

Relationship between Chirality Content and Stereinduction: Identification of a Chiraphore

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In this paper we posit the following fundamental question: What is the relationship between chirality per se, and enantio-differentiation? Clearly chirality needs to exist for a stereodifferentiating task to take place, whether it be chiral recognition by a receptor or host molecule or for a catalyst to induce asymmetry in a synthetic transformation. But, how much chirality is needed? If one considers an unsymmetrically substituted biphenyl as an example, it is clear that no chirality exists when the system is completely planar so that no chiral recognition or induction can take place. Yet, by twisting the rings out of plane, even 1/100th of a degree, a chiral system is generated (P and M enantiomeric forms). If one could isolate and retain that twisted form, most chemists would feel confident that neither chiral recognition nor stereinduction would be observed because the molecule is not twisted enough, i.e., it lacks enough chirality content to carry out a stereodifferentiating task effectively. Contrarily, that biphenyl twisted, say 45°, would be viewed by most chemists as a system that would be a suitable candidate for stereodifferentiating tasks, and indeed, there exist a plethora of such axially chiral biphenyls, binaphthyls, and so on in the literature capable of expressing chiral recognition.

Thus, somewhere along the twisting coordinate, beginning from a nonchiral planar form to a chiral twisted form, the chirality content of the system must increase to a maximum value, but then it must decrease back to zero as the system again becomes achiral in its planar form. The idea that one should be able to quantitate chirality has been the focus of a small group of mathematical chemists who, during the past decade, have developed a variety of mathematical and computational methods for determining how chiral an object is, whether that object is a molecule, a collection of molecules, or even large random supramolecular structures such as spiral diffusion-limited aggregates.^{1,2} In fact, some of these researchers have already applied their methodologies to biphenyl itself.^{3,4} What we want to accomplish here is to determine what relationship exists, if any, between computed chirality metrics and a stereodifferentiating task measured from experiment. To do this we adopt Avnir's continuous chirality measure (CCM) to compute the chirality content of molecules.^{5,6} The CCM is calculated using eq 1

$$S(G) = \frac{1}{nD^2} \sum_{i=1}^n (p_i - \hat{p}_i)^2 \quad (1)$$

(1) *New Developments in Molecular Chirality*; Mezey, P. G., Ed.; Kluwer: Dordrecht, 1991; chapters therein.

(2) For additional review articles, see: (a) Buda, A. B.; Auf der Heyde, T.; Mislou, K. *Angew. Chem., Int. Ed. Engl.* **1992**, *31*, 989. (b) Gilat, G. In *Concepts in Chemistry: A Contemporary Challenge*; Rouvray, D. H., Ed.; Research Studies Press: Taunton, 1996, Chapter 10, pp 325–354. (c) Avnir, D.; Katzenelson, O.; Keinan, S.; Pinsky, M.; Pinto, Y.; Salomon, Y.; Zabrodsky Hel-Or, H. *ibid.*; Chapter 10, pp 283–324.

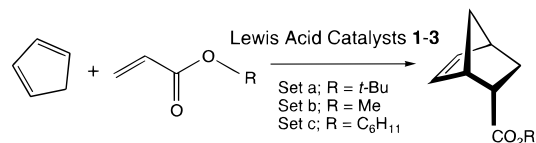
(3) Ospov, M. A.; Pickup, B. T.; Dunmur, D. A. *Mol. Phys.* **1995**, *84*, 1193.

(4) Grant, J. A.; Gallardo, M. A.; Pickup, B. T. *J. Comput. Chem.* **1996**, *17*, 1653.

(5) Zabrodsky, H.; Avnir, D. *J. Am. Chem. Soc.* **1995**, *117*(1), 462.

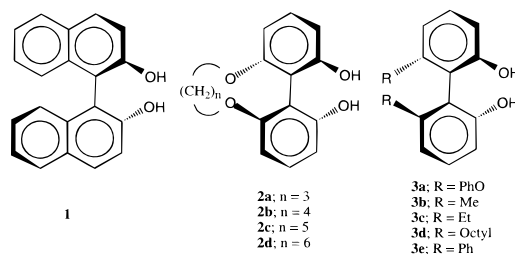
(6) The ability of the CCM approach to quantify structure–activity correlations in bioreceptors has been published: Keinan, S.; Avnir, D. *J. Am. Chem. Soc.* **1998**, *120*(24), 6152.

where n are the number of vertices located at positions p_i and given by symmetry point group G and the \hat{p}_i are the corresponding points in the nearest G -symmetric configuration while D is a distance normalization factor to make the CCM value size-invariant. The CCM is a special distance function in that there is no ideal reference structure used for comparison a priori; rather, it is the distance to the nearest structure with the desired symmetry. The experimental system we apply our analysis to are the 2,2'-biaryldiol ligands used by Harada et al. for asymmetric Diels–Alder reactions of acrylates with cyclopentadiene.⁷



We use this set of experimental data because a large number of catalysts were prepared and evaluated for their ability to induce asymmetry (in comparison to most literature reports where only one or two catalysts are usually studied).

Harada considered the Lewis acid catalysts **1** as well as biphenyl diols where the asymmetry around the hydroxyl groups were controlled by either an alkylendioxy bridge, **2**, or substituents at the 6 and 6' positions, **3**. Three sets of reactions were carried out where the R group of the acrylate was altered. These three sets of reactions are designated as set **a**, **b**, and **c**.



Both the yields and the enantiomeric excesses (ee's) were variable, but an insightful discovery by Harada was that by plotting the biphenyl twist angle, derived from quantum mechanical calculations of an aluminum chloride complex, one finds a nonlinear, nearly parabolic relationship between the extent of biphenyl twisting and the experimental ee's. We have repeated these calculations,⁸ and we find a similar, albeit not identical, relationship (Figure 1 left side panels).

These results are both logical and intuitive; as the twisting increases, the stereinduction increases until a mismatch is created at which point the ee's begin to drop. We find for these reactions the maximum twist angle is around 60°. In this analysis four atoms, C₂–C₁–C_{1'}–C_{2'}, are used to define the twist of the biphenyl, and this internal coordinate alone seems to express well the relationship between chirality and stereinduction. But, *how much chirality is involved*, and what is the relationship between stereinduction and chirality content? Moreover, what part of the catalyst is responsible for the observed stereinduction, certainly not just the four above-mentioned atoms? Here we introduce the second point of this paper: the idea of the *chiraphore*.

(7) Harada, T.; Takeuchi, M.; Hatsuda, M.; Ueda, H.; Oku, A. *Tetrahedron: Asymmetry* **1996**, 2479.

(8) Conformational searches of the pendant groups in compounds 2–3 were carried out with the grid-based method of Spartan version 4.1, Wavefunction Inc., 18401 Von Karman, Suite 370, Irvine, CA 92715. The same metal and semiempirical Hamiltonian used in ref 7 was implemented by us. The lowest energy conformer for all systems evaluated was used to determine the bi-aryl twist angle and also for the CCM calculations.

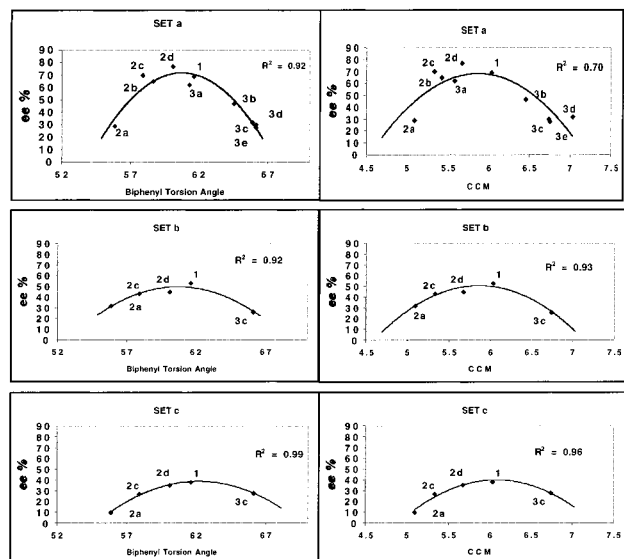


Figure 1. Left panels: plots of bi-aryl torsion angle versus ee for acrylate sets **a–c** reacting with cyclopentadiene in the presence of axially chiral catalysts described in the text. Right panels: plots of computed chirality content (CCM) versus experimental ee's for the same systems.

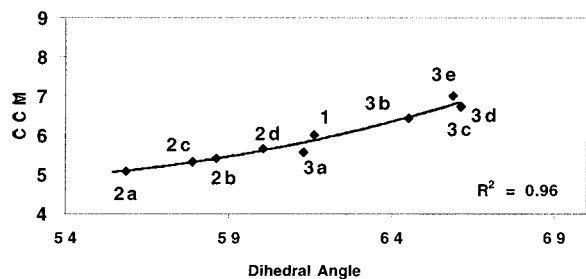


Figure 2. Plot of computed chirality metrics (CCM) versus computed dihedral angles for the 10 catalytic systems studied.

Before presenting our results about the relationship between chirality content of these catalysts and experimental stereoselection we need to point out that the “most chiral” catalyst need not be the best for stereoselection. This is because parts of the catalyst far removed from the reaction site may have no direct influence on the asymmetric induction taking place at the site of reaction (they may indirectly influence the outcome by virtue of inducing more or less twist to the biphenyl, however). Hence we need to address the issue of global versus localized chirality. Not all of a molecule needs to be considered for understanding and predicting the properties and behavior of that molecule. The most familiar example of this is the idea of functional groups in organic chemistry where localized collections of atoms embedded in a molecule are most responsible for the chemistry of that molecule. Likewise, the concepts of chromophores and pharmacophores exist. By analogy we introduce here the concept of the *chiraphore*. In this paper we focused on the biphenyl fragment as being the chiraphore. This is somewhat obvious but it is also the reason we selected this particular system for study.

Presented in Figure 1, right side panels, are plots of computed chirality content versus experimental ee's. The chirality metric is Avnir's CCM⁵ computed using the nuclear coordinates of the global minimum energy structures derived quantum mechanically for catalysts **1–3**. What we find is a nonlinear relationship between chirality content of catalysts and experimental stereoselection. In fact, the same relationship between CCM versus ee's exists as is found for twist angle versus ee's above. Accordingly a linear relationship between CCM and twist angle should exist and it does as shown in Figure 2.

Several points need to be made about these results. First, the plots are fitted to a parabolic function for the sake of illustrating a relationship only; some other function may better reproduce

the trend. However, this is the simplest and most intuitive function, and thus we retain it. Second, the curvature of these plots are slightly different, as are the curves for the biphenyl twist angle, indicating there exist different sensitivities to chiral induction being expressed by the catalysts for the slightly different sets of acrylate esters. Third, several chiraphores were considered including: (a) the entire catalyst, giving no correlation, (b) randomly selected parts of the catalyst, also showing no correlation, (c) the bi-aryl with the aluminum chloride, showing a good correlation (r^2 values are 0.63, 0.89, 0.92 for sets a–c respectively) and (d) only the bi-aryl fragment with its immediately attached atoms (including the oxygen atoms) which gave the best correlation depicted in the figure above. Hence we believe this localized part of the catalyst is the fragment that is directly responsible for the stereoselection and as such constitutes the first example of a chiraphore.

Further comments concerning these results are also warranted. First, while it is satisfying that the trends in torsion angle and CCM parallel one another, we point out that the CCM offers additional information not available from a dihedral angle alone. In particular we find that the bi-aryl ligands become distorted when ligated to the metal two ways: (1) the axis along the bond connecting the two aryl rings is no longer linear but instead is slightly bent, and (2) the aromatic rings are not planar; instead, they are somewhat curved and adopt a twist that we find amplifies the chirality content of these already chiral ligands (the CCM values reported here are approximately twice as large as those for the free ligand held fixed at the same dihedral).⁹ Hence, the CCM can provide additional chirality information that is lacking from a single torsion angle alone. Second, although the work described here involves catalysts having an axis of chirality, the treatment should be applicable to those containing central or planar chiralities. In these cases, however, it may be more difficult to find the less obvious chiraphore. Third, the experimental ee's will be temperature-dependent and depend on both entropic and enthalpic contributions to the free energy. For the moment we focus only on the total free-energy result because no data concerning temperature in this system exists. However, we point out that most Diels–Alder reactions are dominated by enthalpic contributions, and the results described here are most likely an enthalpy defining the molecular recognition between the catalyst and the reagents. We anticipate that similar results will be obtained for the same set of catalysts run at other temperatures with both the maxima and the curvature of our plots being shifted.

The goals of this research were 2-fold, both of which were successful. First we wanted to find what relationship exists between chirality content and enantiodifferentiation; in this case we considered a series of related catalysts and found that a parabolic relationship exists between computed chirality metrics and experimental ee's. Second, we wanted to bring to the fore the concept of local chirality versus global chirality and in this regard to introduce the concept of the chiraphore. In this catalytic system the chiraphore, or key fragment responsible for stereoselection, is the biphenyl fragment alone. Finally, more work is certainly needed to further understand the relationship between chirality content and a molecule's ability to carry out an enantiodifferentiating task. Because the literature is so devoid of experimental studies such as that described here we are asking the scientific community to assist us by bringing to our attention published or unpublished works so that other relationships may be evaluated.

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(9) A reviewer remains skeptical that the chirality metrics offer any advantages over the dihedral angle. In addition to providing a quantitative measure of chirality (something a dihedral angle does not provide) we point out that due to the warping of the aryl rings the value of the dihedral angle will change, depending upon which atoms are used to define that internal coordinate (in compound **2a**, for instance, the value is 56.5° when the four contiguous atoms are those proximal to the hydroxyls, while it is 54.5° when the four distal atoms are used instead; in another system we have been studying the differences are as large as 6°).