Computation of Physical Chirality: An Assessment of Orbital Desymmetrization Induced by Common Chiral Auxiliaries

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Abstract: The continuous chirality measure (CCM) of Avnir is extended to treat equiamplitude surfaces of wave functions in three dimensions. By implementing this methodology, we evaluate the amount of orbital desymmetrization that is induced by common chiral auxiliaries used in asymmetric syntheses. We find that, while some chiral auxiliaries themselves have very little chirality content, the molecule as a whole to which they are attached can be very chiral and that significant orbital desymmetrization is induced by these auxiliaries. Generally, the chirality content of the frontier orbitals of these molecules is large, being comparable in magnitude to the structural chirality of the molecules themselves.

Introduction

A dramatic increase in the number of studies focusing on the topic of chirality has now thrust it into the scientific forefront in several disciplines of the chemical sciences, especially in organic and biological chemistry. Reflecting this interest are new journals dedicated to the topic of chirality including *Tetrahedron: Asymmetry*, *Enantiomer*, *Chirality*, and *Molecular Asymmetry*, all of which complement existing journals that are themselves replete with papers on chirality. Workshops, symposia, and conferences are now common and popular. Further attesting to the interest in this topic is a series of feature articles in *Chemical & Engineering News* laying bare the fact that a whole new industry based on chirality now exists.[1] This industry, designated as "chiroscience", is a young but robust industry transcending traditional boundaries separating biology and chemistry.

One of the pedestals upon which chiroscience is built is asymmetric synthesis,[2−4] and in this regard, while much effort is now being placed on creating catalysts capable of generating the desired enantiomer directly, the workhorse to date has been to use chiral auxiliaries. By introducing a suitable element of chirality into an otherwise nonchiral reagent, one can generate products having both high yields and high stereochemical purity. The products formed from these reactions are diastereomeric in nature, but the chiral auxiliaries typically used are easily removed, thus affording the desired enantiomer.

Much work has also been directed toward understanding the origins of the observed stereoselection when chiral auxiliaries are used, and a variety of models have been presented to rationalize the diastereoselection of such reactions.[5] Most of those models and rationalizations focus the attention of the chemist on the chiral auxiliary itself. Here the trajectory of incoming reagents is directed by steric or electrostatic effects of that particular auxiliary. However, the chiral auxiliary also induces a desymmetrization of the frontier molecular orbitals at the reaction site, making them chiral as well.[6,7] The question we pose in this paper is, how much orbital desymmetrization is induced by common chiral auxiliaries? Our query, then, begs the following question: How can one define the "chirality content" of an orbital? In this research paper we (1) develop a computational procedure for evaluating the chirality content of molecular orbitals in general and (2) assess how much desymmetrization is induced by common chiral auxiliaries.

Chirality Metrics. Most chemists' working knowledge of chirality is that it is an "either/or" phenomenon, i.e., either the system has chirality or it does not. When further probing those same chemists about this topic, however, they are quite eager to express that some systems are, in some ill-defined way, more chiral than others. For example, a planar biphenyl is nonchiral, while one that is twisted $\pm2°$ is chiral, but one that is twisted $\pm30°$ is even more chiral. Likewise, in some intangible way, a tetrahedral stereocenter containing four somewhat similar (albeit distinguishable) ligands is less chiral than that same center with four distinctly different ligands.

The idea that one should be able to quantitate chirality has been the focus of a small group mathematical chemists who,

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(1) (a) Stinson, S. C. Chiral Drugs: Market Growth in Single-Isomer Forms Spurs Research Advances (cover story and feature report). *Chem. Eng. News* **1995** (Oct 5), 44−74. (b) Stinson, S. C. Chiral Drugs: Single-Isomer Products Drive Development of New Syntheses and Separation Technologies (cover story and feature article). *Chem. Eng. News* **1994** (Sep 19), 38−72. (c) Stinson, S. C. Chiral Drugs: Wave of New Enantiomer Products Set to Flood Market (cover story and feature article). *Chem. Eng. News* **1993** (Sep 27), 38−65. (d) See also: Sheldon, R. D. *Chirotechnology*; Dekker: New York, 1993.
(2) Rahman, A.; Shah, Z. *Stereoselective Synthesis in Organic Chemistry*; Springer-Verlag: New York, 1993.
(3) Ager, D. J.; East, M. B. *Asymmetric Synthetic Methodology*; CRC Press: Boca Raton, FL, 1996.

(4) Gawley, R. E.; Aubé, J. *Principles of Asymmetric Synthesis*; Elsevier Sciences Ltd.: Oxford, U.K., 1996.
(5) (a) See especially Chapter 2 of ref 3. (b) Eliel, E. L.; Wilen, S. H. *Stereochemistry of Organic Compounds*; Wiley: New York, 1994; Chapter 12 by L. N. Mander.
(6) For seminal papers concerning orbital polarization and its influence on stereochemical outcome, see: Burgess, E. M.; Liotta, C. L. *J. Org. Chem.* **1981**, *46* (8), 1703 and references therein.
(7) An early attempt at quantifying HOMO and LUMO chiralities for chiral conformers of 1-butene and skewed ethene was done by: Eisenstein, O.; Klein, J.; Lefour, P. *Tetrahedron* **1979**, *35*, 225. For earlier studies, see references cited.

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.[8–11] It is pointed out here that all computed measures are size invariant, meaning that comparisons can be made between different sized objects. In our work we use the methodology and algorithms developed by Avnir for continuous symmetry measures[12] (CSMs) that have been extended to assess chirality as continuous chirality measures (CCMs).[13] While the idea of quantitative measures of chirality has existed before CSM, one of the special features of in Avnir's approach is that it quantifies symmetry in general, so that chirality measures become a more special case of the more general approach. Avnir's methodology and its application to a wide range of problems has been reviewed[9c] and will not be described here. In its simplest form the CCM provides the minimum distance of the object from having an improper element of symmetry. In the majority of cases, including all cases analyzed here, that element is simply the mirror plane.

Gilat has pointed out that a sharp distinction exists between "geometric" and "physical" chiralities. To quote Gilat, "The distribution of a geometric entity such as a curve, surface, area or volume is always *homogeneous* within its dimensionality, i.e., the "density" of a curve is constant along the curve, as are the area and volume densities of any given geometric object. This is not necessarily the case for the distribution of a physical property."[9b] Examples of physical properties would include wave functions, electron densities, gradients of electric fields, or any other physically relevant distribution of interest.

The CCM is a distance metric suitable for geometric considerations. Indeed, most of its use to date has focused on geometric aspects of chirality.[14] It has been pointed out by Zabrodsky and Avnir, however, that one can extend CCM measures to physical properties by evaluating the CCM of equiproperty contours. The example given by those authors involved plotting the equiamplitude cross-sectional contours of a wave function (see Figure 10, ref 13) and then using the folding–unfolding algorithm to seek the minimum chirality metric. In this paper, we extend this approach and then compute chirality metrics for orbitals that are known to play roles in stereochemical reactions.

Computational Methods

Software. All molecular orbital calculations were carried out using Spartan 4.1.[15] To expedite this study, geometries and conformer searches (when needed) were carried out with the AM1 or PM3 Hamiltonians using the default geometry optimizer and convergence criteria. Single-point SCF ab initio calculations were then done on those structures using one of several standard Gaussian basis sets (see below). An in-house program was written that uses the LCAO coefficients from Spartan and plots the wave functions in three dimensions. Pople's standard STO-nG contraction scheme for the orbitals was used.[16] Equiamplitude surfaces of the wave function under investigation were created by selecting data points within a thin shell 0.030−0.032 au for the CCM measures described below (parenthetically Spartan uses a value of 0.030 in their orbital displays). Wave functions are visualized using Silicon Graphics Explorer.[17]

Methodology. CCM calculations were done using a modification of the folding−unfolding algorithm described by Zabrodsky and Avnir.[13] Given a configuration of points (in our case equiamplitude surface points defining the wave function), the chirality content of the object is determined by finding the nearest configuration of points which has an improper element of symmetry. This is done by calculating the distance between those two sets of points using eq 1 of ref 13. To ensure that the chirality metric being computed with the folding/unfolding algorithm is the minimum value, all possible divisions of sets are made and all possible reflection planes are considered, thus making this a combinatorial problem that appears to quickly limit the number of points that can be considered. In practice, though, the minimization process can be greatly simplified by dividing the points into sets based on topology. Hence the resulting chirality measure of a connected configuration of points lists all possible divisions of points into pairs by taking into account only the connectivity of the points. For the size of molecules we are studying in this report, we typically have 2000 surface points. To make this a tractable problem, we divide the orbital into slices of some given thickness (thin slabs) containing a subset of points as in Figure 1.

The points within each slab are topologically connected as a series of uniform surface points (identical to what was done in Figure 10 of ref 13), and the CCM for all data points within all slabs is evaluated. Note that the number of points included in the CCM calculation of the wave function depends on the slab thickness and the number of slabs used (in addition to the inherent density of points used to map the orbital initially). The sampling must be dense enough to preserve the general shape of the orbital. In our studies we generate (typically) 10 equally spaced slabs spanning the entire wave function. The thickness of each slab is variable, being 1% of the length of the molecular orbital being evaluated. The location of these 10 slabs will define which points are to be included or excluded in the ensuing CCM calculation. Moreover, the number of surface points used for computing a particular CCM will depend on where those slabs are positioned. To account for this, we repeat the computation by displacing the slabs slightly from the previous run and recomputing a new CCM. Multiple reslicing followed by subsequent CCM evaluations is then carried out to provide the average CCM along with a standard error. Finally, note that the CCM may change with the number of selected points, if that number is too low to preserve the general shape of the orbital. We have selected a large enough number to avoid this pitfall. At the time of this writing we were made aware of a paper that describes an alternative approach to computing orbital chiralities.[18] The essential distinction between that CCM approach and ours is that Grimme treats the wave functions themselves, which is based on the quantum mechanical expectation value of an appropriate geometric transformation operator, while we treat the shape of the orbital amplitudes.

Results and Discussion

Achiral Orbitals. It is imperative that orbitals containing planes of symmetry have zero chirality content. To test our

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

(9) For additional review articles, see: (a) Buda, A. B.; Auf der Heyde, T.; Mislow, K. *Angew. Chem., Int. Ed. Engl.* **1992**, *31*, 989. (b) Gilat, G. The Concept of Structural Chirality. 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. The Measurement of Symmetry and Chirality: Conceptual Aspects. *Ibid.* Chapter 10, pp 283−324.

(10) (a) Gilat, G. *J. Math. Chem.* **1994**, *15*, 197. (b) Weinberg, N.; Mislow, K. *Ibid.* **1995**, *17*, 35.

(11) For leading references, see: Randic′, M.; Razinger, M. *J. Chem. Inf. Comput. Sci.* **1996**, *36*, 429.

(12) Zabrodsky, H.; Peleg, S.; Avnir, D. *J. Am. Chem. Soc.* **1992**, *114*, 7843.

(13) Zabrodsky, H.; Avnir, D. *Ibid.* **1995**, *117*, 462.

(14) (a) Pinto, Y.; Zabrodsky Hel-Or, H.; Avnir, D. *J. Chem. Soc., Faraday Trans.* **1996**, *92* (14), 2523. (b) Keinan, S.; Zabrodsky Hel-Or, H.; Avnir, D. *Enantiomer* **1996**, *1*, 351. (c) Katzenelson, O.; Zabrodsky Hel-Or, H.; Avnir, D. *Chem. Eur. J.* **1996**, *2* (2), 174. (d). Pinto, Y.; Salomon, Y.; Avnir, D. *J. Math. Chem.* **1998**, *23*, 13. (e). Keinan, S.; Avnir, D. *J. Am. Chem. Soc.* **1998**, *120*, 6152. (f). Pinto, Y.; Fowler, P. W.; Mitchell, D.; Avnir, D. *J. Phys. Chem. B* **1998**, *102*, 5776.

(15) Spartan version 4.1, Wavefunction Inc., 18401 Von Karman, Suite 370, Irvine, CA 92715.

(16) Hehre, W. J.; Radom, L.; Schleyer, P. v. R.; Pople, J. A. *Ab Initio Molecular Orbital Theory*; Wiley: New York, 1986.

(17) IRIS Explorer Center (North America), Downers Grove, IL 60551-5702 or via <URL http://www.nag.co.uk/1h/Welcome_IEC>.

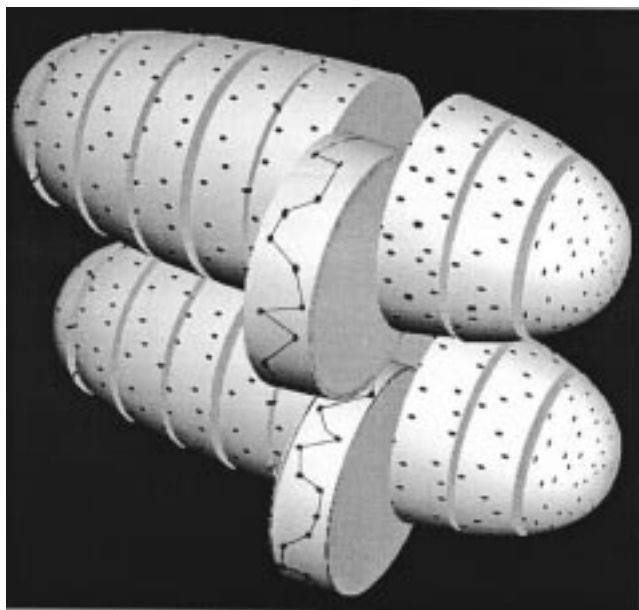(18) Grimme, S *Chem. Phys. Lett.* **1998**, *297*, 15.

Figure 1. Cartoon of orbital slicing. Depicted here is a caricature of a π-like orbital that has been sliced into 10 slabs of uniform thickness (signs of the wave function are irrelevant to our calculations and not illustrated here). The speckles on the surface define the shape of the orbital (see text). Those data points are connected topologically as depicted in the extruded slice to make the CCM calculations tractable. In this cartoon the slabs are much thicker than the ones used to compute the CCM, and the number of data points defining the shape of the orbital is much smaller than what is typically used to carry out the calculations.

computational protocol, then, several symmetric systems such as ethene and symmetric propenes were evaluated. The LACO molecular orbitals were determined, and the CCM of the HOMO and LUMO for each molecule was assessed. As expected, the chirality content of these orbitals was zero.

Distorted Ethene. Twisting a localized π bond makes it chiral. To assess the chirality content of twisted ethenes we evaluated the HOMO of ethene with dihedral angles of 10°, 20°, and 30°. The corresponding average CCMs for the HOMOs are 6.9 (± 1.0), 7.6 (± 2.0), and 8.4 (± 1.5), respectively, using an STO-3G basis set and 4.6 (± 1.5), 6.5 (± 1.5), and 7.2 (± 0.5), respectively, for the 6-31G** basis set. Note that the values cited here are averages from six separate slicing calculations (i.e., six different locations of the 10 slabs), where the slices have been offset from the prior calculation as described in the methods section above. To put the chirality content of these orbitals into perspective, we compare these values to the CCM of the ethene structure itself, i.e., by calculating the structural chirality using the atomic coordinates of the twisted ethene. For ethene twisted 10° the computed structural CCM is only 0.04; for ethene twisted 20° the CCM is 0.7; and for a 30° twist the value is 1.43. What we find from this analysis, then, is that the chirality contents of moderately distorted ethene HOMOs (1) are essentially independent of basis set (see also below) and (2) contain more chirality (larger in magnitude) than the molecule itself (as being defined by the nuclei). We also note here that the CCMs of the nuclei are far more sensitive to the twist than are the CCMs of the HOMOs: the former changes from 0.04 to 1.43 whereas the range of change in the latter is much smaller.

Enolates. Enolates are common reactive intermediates in synthesis. Here we consider several enolates with and without chiral auxiliaries attached. The simple enolate **1** below has no chirality and has a CCM of zero in terms of its structure defined by nuclear coordinates as well as its orbitals. Both Z and E enolates of **2** are chiral, however, and the influence of the stereogenic centers on the enolate HOMOs for each molecule has been computed. In these calculations the hydrogen of the stereogenic carbon was fixed in the plane of the enolate; all other degrees of freedom have been optimized using the AM1 Hamiltonian. That geometry was then used for the ab initio, single-point calculations to derive the molecular wave functions that in turn were used for the CCM calculations.
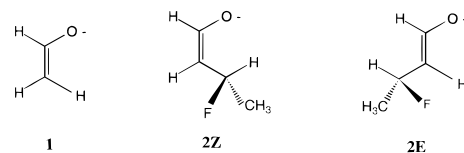
The computed CCM for the HOMO of **2Z** is 7.93 $\pm$ 1.50 (STO-3G) and 12.21 $\pm$ 0.20 (6-31G**). The HOMO for the **2E** enolate is 5.37 $\pm$ 1.00 (STO-3G) and 8.17 $\pm$ 0.20 (6-31G**). Again for comparison the structural chirality using the atomic coordinates was also computed. For **2E** the nuclear CCM is 7.26 and that for **2Z** is 8.94. Two relevant points need to be made here. First, the HOMO of the Z isomer has more chirality content than does the HOMO of the E isomer. The genesis of this difference in chirality is that the perturbing chiral auxiliary is "nearer" to the enolate when in the Z configuration than when in the E configuration. This crowding polarizes and desymmetrizes the enolate more than when in a noncrowded, extended geometry. The second point is that the CCM values of the orbitals are comparable in magnitude to the structural CCM of the molecules. Finally, note that the HOMO and LUMO are not completely localized on the enolate carbon and oxygen atoms only; there exist significant coefficients contributing to these orbitals from the auxiliary's atoms as well.

To explore if one can significantly enhance the chirality content of chiral enolate orbitals, we computed the wave functions for **3Z** and **3E**, anticipating that polarizing the system
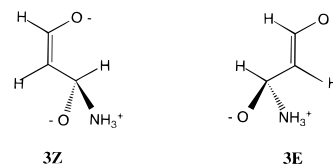

in a chiral manner with strongly interacting groups might lead to orbitals with even greater chirality content.

The CCMs of the HOMO for **3Z** are 9.08 $\pm$ 0.60 (STO-3G) and 9.24 $\pm$ 1.50 (6-31G**). The CCMs of the **3E** HOMO are 4.89 $\pm$ 0.80 (STO-3G) and 7.98 $\pm$ 0.50 (6-31G**). Evidently zwitterionic chiral auxiliaries have little influence on desymmetrizing enolate ions compared to uncharged groups. The structural chirality of **3E** computed using nuclear coordinates is 7.79, and that for **3Z** is 11.44. Again what we find is that the chirality contents of the enolate HOMOs are comparable to the chirality content of the molecule.

In solution the above-mentioned systems are associated with metal counterions, especially lithium. The lithium enolate of **1**, computed with the MNDO Hamiltonian is similar in structure to that recently described by Wang, Sun, and Deng,[19] who used extended basis sets to evaluate the local minima and transition structures of C_2H_3OLi. The most stable structures of $CH_2{=}CH(OLi)$ are a planar species and a bridging structure similar in nature to allyllithium, with the bridging structure being 10.6 kJ/mol more stable. The bridging structure is chiral, and

the CCMs for the HOMO are 8.34 ± 0.70 (STO-3G) and 8.46 ± 1.00 (6-31G**) while the CCMs of the LUMO are 11.02 ± 1.00 (STO-3G) and 5.91 ± 1.00 (6-31G**). We attempted to compute the metal enolates of **2** and **3** above, but those calculations left some doubt about their veracity. In particular, the Li...F associations always led to the same planar global minimum for **2Z** and **2E** so we did not consider further the role of the metal in these systems (we did in others described below, however).

Oxazolines and Oxazolidinone Imides. These are examples of azaenolates where intraligand asymmetric induction takes place. The former was developed by Meyers[20] and the latter by Evans,[21] but both are examples of metal chelation by a heteroatom so that there exist beneficial restrictions on conformational mobility as well as positioning of the chiral auxiliary stereocenter near the α carbon of the enolate. The systems we studied are **4** and **5**.
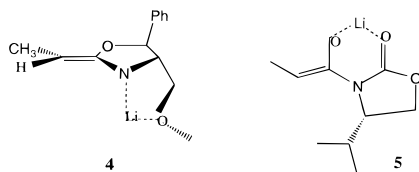
The CCMs of the HOMO of **4** are 8.22 ± 1.50 (STO-3G) and 8.13 ± 1.50 (6-31G**). The CCMs of the HOMO of **4** that had been recomputed without the metal ion present are 5.69 ± 1.00 (STO-3G) and 7.32 ± 0.70 (6-31G**). While the presence of the lithium cation does further distort the enolate in a chiral way, the influence of that metal ion is small. The nuclei's structural chirality for this molecule containing the metal is 4.93; hence, we again find that the chirality content of the HOMO is larger than that of the molecule defined by its nuclear coordinates. The CCMs of the HOMO of **5** are 7.71 ± 2.00 (STO-3G) and 8.18 (6-31G**), and the nuclear structural CCM is 11.60. Hence, for these two venerable examples of enolates that are known to lead to good stereoinduction, the chirality contents of the frontier orbitals most responsible for alkylations with electrophiles are comparable in magnitude to the structural chirality of the molecules.

Pericyclic Reactions. Alkenyl sulfoxides containing chiral auxiliaries can undergo ene and Diels−Alder reactions with high stereoselection. Tietze has recently evaluated the conformational preference of unsaturated sulfoxides and their Lewis acid complexes to better understand the mechanism of asymmetric induction,[22] and we select several vinyl sulfoxides studied by Tietze for our CCM measurements, including the (*Z*)- and (*E*)-β-methyl-substituted vinyl sulfoxides **6** and the α-cyano-substituted sulfoxide **7** (electron-withdrawing groups at that
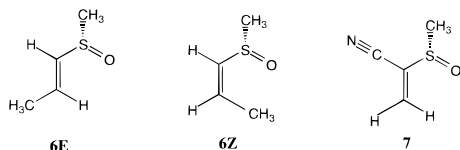

location are used to increase the reactivity of these pericyclic reactions). The wave functions were computed, and the CCMs of the frontier orbitals for these chiral sulfoxides were determined. The results are compiled in Table 1. Also included in this table in column 1 are the corresponding structural chirality metrics of these molecules computed from their nuclear

Table 1. Chirality Content of HOMO (HO) and LUMO (LU) of Compounds **6**−**11**

molecule and nuclear CCM	HOMO (STO-3G)	HOMO (6-31G**)	LUMO (STO-3G)	LUMO (6-31G**)
6E (2.24)	12.60 ± 3.00	8.35 ± 1.00	7.56 ± 1.50	7.20 ± 0.60
6Z (8.99)	9.29 ± 2.00	7.76 ± 1.00	9.37 ± 3.00	5.80 ± 0.50
7 (10.02)	13.41 ± 2.00	7.88 ± 1.00	6.91 ± 2.00	7.33 ± 1.20
8 (2.58)	9.15 ± 1.00	6.76 ± 0.60	7.86 ± 0.80	8.08 ± 0.50
9 (9.57)	5.96 ± 0.40	5.28 ± 1.00	6.70 ± 1.20	8.32 ± 0.40
10 (10.26)	9.62 ± 2.00	5.41 ± 1.00	5.01 ± 2.00	5.41 ± 1.00
11 (6.35)	8.17 ± 0.60	4.8 ± 2.00	9.49 ± 2.50	9.62 ± 0.80

coordinates. Evident here is that once again the frontier orbitals have very similar chirality contents when compared to the molecules themselves and in some cases such as **6E** and **8** far exceed the geometric chirality of the molecule. However, in **4**, it is the opposite, so one cannot generalize here.
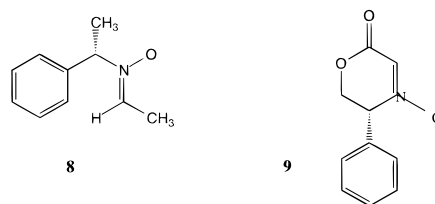
The 1,3-dipolar cycloaddition of chiral nitrones with alkenes to give isoxazolidines is well-established and has been recently reviewd by both Fredrickson[23] and Gothelf and Jorgensen.[24] The most commonly used chiral substituent at the nitrogen is the 1-phenylethyl group, and accordingly, we carried out our calculations on a simple example of this, **8**.[25] Also included in our calculations was the cyclic acyl nitrone of Baldwin, **9**.[26] The CCMs of the frontier orbitals of these compounds are also included in Table 1, where again high chirality content of the dominant orbitals in these pericyclic reactions is found to exist.

Finally, we consider here axially chiral anilide and maleimide derivatives **10** and **11**, recently prepared by Taguchi, which are
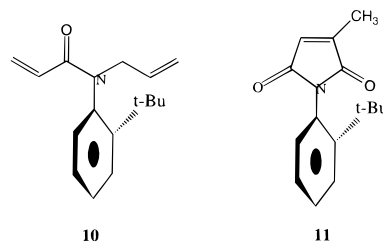
capable of "atroposelective" Diels−Alder reactions.[27] The CCM values of the HOMO and LUMO of these molecules are also included in Table 1. These orbitals, like the frontier orbitals of the other molecules above, appear to have chirality contents that are comparable in magnitude to the structural chirality content of the molecules as defined by their nuclear coordinates.

(19) Wang, Y.-g.; Sun, C.-j.; Deng, C.-h. *J. Mol. Struct. (THEOCHEM)* **1998**, *429*, 207.

(20) Lutomski, K. A.; Meyers, A. I. In *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic: Orlando, FL, 1984; Vol. 3, pp 213−273 and earlier reviews cited therein.

(21) Evans, D. A.; Takacs, J. M.; McGee, L. R.; Ennis, M. D.; Mathre, D. J. *Pure Appl. Chem.* **1981**, *53* (6), 1109−1127.

(22) Tietze, L. F.; Schuffenhauer, A.; Schreiner, P. R. *J. Am. Chem. Soc.* **1998**, *120*, 7952.

(23) Frederickson, M. *Tetrahedron* **1997**, *53* (2), 403.

(24) Gothelf, K. V.; Jørgensen, K. A. *Chem. Rev.* **1998**, *98*, 863.

(25) See ref 24, page 867.

(26) Baldwin, S. W.; Young, B. G.; McPhail, A. T. *Tetrahedron Lett.* **1998**, *39*, 6819.

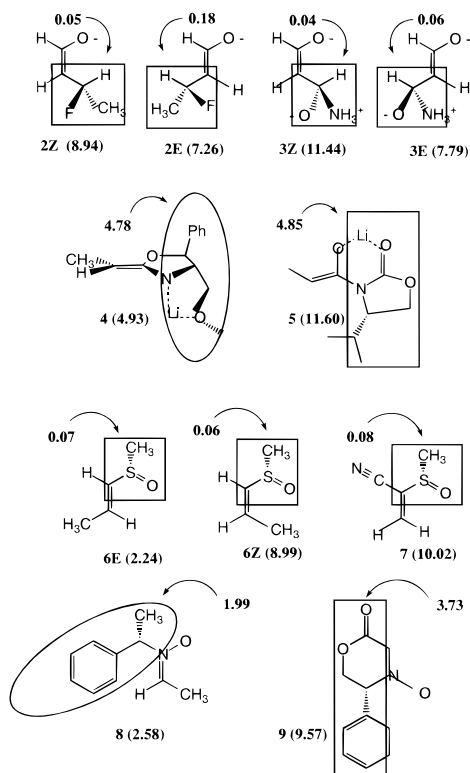(27) Kitagawa, O.; Izawa, H.; Sato, K.; Dobashi, A.; Taguchi, T. *J. Org. Chem.* **1998**, *63*, 2634.

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Figure 2. CCM values for molecules **1**−**9** and their corresponding chiral auxiliaries. The CCM of the entire molecule is given in parentheses following the molecule number. The circled or boxed atoms are the atoms used to define the chiral auxiliaries. The CCMs of those auxiliaries are given with arrows pointing to the corresponding auxiliary.

Chirality Content of Auxiliaries. One aspect of desymmetrization that we can now address involves the chirality content of the chiral auxiliaries themselves. Before we present our results, however, we point out that the CCM are not additive for various portions of the molecule. Hence one cannot compute the CCM of the π system and then of the auxiliary and add those values together; however, one can compare relative measures for the auxiliaries themselves. We have partitioned the above molecules so that the CCM of only the chiral auxiliary itself is computed. The results of these calculations are presented in Figure 2. In this figure the CCM of the entire molecule is given in parentheses next to the structure number, the auxiliary atoms used in the calculations are designated, and the CCM values of that fragment are given. Perhaps counterintuitive is the finding that the chirality content of auxiliaries of compounds **2**, **3**, **6**, and **7** is smaller than the chirality of the whole molecule. However, a closer look at the structures of the nearest achiral shapes (which the CCM is based on) reveals the reason for the very small chirality content of these auxiliaries.

Let us consider one of the examples above, say, **2E**. The CCM is a distance measure. It is the minimum distance to achirality, which here is the smallest distance of all points of a chiral object from the nearest configuration of points having an improper element of symmetry (mirror plane). For the chiral auxiliary of **2E** the C(H)(F)(C)(CH$_3$) moiety is almost perfectly staggered with the mirror plane passing through the auxiliary as shown in Figure 3.

Clearly shown here, then, is that a very small difference between a F atom on one side of the plane and a H atom on the other side is responsible for breaking the symmetry, and hence, one derives a very low CCM measure for this particular
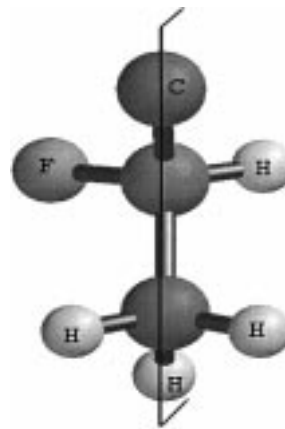

Figure 3. Chiral auxiliary of molecule **2E** contains little chirality content because in its most stable conformation there exists a pseudo-plane of symmetry where the only difference between right and left sides is a H atom versus a F atom.

auxiliary. The same can be said for the other examples where low CCM values exist but generalizations cannot be made. For example, one cannot say that planar systems having simple sp^3-hybridized auxiliaries will always have nearly achiral auxiliaries, since the example of compound **8** has a relatively high value. While some of the chiral auxiliaries themselves are nearly achiral, the picture of the whole molecule is different. In essence what one has is a stereogenic carbon atom with four very different arms attached: C−H, C−F, C−CH$_3$, and a very long C−C=C−O. Here, the nearest achiral structure is much further removed and rather large CCM values are obtained.

Summary

The purpose of this work was two-fold. First we wanted to develop a method that would allow us to extend Avnir's CCM to the three-dimensional presentation of orbitals. Furthermore, the solution to this problem opens the way for analysis of practically every continuous molecular property that is dependent on the electronic structure, thus overcoming the inherent difficulty of symmetrization of a molecule composed of different, non-interchangeable nuclei. This was done by creating isosurfaces and slicing them in a way that makes the computational procedure tractable. The slicing and reslicing provides an averaged CCM and with small errors. It is our intention to eventually use this methodology to assess the chirality content of van der Waals surfaces and isopotential electrostatic surfaces of molecules of relevance to the pharmaceutical industry to see if chirality measures can enhance existing QSARs.

The second purpose of this work was to answer the following question: How much orbital desymmetrization is induced by common chiral auxiliaries? From the examples we selected for this study, which are representative of the many chiral auxiliaries used in modern synthesis, we see that significant orbital desymmetrization is induced by these auxiliaries. Generally the chirality contents of the frontier orbitals are comparable in magnitude to the structural chirality of the molecules themselves. Moreover we find that in some instances the chiral auxiliaries themselves are nearly achiral in nature yet, when incorporated into the reacting molecule, the molecule as a whole becomes very chiral and has associated with it very chiral orbitals. Yet it should be noted that in general this trend should pass through a maximum. Thus, if to a very large achiral molecule, a small chiral moiety is added as a substituent, then this chiral perturbation will not affect greatly the achirality of the whole.

It is thus evident that the rules governing the additivity of the CCM values of fractions are not simply linear; elucidation of their nature is in progress. Finally, we point out that many factors contribute to the observed enantioselectivity. One of these factors, not considered here, involves the size of the auxiliaries themselves. At this stage of our studies, we cannot say whether it is the steric factors or the desymmetrized molecular orbitals that play a more important role in asymmetric induction. Our suspicions are that steric effects will be more important, however.

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