bulkier than R_2 . Reactions falling into this category are of broadest utility, outstanding examples being the hydrogenations by Noyori's BINAP-derived complexes.^{20,21} However, when catalysts and substrates are less matched in helical characters, and/or when helical electronic effects and steric effects function uncooperatively, both the sense and the magnitude of enantioselection become sensitive to reaction conditions. It is under these situations that the subtleties of the effects of steric effects, solvent, concentration, pressure, counter ion, additivity, central metal, etc. are most frequently appreciated experimentally. They constitute the bulk of work in current asymmetric catalysis.^{20,21}

For class **B** substrates, where substituents' polarizability differences are minimal or absent, asymmetric reactions, even with significant steric distinctions, do not seem in general to lead to high ee. In fact, asymmetric catalysis involving these substrates represents a completely undeveloped field, as no reasonable solutions to such examples as reduction of dialkylketones, oxidation of dialkylsulfides, epoxidation, and dihydroxylation of *cis*-dialkyl alkenes appear to have been developed.^{20,21} With the lack of helical electronic effects, steric bias in diastereomeric

Asymmetric reactions classified by substrate polarizability properties



Class A: Substrates are capable of defining significant helical characters in reaction transition states, thus catalyst/substrate homohelical character matching leads to strong helical electronic control. They include:

I, IV, VI, in which $\text{R}_1 = \text{Ar}$, $\text{R}_2 = \text{Alk}$; and **II, III, V**, in which $\text{R}_1, \text{R}_2 = \text{Ar}$ or Alk .

Class B: Substrates are incapable of defining significant helical characters in reaction transition states, thus helical electronic effects are weak or absent and stereochemical courses are largely under steric control. They include:

I, IV, VI, in which $\text{R}_1 = \text{R}_2 = \text{Ar}$, or $\text{R}_1 = \text{R}_2 = \text{Alk}$.

Scheme 4. Classification of asymmetric catalytic reactions on the basis of substrate polarizability properties; X = O, NH, or NR; Func, coordinative functional group; Ar, aromatic or other π -electronic group; Alk, alkyl group.

transition states alone often seems incapable of executing high enantiocontrol. Highly enantioselective transformations of these substrates are therefore expected to be exceedingly challenging to realize.

It is intriguing to appreciate why this may be so. Unlike enzymatic processes, in which reactions take place in highly organized transition states that presumably employ a judicious balance of electronic and steric controls to achieve stereospecificity, man-made systems are generally less stereochemically organized, especially in the local reaction regions where the bond-breaking and bond-forming events occur. A consequence is that steric distinctions in the competing diastereomeric reaction channels may be effectively smoothed by dynamic conformational ensembles. By contrast, helical electronic effects, which are relatively independent of conformational fluctuations and can be strong, may emerge as major control elements. Furthermore, although the enantioselectivity in a reaction often requires cooperative interactions of several interplaying factors, it may be asserted here that, for broadly useful, highly enantioselective catalysis to be realized, the consideration on and the employment of the helical electronic control may be generally more advantageous than those with steric effects, since the former is evidently more tolerant of variations on sizes and conformations. The literature,^{20,21} when viewed with this helix approach, in fact supports this assertion. Steric effects appear to prevail in only a few highly enantioselective systems that feature prominently well-defined transition-state architectures, such as those templated by multiple chelation effects in square-planar bis(oxazoline)-metal complex-catalyzed reactions.²²

From a more global view concerning electronic polarizability and chemical reactions, we note that this work has its roots in earlier theories,²³⁻³⁴ and in them it has been suggested that polarizability (softness) or its inverse, hardness, is a parameter as universal and fundamental as energy; that there may be such general rules as the principles of the maximum hardness and of the minimum polarizability dictating the reactivity and selectivity in chemical processes;³⁵ and that electron movements in chemical reactions follow a polarizability rule: it is the more polarizable bonds that break more easily and the less polarizable bonds that form more easily.^{36,37} It is gratifying to see this polarizability notion, when applied to chiral systems, yields useful helix implications. The helical characters matching in a three-dimensional chiral space is essentially a chiral version of the classical hard and soft acid-base theory.

CONCLUSION

As a continuation of the efforts to develop an electronic theory for molecular chirality and chiral interactions, we suggested a theoretical basis for the principles of helicity conservation and helical character matching. Although the present focus is on asymmetric catalysis, there seems to be no reason to suppose that these conclusions are not generally valid in other chiral interactions. The discussion suggests that chiral interactions are largely local ef-

fects on both electronic and steric grounds, that is, a maximum enantioselection may be associated with a local, but not necessarily a global, transition-state energy minimum along the reaction coordinate. This conclusion is in line with the proposals of Pearson and Parr et al., who suggested that the local softness/hardness generally serve as more effective determinants for a molecule's stability and reactivity.^{26,28-33} It is envisioned that, in conjunction with steric considerations, the development of a computational strategy that can quantitatively address such local helical electronic effects would aid rational design of chiral systems. Given the considerable advances achieved in polarizability calculations in recent years,³⁸⁻⁴⁰ the development and implementation of such a strategy should be feasible. Efforts along this line are now in progress.

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