

**Development of Weighted Chirality Indices: Their Use in Modeling Nickel
Dithiolene Systems**

Anthony Noto

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ABSTRACT

Weighed, scaled chirality indices have been calculated for a group of chiral nickel dithiolene dyes based on an intrinsic molecular chirality tensor. To improve the accuracy of the index, each atom in a given molecule was weighted according to its atomic mass. The index was scaled to allow comparison of molecules with different atom counts. Assigning weights can reduce the effect of lighter elements on the chirality index while preserving the general trend of the index. This method permits the relationship between individual atoms and the chirality index to be better modeled. The results for chiral nickel dithiolene dyes, a relatively rigid system of molecules, show an increase in the chirality index when the chiral centers are in close proximity to one another. The most promising dyes of this class reach their maximum chirality index when their carbon spacers are three atoms long.

I. INTRODUCTION

Since Louis Pasteur's discovery of molecular chirality in 1848¹, scientists have mainly classified chiral molecules qualitatively, in terms of their absolute configuration or the direction in which they rotate the plane of polarized light. A chiral molecule is classified as being in a *sinister* (S) or *rectus* (R) configuration. It is also classified as positive or negative according to the direction that polarized light is rotated. There is no definite correlation between the two classification systems. Recently, scientists have taken an interest in representing chirality quantitatively. A quantitative measurement of chirality could be used in applications ranging from pharmacology to the prediction of optical properties.

The main application for chiral molecules is found in the pharmaceutical industry. The action of certain chiral drugs depends on the configuration. For example, one chiral form of Ritalin is pharmacologically active, while its mirror image form is not. One chiral form of thalidomide can prevent nausea, while its mirror image form can cause birth defects. The use of chiral drugs in pharmacology can also cause a decrease in the dosage, a decrease in the likelihood of side effects and an increase in the speed of production.

Until recently, scientists were unable to accurately predict with any certainty a molecule's handedness with respect to optical rotation. Accordingly, they were also unable to predict the molecular structures that gave rise to chiral properties. Generally, chiral compounds were formed through the study of existing compounds and groups based on previous literature and intuition. This method was considered to be an educated trial and error process. To then synthesize and characterize the compound was the only way one could ascertain a molecule's chirality. However, experimentation tends to be a

very time consuming and costly process. If this step can be eliminated through the use of a theoretical chirality index, the speed at which chiral compounds can be created will increase significantly. The increase in speed of molecular design can greatly benefit the pharmaceutical industry in particular. If molecular properties can be accurately predicted through the use of this index, drugs can be developed with less cost for the consumer.

For a theoretical chirality measure to be effective it must exhibit certain properties. First, the index must be invariant under rotation and translation. Also, a sign change should be observed for the two optical isomers of a chiral molecule. To make the index meaningful it must be invariant of the molecular size, in terms of the number of atoms. Finally, an ideal index could be used to predict a desirable property that is difficult to calculate empirically.

The two main methods that are currently used to compute chirality are innately different from each other in their level of development, ease of use and efficiency. The first method, explored in 1995 by Zabrodsky and Avnir,^{2,3} attempts to find the absolute distance between the two configurations of a chiral molecule if they were to be superimposed over one another. This method is well developed and has been explored thoroughly. However, due to the multiple iterations necessary to make this value meaningful, Osipov, Pickup and Dunmar in 1995 proposed a simpler method⁴.

The chirality index proposed by Osipov *et al* follows the aforementioned conditions for an effective index far better than all previous models. Recently, Solymosi *et al* improved the chirality index by introducing a scaling factor that allows comparison between molecules with different numbers of atoms.⁵ Also, their scaled chirality index has been used to find the contributions of individual atoms and atom groups to the overall

chirality of the molecule. This scaled chirality index is useful even in its abstract form; however, preliminary work has been completed by Neal *et al*⁶ that shows a promising correlation between helical twisting power and the scaled chirality index for rigid molecules. Helical twisting power is defined as one divided by the pitch length of the chiral medium, where the pitch length is the distance needed for polarized light to rotate 360° through the medium. This correlation is valid based on the research conducted by Osipov and Kuball⁷ which lays the foundation for the relationship between circular dichroism and helical twisting power. Circular dichroism is observed when optically active matter absorbs left and right hand circular polarized light differently. Correlation to helical twisting power is important because it allows for comparison to a tangible property. Helical twisting power is used in optics for selective light reflection of circularly polarized light with a defined wavelength depending on helical pitch.

This research improves upon the scaled chirality index by introducing the atomic mass of the individual atoms into the calculation to form a weighted index. The effect of using the weighted index is illustrated for a simple chiral system. This index is then applied to a relatively new set of organometallic dyes known as nickel dithiolenes. The largest index is found when the spacers, between the core group and the terminal groups, contain three carbons, thereby identifying the most promising candidate for synthesis. The results of this experiment are explained in terms of steric factors and confirmed by modeling a hypothetical biphenyl system.

II. THE WEIGHTED, SCALED CHIRALITY INDEX

The basis for the scaled chirality index is the gyration tensor \mathbf{G} . Modifying a simple model for optical activity, Osipov *et al*⁴ created the gyration tensor which is defined as

$$\mathbf{G} = \int d\mathbf{r}_1 d\mathbf{r}_2 d\mathbf{r}_3 d\mathbf{r}_4 \rho(\mathbf{r}_1) \rho(\mathbf{r}_2) \rho(\mathbf{r}_3) \rho(\mathbf{r}_4) \times \frac{[(\mathbf{r}_{12} \times \mathbf{r}_{34}) \otimes \mathbf{r}_{14}](\mathbf{r}_{12} \cdot \mathbf{r}_{23})(\mathbf{r}_{23} \cdot \mathbf{r}_{34})}{(r_{12} r_{23} r_{34})^n r_{14}^m} \quad (2.1)$$

where $\mathbf{r}_{ij} = \mathbf{r}_i - \mathbf{r}_j$, $\hat{\mathbf{r}}_{ij} = \mathbf{r}_{ij} / r_{ij}$, m and n are arbitrary integers and ρ is the density concentration. The density concentration is a sum of weighted δ functions representing the locations of the N atoms in the molecule. The unscaled chirality index G_O is given by 1/3 the trace of the gyration tensor \mathbf{G} :

$$G_O = \frac{1}{3} \int d\mathbf{r}_1 d\mathbf{r}_2 d\mathbf{r}_3 d\mathbf{r}_4 \rho(\mathbf{r}_1) \rho(\mathbf{r}_2) \rho(\mathbf{r}_3) \rho(\mathbf{r}_4) \times \frac{[(\mathbf{r}_{12} \times \mathbf{r}_{34}) \cdot \mathbf{r}_{14}](\mathbf{r}_{12} \cdot \mathbf{r}_{23})(\mathbf{r}_{23} \cdot \mathbf{r}_{34})}{(r_{12} r_{23} r_{34})^n r_{14}^m}. \quad (2.2)$$

This chirality index is invariant of translation and rotation. If $n = 2$ and $m = 1$ the index is invariant of dilation as well. With these values of n and m the index becomes dimensionless and it is in this form that the index will be used throughout this paper. Since the chirality index G_O scales as N^4 where N is the number of atoms, a scale factor is applied to enable comparison between molecules of different atom counts. The scaled chirality index $G_{OS} = (4! / N^4) G_O$ is a more useful value. Despite its apparent usefulness, G_{OS} does not determine any measurable property such as optical rotation. It is constructed to be large for a molecule with a strong helical structure and to vanish for a

molecule with any symmetry that precludes chiral behavior. The numerical expression for the scaled chirality index is⁵

$$G_{OS} = \frac{4!}{N^4} \frac{1}{3} \left[\sum_{\substack{\text{all permutations of} \\ i,j,k,l=1}}^N w_i w_j w_k w_l \times \frac{[(\mathbf{r}_{ij} \times \mathbf{r}_{kl}) \cdot \mathbf{r}_{il}](\mathbf{r}_{ij} \cdot \mathbf{r}_{jk})(\mathbf{r}_{jk} \cdot \mathbf{r}_{kl})}{(r_{ij} r_{jk} r_{kl})^n r_{il}^m} \right] \quad (3.1)$$

where w_i , w_j , w_k , w_l are values that represent the weights of the individual atoms i thru l . While Solymosi *et al*⁵ suggested using the atomic mass as the weight, the weights have been set to 1.0 in their work and in all previous research. However this may not accurately model a real world situation since all atoms do not contribute equally to the chirality of the molecule. Substituting the atomic mass into the calculation as the weight, as first suggested by Solymosi *et al*⁵ is a viable approach. The calculations presented here are the first to use atomic mass as the weight. The effects of this substitution will be discussed further in section IV.

III. METHODS

To facilitate this research, a computer program was written using Microsoft Visual C++ 5.0. This program is used to compute the chirality index and the scaled chirality index. The program takes input in the Protein Data Bank format from data generated by many available computational chemistry modeling software packages (e.g., Hyperchem, Spartan and Mopac). The data comprises the atomic symbol, atomic number, atom number (in the molecule) and the Cartesian coordinates of the atom.

The program then allows the user to choose how the atoms will be weighted: all atoms can be given a weight of one, the program can automatically set the weight to the atomic mass, or the user can input each atom's weight individually. This allows many

types of weighting systems to be explored without changing the code. Finally, the program allows the user to enter the arbitrary integer values n and m to change the dimensionality of the index.

Currently, the computational algorithm requires a runtime of $O(N^4)$ and it can, therefore, take some time for large molecules to run on a single thread. To decrease the actual runtime, a multithreaded version was written to run 16 parallel threads on a 64-processor SGI Origin 2000 UNIX computational server. The code has been optimized and executed on computers running Microsoft Windows 2000, Microsoft Windows XP and SGI IRIX 6.5.

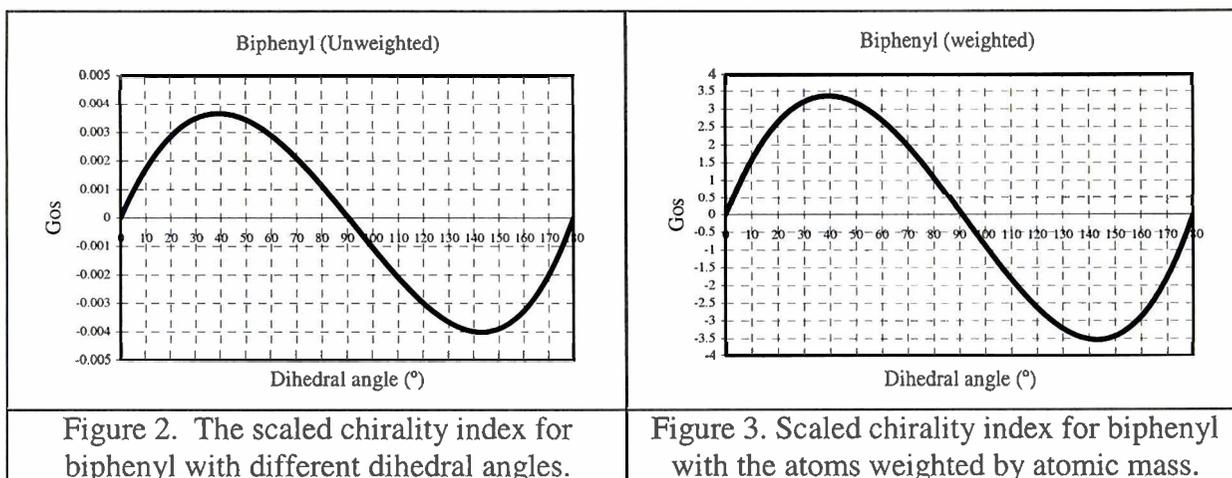
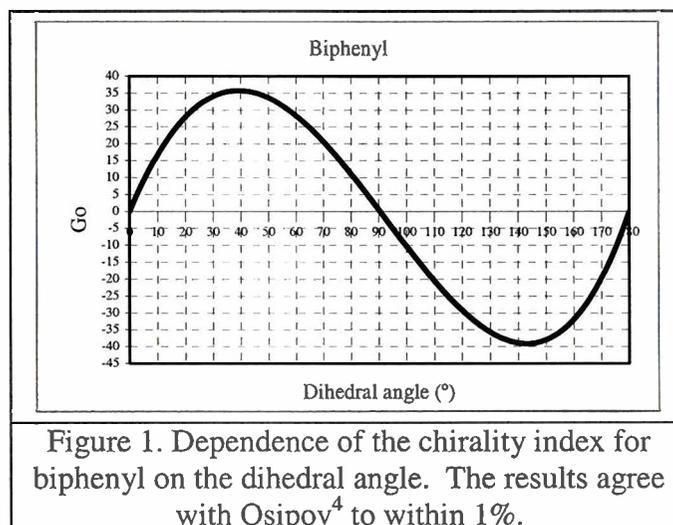
Multithreading effectively decreased the runtime to a reasonable level for average sized molecules with approximately 200 – 300 atoms. For molecules larger than 500 atoms, the algorithm is not efficient enough to finish the computation in a reasonable time of approximately one week. The algorithm will continue to be analyzed for efficiency improvements.

After the program has finished computing the indices, the results are sent to an external text file whose location is specified at the beginning of the program. The text file is formatted for easy importation into Microsoft Excel or an alternate spreadsheet program for analysis.

IV. APPLICATION TO BIPHENYL

Biphenyl was utilized previously as a test molecule for the chirality index⁴ and the scaled chirality index⁵. As in previous papers, this research used the biphenyl system with different dihedral angles between the rings as an assessment of the program's functionality and accuracy. The molecules were constructed using Hyperchem 7.1, from

Hypercube, and modeled on a Microsoft Windows 2000 Pentium 4. The molecules were then energy minimized using the MM+ force field. The MM+ force field is a basic calculation completed through Hyperchem to manipulate the molecular structure based on the interactions between atoms and bonding groups. The results are presented in Figures 1 and 2. Reassuringly, the program computed the chirality index to within two decimal places of the results attained by Osipov *et al*⁴. However, the scaled index computed by the program was approximately one third of the result attained by Solymosi *et al*⁵, although it followed the same general trend. Applying the scale factor to Osipov's chirality index should result in the scaled chirality index of Solymosi *et al*⁵.

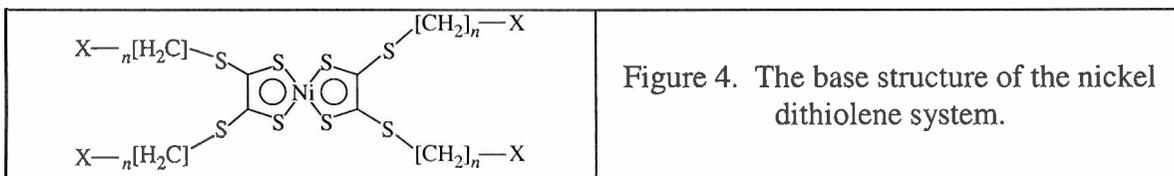


After the program was thoroughly tested using previous results, the individual atoms of the biphenyl series were weighted according to the atomic mass. The results are shown in Figure 3. The differences in trend between the weighted and un-weighted system were negligible. The y-scales were different due to the substitution of the atomic mass for the weight in the calculation. However, the trend was preserved and therefore can theoretically still be used in applications such as correlation to helical twisting power as explored by Neal *et al.*⁶

The true benefit of introducing the weights is in the overall model flexibility. This flexibility may potentially lead to a chiral index that correlates well with experimental data of helical twisting power or another desirable molecular property.

V. APPLICATION TO THE NICKEL DITHIOLENE SYSTEM

The nickel dithiolenes are a relatively new group of organometallic dyes that absorb light in the near infrared region. These molecules are based on a rigid dithiolenes core centered on a nickel atom (see Fig. 4).



From the core extend four flexible carbon spacers indicated as $[CH_2]_n$. The spacers can contain $n = 0, 3, 6,$ or 9 carbons. Either a chiral or a non-chiral terminal (x) group can be attached to each of the spacers (see Fig. 4). Each x -group can contain 1 to 3 chiral centers for a total of 4 to 12 chiral centers in each molecule. A chiral center is defined as an atom in a molecule that is bonded to four different chemical species, thus

creating an optical isomer. Optical isomers can rotate the plane of polarized light in either direction depending on the configuration of the molecule. The x-groups and the nomenclature used throughout this research are shown in Figure 5.

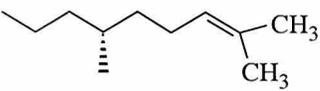
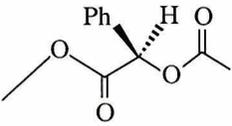
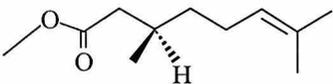
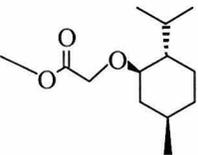
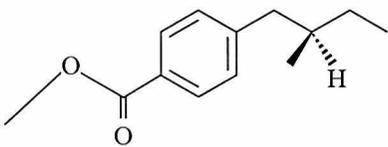
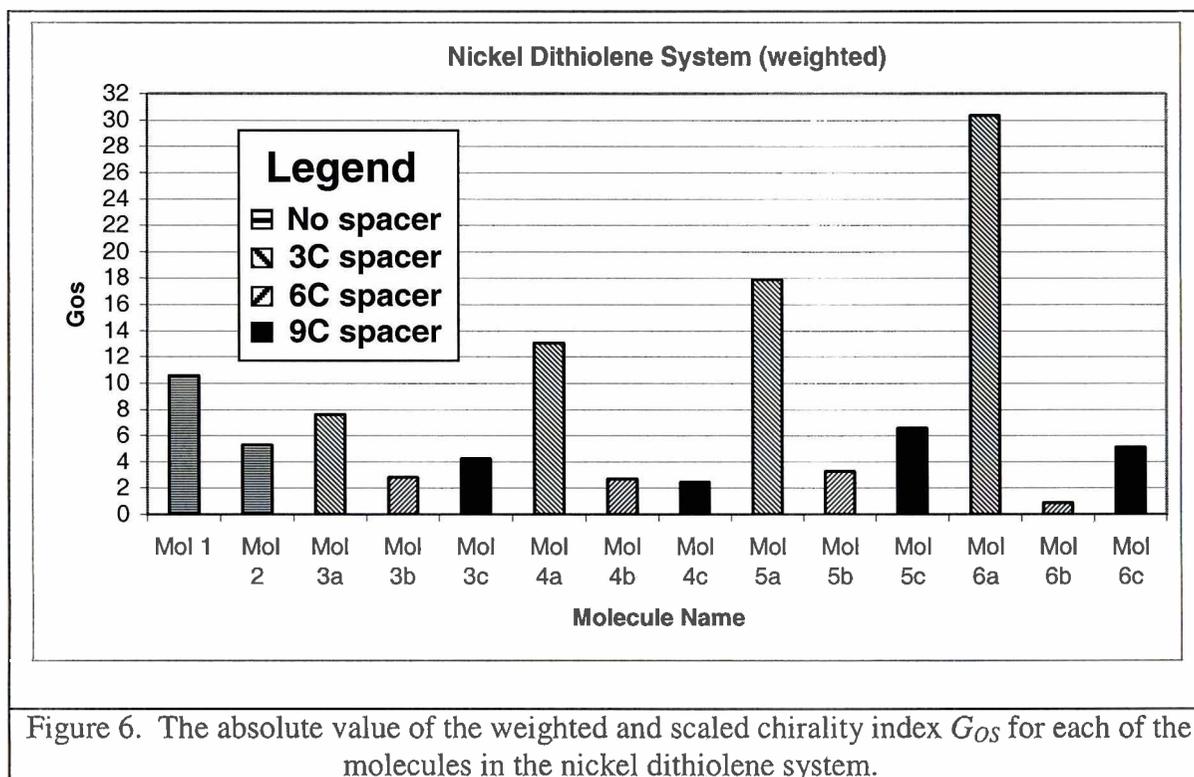
Nomenclature		X-group	Spacer (<i>n</i>)	Weighted and Scaled Chiral Index
Mol 1			0	10.56
Mol 2			0	5.28
Mol 3	a		3	7.60
	b		6	2.81
	c		9	4.24
Mol 4	a		3	13.08
	b		6	2.72
	c		9	2.48
Mol 5	a		3	17.90
	b		6	3.26
	c		9	6.56
Mol 6	a		3	30.35
	b		6	0.87
	c		9	5.13

Figure 5. The chiral X-groups and the nomenclature for the nickel dithiolene system. The largest values of the weighted and scaled chirality indices are found for molecules with spacers containing $n = 3$ carbon atoms.

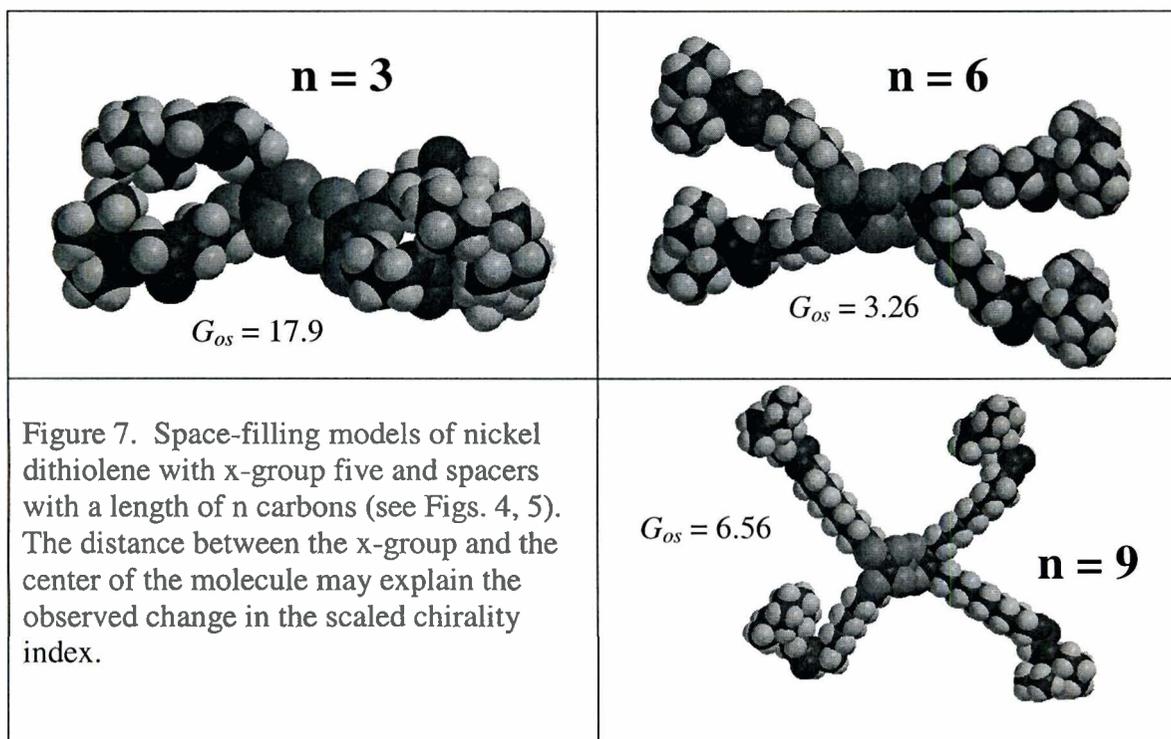
Weighted and scaled chirality indices were calculated for each of the compounds shown in Figure 5. Interesting trends were observed in the chirality index of the molecules.

Figure 6 shows the absolute value of the chirality index for each of the molecules in the nickel dithiolene system. The overall trend shows that with each of the molecules that have a flexible spacer, the chirality index is the greatest when the spacer has three carbons. The scaled chirality index is lowest when there are six carbons in the spacer and increases slightly as the spacer grows to nine carbons.



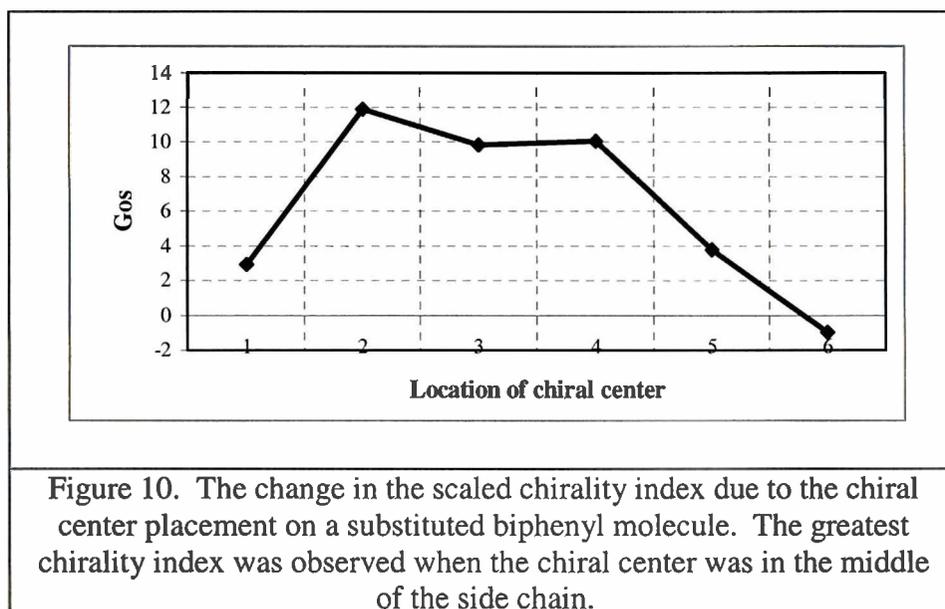
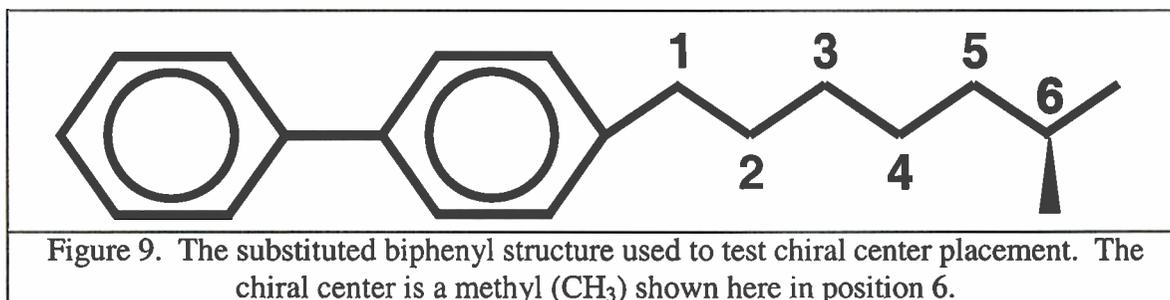
One possible explanation for this pattern is the interactions between the atoms in a molecule. These interactions are known as steric factors and may have a large effect on the chirality index. When the chiral centers of the x-groups are in close proximity to the core, a large stress occurs and thus the chirality increases. When the spacer has six

carbons, the x-groups are at the maximum possible distance from one another in the energy-minimized form. Consequently, the stress on the rings is lessened and the chirality index is smaller. When the flexible spacer has nine carbons, the x-groups begin to wrap back towards the core causing the distance between the groups to shrink and the stress to increase. This is one possible explanation for the observed increase in the chirality index. Figure 7 shows the molecules with x-group five as an example of this occurrence. These space-filling models were exported from the molecular modeling package Spartan 2002, from Wavefunction, and the index was calculated on a SGI Origin 2000 UNIX server with the IRIX 6.5 operating system. They were minimized using the MM2 force field, a version of the MM+ force field discussed earlier.



VI. EFFECT OF MOVING THE CHIRAL CENTER

To test the hypothesis that the scaled chirality index for the nickel dithiolene system depends strongly on the length of the carbon spacers, a modified biphenyl structure was created with a seven-carbon chain attached to one side of the rings (see Fig. 9). To negate the effect of the biphenyl itself, the bond between the rings was frozen at a 0° dihedral angle during energy minimization. A chiral center consisting of a methyl (CH_3) group was moved down the chiral chain from position 6 to position 1, as shown in Figure 9. The graph depicted in Figure 10 shows the result of this movement: the scaled chirality index is the largest when the methyl group is in positions 2 through 4.



One possible explanation for this result is the stresses exerted on the biphenyl rings. When the chiral center was close to the ring structure, little stress occurred because the torque on the rings was not large. One can think of this effect in terms of a lever. If the fulcrum of the lever is close to where the force is applied, it is much harder to do work. In the same way, when the chiral center is close to the rings, a lower chirality index is observed because the force of the chain is less. Likewise, as the chiral center is moved out from the inner rings, a greater chirality index is observed. However, if the chiral center becomes too far away, as observed in the nickel dithiolenes when the spacer had six carbons, the chirality index begins to decrease.

VI. CONCLUSION

A program was written to provide a usable engine to calculate the chirality index for a variety of molecules based on Osipov's initial equations.⁴ This program produced the same results as Osipov *et al*⁴ for a test biphenyl system and scaled these results based on the scale developed by Solymosi *et al*⁵. Functionality was added to allow the weighting of the molecules before calculation. The program was then used to calculate the weighted chirality index for the nickel dithiolene system of molecules. The greatest chirality index was found when the spacers contained three carbons. This result may be explained by the steric factors present in the molecule caused by the location of the chiral centers. This explanation was then confirmed using a substituted biphenyl system.

The weighting system for the chirality index was used to increase the chance of finding a good correlation with, as yet unmeasured, physical properties. As helical twisting power data becomes available for the nickel dithiolene system, a correlation between the weighted scaled chirality index and helical twisting power will be attempted.

Also, to test the weighted calculation of the scaled chirality index, correlations to molecules with known helical twisting power will be made. If substantiated through experimental measurements, this weighted algorithm could be applied to other systems of molecules and enhance the methods of chemical development for industries such as pharmaceuticals and optics.

VII. ACKNOWLEDGEMENTS

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