Information Theoretical Study of Chirality: Enantiomers with One and Two Asymmetric Centra

Sara Janssens,[†] Alex Borgoo,[†] Christian Van Alsenoy,[‡] and Paul Geerlings*,[†]

Free University of Brussels (VUB), Faculteit Wetenschappen, Eenheid Algemene Chemie (ALGC), Pleinlaan 2, B-1050 Brussels, Belgium, and University of Antwerp (UA), Department of Chemistry, Universiteitsplein 1, B-2610 Antwerp, Belgium

Received: December 19, 2007; Revised Manuscript Received: August 13, 2008

In this work, the Kullback–Leibler information deficiency is probed as a chirality measure. It is argued that the information deficiency, calculated using the shape functions of the *R* and *S* enantiomers, considering one as reference for the other, gives an information theory based expression useful for quantifying chirality. The measure is evaluated for five chiral halomethanes possessing one asymmetric carbon atom with hydrogen, fluorine, chlorine, bromine, and iodine as substituents. To demonstrate the general applicability, a study of two halogen-substituted ethanes possessing two asymmetric carbon atoms has been included as well. The basic expression of the sum of the local information deficiency over all atoms can be decomposed into separate summations over coinciding and noncoinciding atoms, or into a global and a mixing entropy term, or into a local entropy contribution for each atom individually based on the Hirshfeld partitioning. Avnir's continuous chirality measure (CCM) has been computed and confronted with the information deficiency. Finally, the relationship between chirality and optical rotation is used to study the proposed measure. The results illustrate Mezey's holographic electron density theorem with an intuitively appealing division of the strength of propagation of the atomic chirality from an asymmetric carbon atom throughout the molecule. The local information deficiency of the carbon atom is proposed as a measure of chirality; more precisely, the difference in information between the *R* and the *S* enantiomer turns out to be a quantitative measure of the chirality of the system. It may be evaluated as the arithmetic mean of the different alignments, or considering only the alignment resulting in the highest similarity value, or using the QSSA alignment.

1. Introduction

In the past decade, the discrete black or white character of chirality has been replaced by a continuously varying property, as advocated – among others – by Avnir et al.[1,2] and Petitjean et al.[3] (For a recent extensive account on chirality and symmetry measures, see the 2003 review published by Petitjean.[4]) This implies that a molecule can be more or less chiral compared to another one. In previous work, we assumed that the degree of chirality is linked to the (dis)similarity of the two enantiomers. A question rising then is how to quantify the molecular similarity. In recent years Carbó[5] and Hodgkin and Richards,[6] among others,[7] presented quantum molecular similarity indices (QSI) based on the electron density – both indices becoming equivalent in the case of enantiomers, providing information about the similarity of shape and extent of the electron distribution of the systems considered. Because of the fundamental role of the electron density in the QSI, there is an important link with density functional theory (DFT)[8] in general and conceptual DFT[9−12] in particular.

Earlier, our research group was concerned with a similarity analysis applied to enantiomers of the halomethane CHFClBr,[13] halogen substituted ethanes,[14] and 1,3-disubstituted allenes[15] representing prototypical chiral systems with respectively one or two asymmetric centra or a chiral axis. Global and local Carbó similarity indices[5] have been evaluated, and a correlation with the optical rotation has been investigated. The asymmetric carbon atom turned out not to possess the highest dissimilarity value, which is counterintuitive because the carbon atom is the only chiral atom in the molecule. Moreover, the similarity index is dominated by the large contribution of the electron density near the nuclei, rather than by chemically more relevant valence regions. These indices have also been used in combination with other reactivity descriptors as for instance the Fukui function $f(\mathbf{r})$ or the local softness.[16−18]

The next step in our chirality measure exploration based on the electron density would be to opt for a different separation operator, for example putting more weight on the valence electrons. A more natural approach was however followed to extract chirality information directly from the density, by introducing concepts from information theory,[19] which recently gained widespread interest in the quantum chemical community.[20]

Gadre et al.[21,22] for example examined a maximum-entropy procedure for several atomic systems by applying information theory techniques for the refinement of Gaussian basis sets. Nagy and Parr[23] argued that information deficiency gives a measure for the quality of an approximate electron wave function. The important work by Nalewajski and Parr[24] should also be mentioned. The authors pointed out that the Kullback–Leibler information deficiency promotes Hirshfeld's stockholder procedure[25] as a natural way to generate atomic charges. The work of Borgoo et al.[26,27] on the information deficiency of atoms

---

* To whom correspondence should be addresssed: Tel:+32 2 6293314. Fax: +32 2 6293317. E-mail: pgeerlin@vub.ac.be (P.G.), sajansse@vub.ac.be (S.J.).

[†] Free University of Brussels (VUB).

[‡] University of Antwerp (UA).

10.1021/jp711895t CCC: $40.75

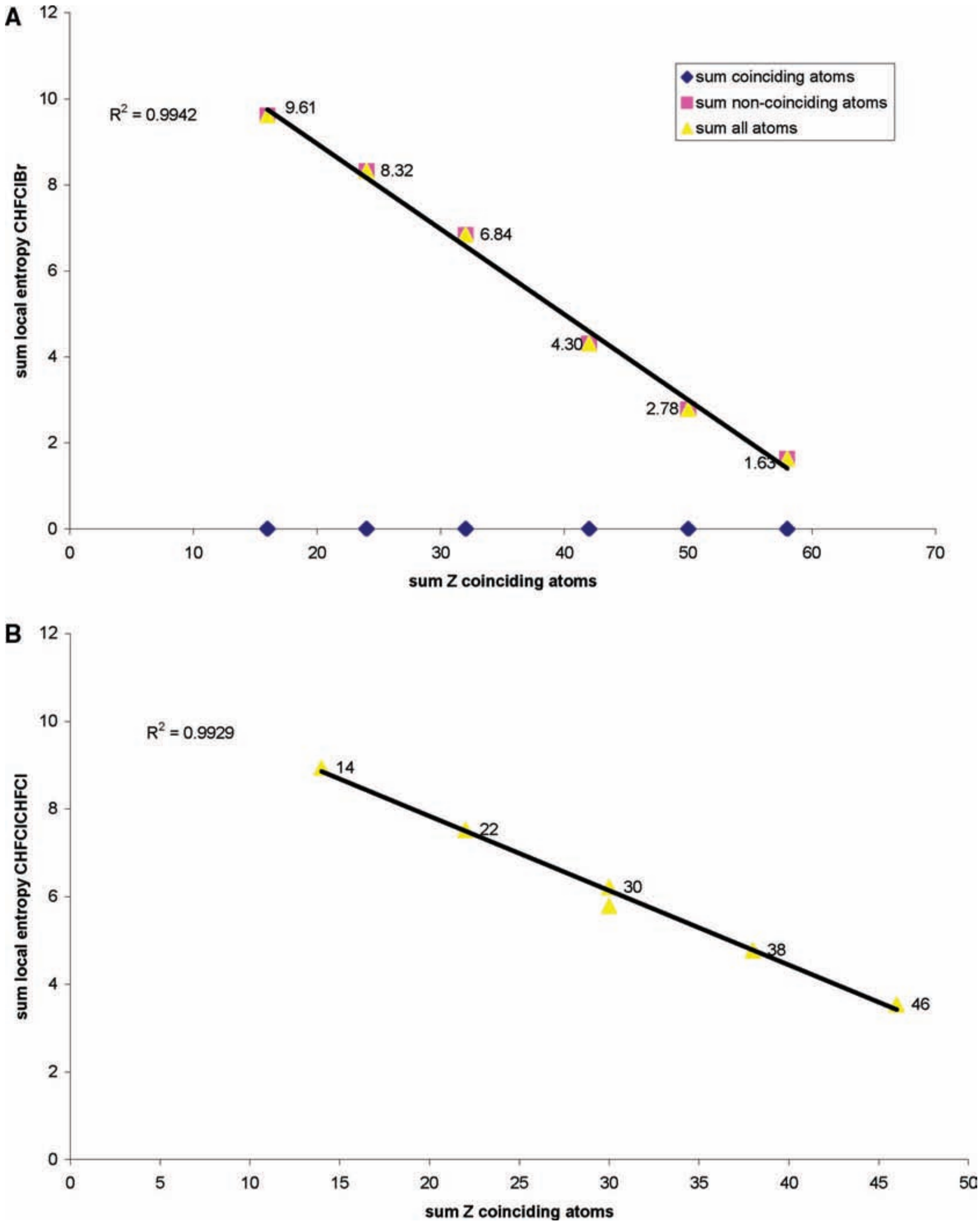

Figure 1. Sum of the local information deficiency over all atoms, over the coinciding atoms and over the noncoinciding atoms for the enantiomers of the halomethane CHFClBr, as a function of the six different alignments represented by the sum of the nuclear charges of their coinciding atoms. Sum of the local information deficiency over all atoms for the *RR*/*SS* enantiomers of the substituted ethane CHFCl−CHFCl, as a function of the nine different alignments represented by the sum of the nuclear charges of their coinciding atoms.

shows that an information theory based approach is markedly superior to quantum similarity calculations in revealing patterns of periodicity. When replacing density functions by shape functions $\sigma(\mathbf{r})$, that is the density per particle $\rho(\mathbf{r})/N$, the results even improved, confirming the fundamental role of the shape function as an information carrier.[28−31]

In the present work, we investigate if an information theory based concept can be employed as a quantum chirality measure. This property will be evaluated globally as well as locally for chiral halomethanes with hydrogen, fluorine, chlorine, bromine, and iodine as substituents, providing five different enantiomer pairs. As a glance on the generalization of this methodology, two halogen substituted ethanes will be investigated as well, comparable with our earlier work.[14] Because of the dependence of the information deficiency on the relative orientation of the molecules, different alignments will be considered. Another chirality measure, the continuous chirality measure (CCM) developed by Avnir et al.,[1] will also be calculated for comparison.

2. Theoretical and Computational Details

2.1. Information Theory. Information theory[19] has recently gained widespread interest in quantum chemical research, as already mentioned in the introduction. The mathematical description of entropy is connected with missing information

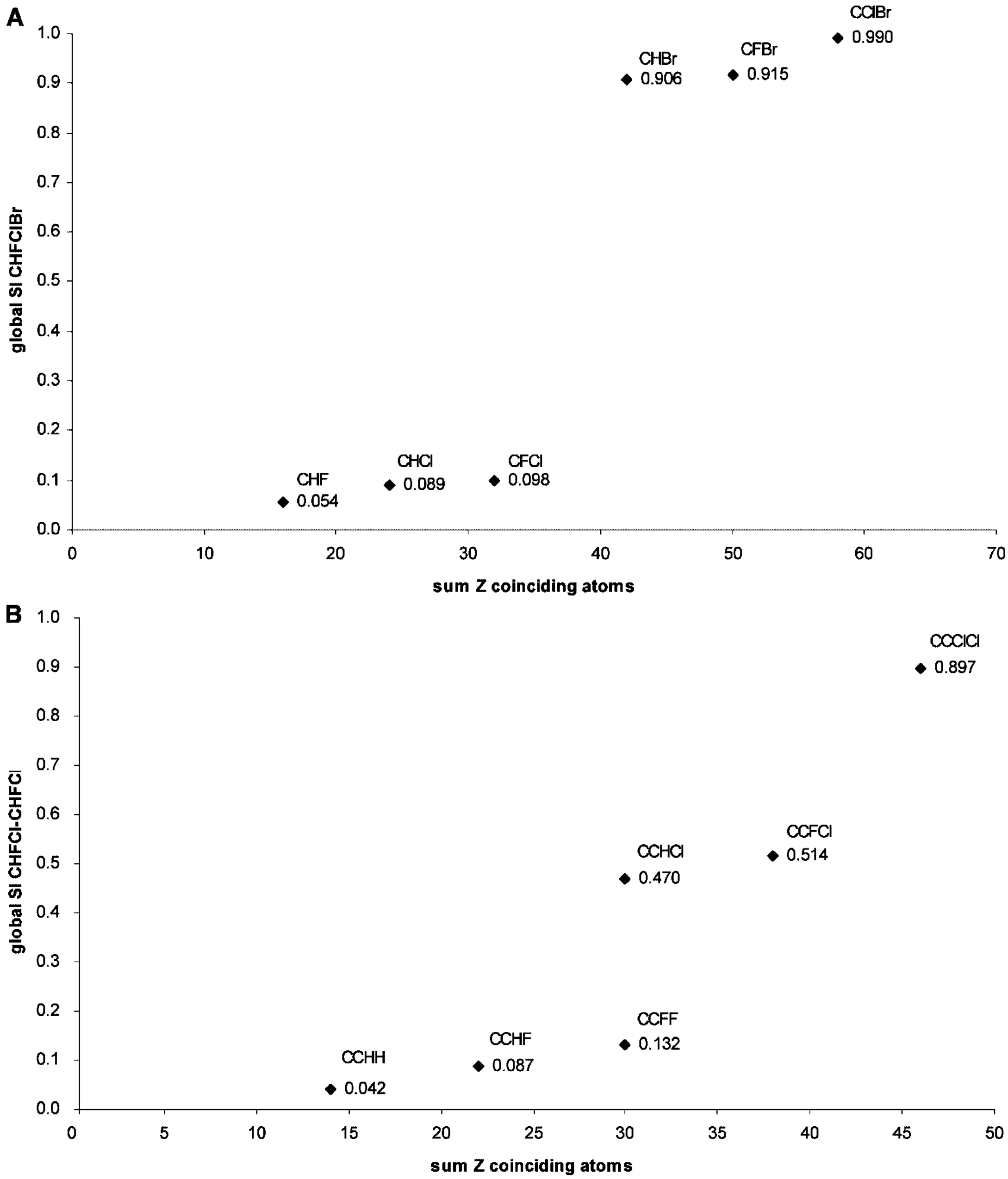

Figure 2. Carbó's global quantum similarity values using the total density for the enantiomers of the halomethane CHFClBr, as a function of the six different alignments represented by the sum of the nuclear charges of their coinciding atoms. Carbós global quantum similarity values using the total density for the *RR*/*SS* enantiomers of the substituted ethane CHFCl−CHFCl, as function of the nine different alignments represented by the sum of the nuclear charges of their coinciding atoms.

or uncertainty, measured through a quantity known as the Shannon entropy[32] defined as,

$$S = -k\sum_i p_i \ln p_i \tag{1}$$

where the sum runs over all events *i* with associated probability p_i, and *k* an arbitrary real constant. Naturally $p_i \geq 0$ and $\Sigma_i p_i = 1$. The Shannon entropy is maximal for a uniform distribution, corresponding to spreading the probability distribution as evenly as possible.

For a continuous probability distribution, one defines the entropy as,

$$S = -\int p(x) \ln p(x) \mathrm{d}x \tag{2}$$

where *S* is a functional of the probability density function *p*. A generalization of the Shannon entropy, by introducing a reference probability density p_0, makes it invariant under coordinate transformations. This measure is termed the Kullback−Leibler entropy.[19,33] Without the negative sign eq 3 is obtained.

$$\Delta S[p/p_0] = \int p(x) \ln \frac{p(x)}{p_0(x)} \mathrm{d}x \tag{3}$$

This quantity is often referred to as information deficiency, entropy deficiency, missing information, or information entropy. It expresses the information discrimination or the information distance between the two distributions *p* and p_0. Notice that ΔS equals zero when $p(x) = p_0(x)$; when $p(x)$ and p_0(x) are equally normalized one can prove that $\Delta S \geq 0$ by employing the inequality $\ln(^1/_x)(1 - x)$ (for positive values of *x*).[38]

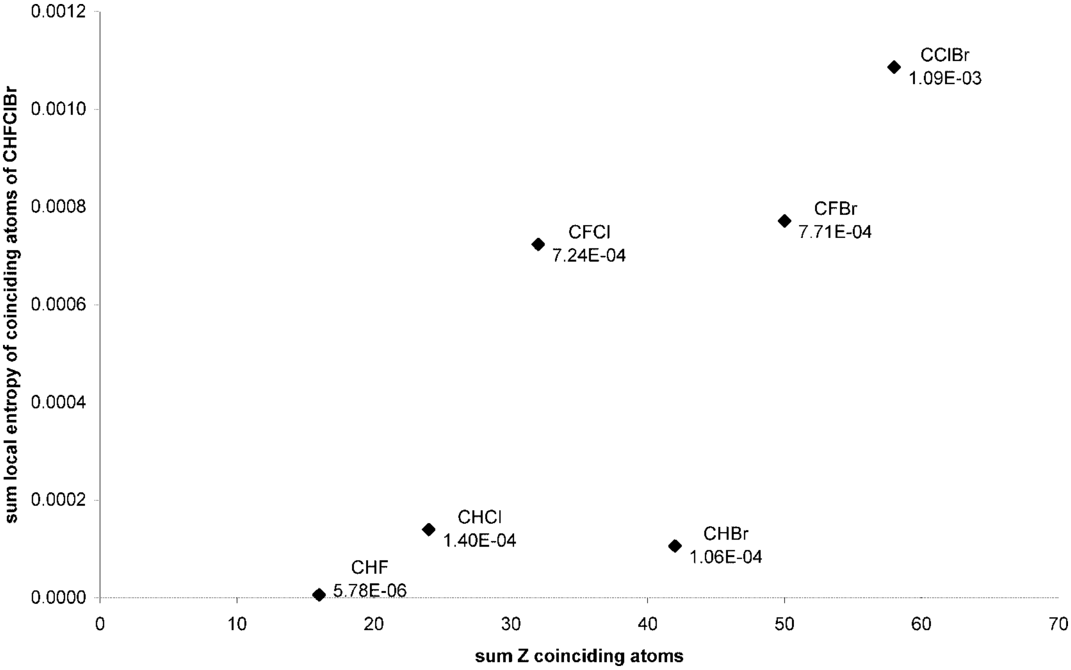

Figure 3. Sum of the local information deficiency over the coinciding atoms as function of the six different alignments, represented by the sum of the nuclear charges of their coinciding atoms, for the CHFClBr halomethane.

On the basis of these considerations, we propose the following expression as a quantification of the similarity of two systems with electron distributions $\rho_1(\mathbf{r})$ and $\rho_2(\mathbf{r})$

$$\Delta S[\rho_1/\rho_2] = \int \rho_1(\mathbf{r}) \ln \frac{\rho_1(\mathbf{r})}{\rho_2(\mathbf{r})} d\mathbf{r} \tag{4}$$

This property can be read as the difference in information between $\rho_1(\mathbf{r})$ and $\rho_2(\mathbf{r})$, not necessarily equally normalized. To get around the normalization issue, we turn to the shape function $\sigma(\mathbf{r})$ defined as the density per particle,[34]

$$\sigma(\mathbf{r}) = \rho(\mathbf{r})/N \tag{5}$$

an entity recently gaining more and more attention in quantum chemical literature.[29,30,30,35] Ayers illustrated, in an extension of the Hohenberg and Kohn theorems to the shape function,[29] that this property is equivalent to the electron density $\rho(\mathbf{r})$ as a carrier of information. The following expression

$$\Delta S[\sigma_1/\sigma_2] = \int \sigma_1(\mathbf{r}) \ln \frac{\sigma_1(\mathbf{r})}{\sigma_2(\mathbf{r})} d\mathbf{r} \tag{6}$$

can thus be expected to contain equivalent information as eq 4.

This form has previously been used for an investigation of atomic density functions,[26,27] and it will be applied in this work for the comparison of molecules for the first time. Two enantiomers *R* and *S* of a chiral molecule yield following information deficiency,

$$\Delta S[\sigma_R/\sigma_S] = \int \sigma_R(\mathbf{r}) \ln \frac{\sigma_R(\mathbf{r})}{\sigma_S(\mathbf{r})} d\mathbf{r} \tag{7}$$

which can be interpreted as a measure for the information distance between *R* and *S* or the information in *R* distinguishing it from *S*.

TABLE 1: Avnir's Continuous Chirality Measure *S* for All Five Halomethanes, Compared with the Sum of the Nuclear Charges of All Atoms

halomethane	sum *Z*	*S*(chiral)
CHFClBr	68	19.4694
CHFClI	86	18.1931
CHFBrI	104	17.3951
CHClBrI	112	18.1562
CFClBrI	120	22.8212

TABLE 2: Theoretically Calculated Values of the Optical Rotation α (Absolute Value) for All Five Halomethanes, Compared with the Sum of the Nuclear Charges of All Atoms

halomethane	sum *Z*	|α|
CHFClBr	68	4.19
CHFClI	86	9.45
CHFBrI	104	7.55
CHClBrI	112	0.6
CFClBrI	120	1.11

As a consequence of Mezey's holographic electron density theorem,[36] molecular regions (for example atomic regions of both asymmetric and nonasymmetric centra in chiral molecules) contain the information about the whole system. Thus, it is of interest to develop a local entropy measure. Similar to the technique used in previous work,[14,15] we concentrate on atomic regions using the Hirshfeld partitioning,[25] which partitions the total electron density $\rho(\mathbf{r})$ of a molecule into atomic contributions $\rho_A(\mathbf{r})$. In this manner, we may write the local entropy as

$$\Delta S[\sigma_{A,R}/\sigma_{A,S}] = \int w_{A,R}\sigma_R(\mathbf{r}) \ln \frac{w_{A,R}\sigma_R(\mathbf{r})}{w_{A,S}\sigma_S(\mathbf{r})} d\mathbf{r} \tag{8}$$

with

$$w_{A,R}(\mathbf{r}) = \frac{\rho^0_{A,R}(\mathbf{r})}{\sum_X \rho^0_{X,R}(\mathbf{r})} \tag{9}$$

and $\rho_{A,R}{}^0(\mathbf{r})$ the electron density of the isolated atom *A*. $\Sigma\rho_{X,R}{}^0(\mathbf{r})$ is known as the promolecular density, built by the superposition of the densities of the isolated atoms placed on the same positions as in the molecule itself. The weight factor for the *S*

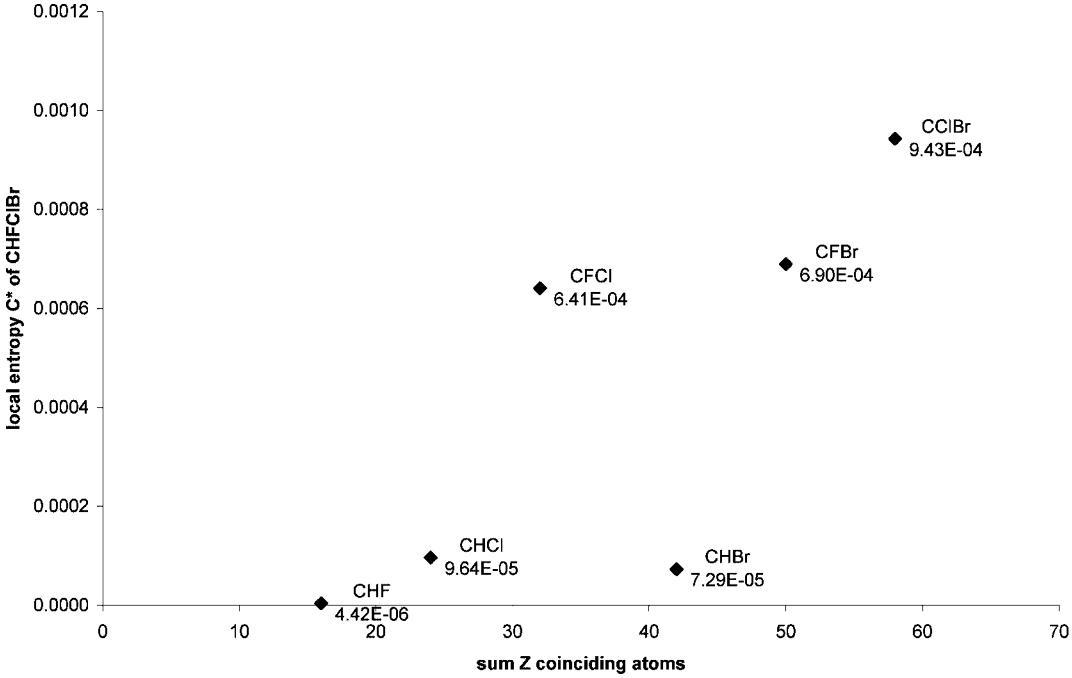

Figure 4. Local information deficiency for the asymmetric carbon atom C* of the CHFClBr halomethane as a function of the six different alignments, represented by the sum of the nuclear charges of their coinciding atoms.

enantiomer can be written analogously. The sum of all weight coefficients $w_{A,R}(\mathbf{r})$ and $w_{A,S}(\mathbf{r})$ is normalized to one.

Note that, as it should be, the information deficiency of the S enantiomer over the R enantiomer $\Delta S[\sigma_S/\sigma_R]$ provides the same results as $\Delta R[\sigma_S/\sigma_R]$ whenever the alignment is such that the geometrical arrangement of the aligned enantiomers contains a mirror plane. Successive symmetry and mirror operations can change one form into the other.

When adding the local entropies of all atoms A, we regain the global entropy augmented by a mixing term as shown below:

$$\begin{aligned}&\sum_A \int w_{A,R}\sigma_R(\mathbf{r})\ln\frac{w_{A,R}\sigma_R(\mathbf{r})}{w_{A,S}\sigma_S(\mathbf{r})}d\mathbf{r}\\ &=\sum_A\int w_{A,R}\sigma_R(\mathbf{r})\ln\frac{\sigma_R(\mathbf{r})}{\sigma_S(\mathbf{r})}d\mathbf{r}+\sum_A\int w_{A,R}\sigma_R(\mathbf{r})\ln\frac{w_{A,R}}{w_{A,S}}d\mathbf{r}\\ &=\int\sigma_R(\mathbf{r})\ln\frac{\sigma_R(\mathbf{r})}{\sigma_S(\mathbf{r})}d\mathbf{r}+\int\sigma_R(\mathbf{r})\sum_A\left(w_{A,R}\ln\frac{w_{A,R}}{w_{A,S}}\right)d\mathbf{r}\end{aligned} \qquad (10)$$

The second term in eq **10**, the entropy of mixing, is directly analogous in form and interpretation to the concept of mixing in classical thermodynamics.

For atoms in molecules, a similar entropy of mixing contribution has been identified by Parr, Ayers, and Nalewajski.[37,38]

The information theory results will be compared to earlier published results on the Carbó QSI,[13,14] defined as

$$R_{RS}=\frac{\int\rho_R(\mathbf{r})\rho_S(\mathbf{r})d\mathbf{r}}{[(\int\rho_R^2(\mathbf{r})d\mathbf{r})(\int\rho_S^2(\mathbf{r})d\mathbf{r})]^{1/2}}=\frac{Z_{RS}}{[Z_{RR}Z_{SS}]^{1/2}} \qquad (11)$$

and to results calculated using Avnir's CCM.[1] Note that for the QSI we limit ourselves to Carbò's definition involving the overlap measure. Previous studies have proven that measures involving other separation operators are computationally much more intensive.[18,39]

In that context, the chirality content of a given set of points $\{P_i\}_{i=1}{}^n$ is determined from its distance to the nearest configuration of points $\{P_i\hat{}\}_{i=1}{}^n$, which has an improper element of symmetry. The distance between the two sets of points is defined by

$$\mathbf{S}'(G_{\mathrm{achiral}})=\frac{1}{n}\sum_{i=1}^{n}||P_i-\hat{P}_i||^2 \qquad (12)$$

When applied to molecules the set of points $\{P_i\}_{i=1}{}^n$ can be taken as the position of the different atoms in space.

The $\mathbf{S}'(G_{\mathrm{achiral}})$ thus obtained is the minimal chirality measure of the given configuration and lies due to scaling[1] on a continuous scale of $0 \le \mathbf{S}' \le 1$ or $0 \le \mathbf{S} \le 100$ with $\mathbf{S} = 100\mathbf{S}'$.

2.2. Alignment of the Enantiomers. An important complication of the molecular information deficiency is the dependence on the relative orientation of the molecules. Several approaches have been proposed to resolve this problem. Some examples of alignment possibilities are alignments according to common physicochemical features, or topological and geometrical features (TGSA[40]), or aligning the molecules so that the resulting molecular similarity is maximized (QSSA[41−45]).

The main method applied in this article is the so-called backbone (BB) alignment, already proven in previous papers to be an efficient alignment method. This choice enables us − as opposed to TGSA and QSSA − to evaluate not only global entropy, but also local entropy measures, for the asymmetric carbon atoms as well as for the nonasymmetric substituents. This local approach allows us to investigate the holographic electron density theorem in a quantitative way. In the case of our halomethanes, we superimpose the asymmetric carbon atom and two of its substituents, yielding six different alignments for each enantiomer couple. In the case of the substituted ethanes, both BB asymmetric carbon atoms are superimposed and on each of these carbon atoms one directly bonded hydrogen or halogen atom of both enantiomers under consideration, yielding three different alignments for each enantiomer couple.

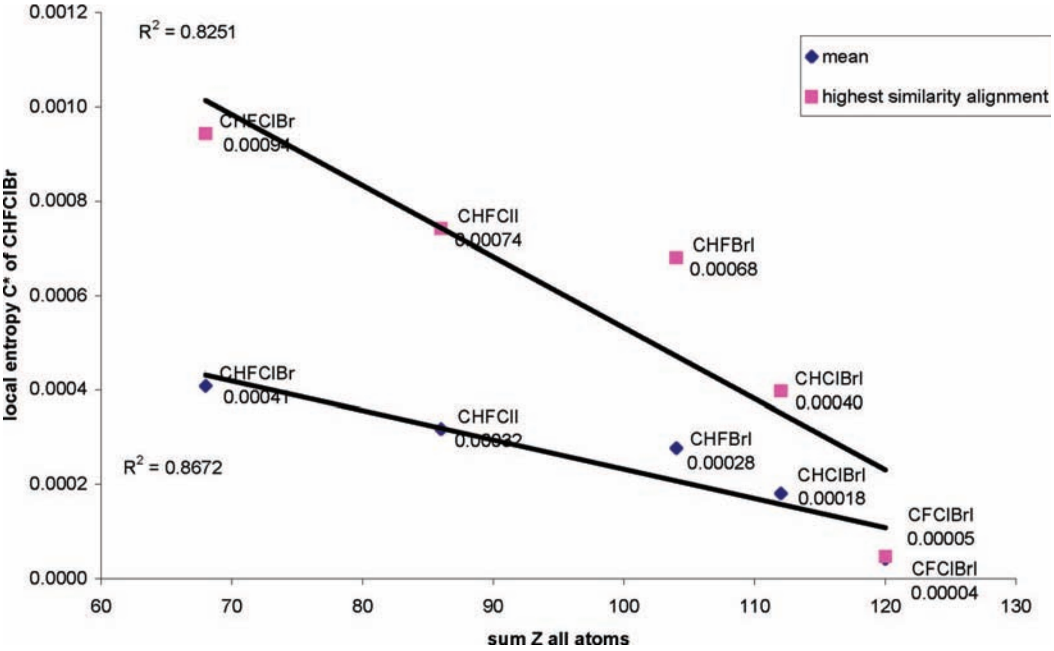

Figure 5. Local information deficiency for the asymmetric carbon atom C*, considering the mean value over all alignments as well as the highest similarity alignments, for the five different halomethanes.

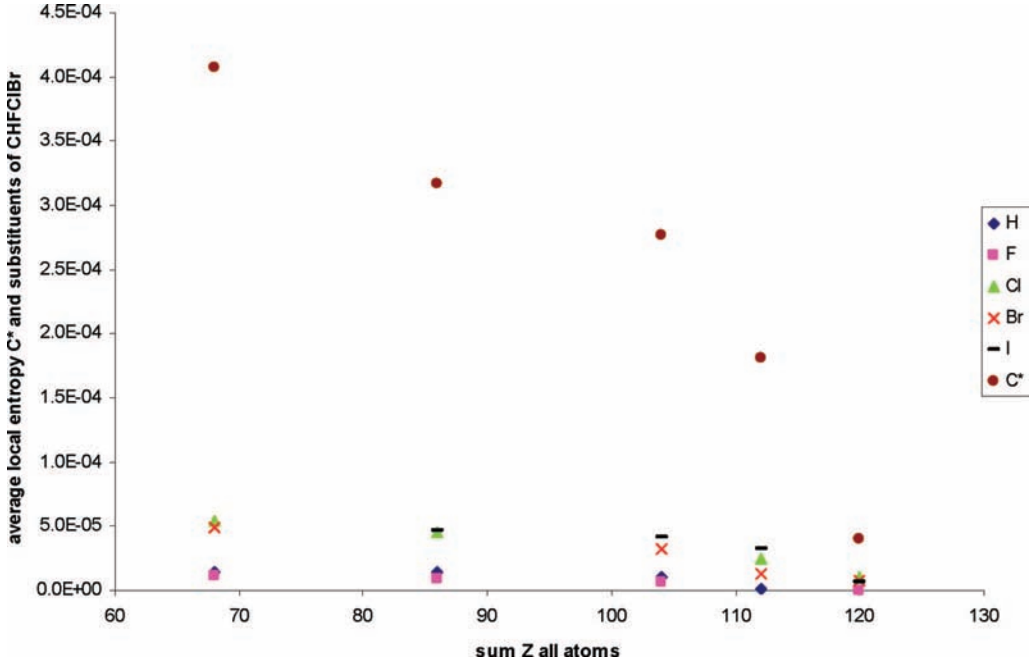

Figure 6. Local information deficiency for all atoms averaged over the alignments in which the considered atoms are coinciding, for the five different halomethanes.

Complementary to this BB alignment, also the QSSA alignment has been evaluated, eliminating the dependence on the relative orientation of both enantiomers.

This alignment problem does not occur when using CCM, generating only one value for each enantiomer couple.

2.3. Optical Rotation. Supposing that the optical rotation, as quantified by the specific rotation $[\alpha]_d$, is an experimentally accessible quantity for the degree of chirality of a molecule and assuming that the dissimilarity between enantiomers describes their chirality, one may try to find a link between the dissimilarity and the optical rotation of enantiomers, as was previously shown by Mezey et al.[46] Note however that previous work[14,47] has shown that prudence needs to be taken when stating a positive correlation between the global similarity and the optical rotation.

The specific rotation $[\alpha]$[48] of a chiral molecule, with molecular weight M, in dilute solution measured at frequency υ is given by,

$$[\alpha]_\upsilon = \frac{28\,800\pi^2 N_{A\upsilon}\upsilon^2}{c^2 M}\gamma_S\beta(\upsilon) \tag{13}$$

where $\beta = {}^1/_2\mathrm{Tr}[\beta_{\alpha\beta}]$, with $\beta_{\alpha\beta}$ the electric dipole−magnetic dipole polarizability tensor; γ_s is the condensed phase solvent effect. The choice for the frequency υ in this work is the traditional one corresponding to the so-called D-line of Sodium.

2.4. Computational Details. All geometry optimizations, electron densities, and optical rotations used in this work were calculated in a DFT approach using the *Gaussian 03* program[49]

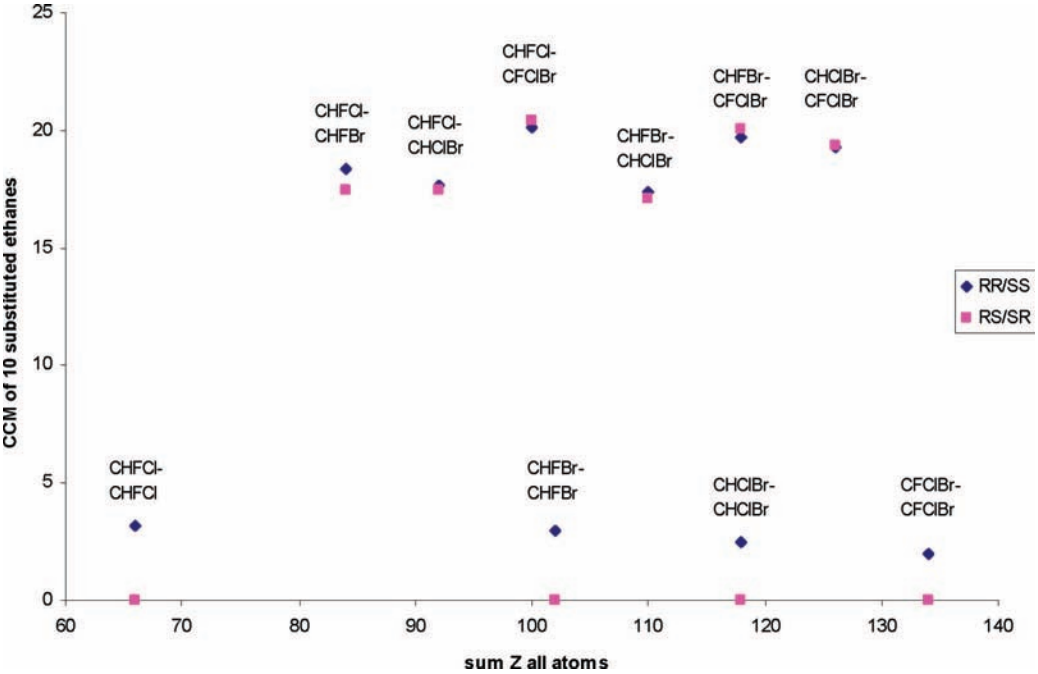

Figure 7. Avnir's continuous chirality measure *S* for the *RR*/*SS* and the *RS*/*SR* enantiomers of ten substituted ethanes CXYZ−CX′YZ′, compared with the sum of the nuclear charges of all atoms.

at the B3LYP/6−311G* level.[50,51] We implemented the necessary integrals of the global and local information deficiency in the *BRABO* program package developed by Van Alsenoy et al.,[52,53] a program already containing the implementation of global and local Carbó similarity indices. The local entropy based on the Hirshfeld partitioning is implemented numerically in the program *STOCK*, part of this *BRABO* package.[52,53]

For the substituted ethanes, geometry optimizations were performed with all three dihedral angles fixed at 180°. We opted to concentrate on the three possible staggered conformations of a given enantiomer, being the lowest energy conformers, and comparing these with the corresponding conformers of its mirror image.

Optical rotations have been calculated using ab initio density functional theory with gauge-invariant atomic orbitals (GIAOs).

The CCM values were calculated using Avnir's freely available program at http://www.csm.huji.ac.il.

3. Results and Discussion

In this section, we show and interpret the results of the information deficiency measure constructed above, with special attention for its merits for quantifying the chirality of halomethanes. These molecules were chosen for there prototypical character as chiral systems with a single asymmetric carbon atom. This includes chiral halomethanes with hydrogen, fluorine, chlorine, bromine, and iodine as substituents, providing five different enantiomer pairs. Following the BB alignment, by superimposing the asymmetric carbon atom and two of its substituents, each of these pairs can be superimposed in six different alignments.

These results will be extended to molecules possessing two asymmetric carbon centra, by looking at two halogen substituted ethanes of the type CXYZ−CX′YZ′, namely CHFCl−CHFCl and CHFCl−CHFBr. For these molecules we replace *R* and *S* in eqs 7 through 11 by *RR* and *SS* or by *RS* and *SR*, respectively. We opted to work with the three possible staggered conformations of each molecule with respect to the corresponding conformers of its enantiomer. Both enantiomers of each conformer may then be superposed in three manners by rotating one enantiomer with respect to the other, with the BB carbon atoms and on each of these carbon atoms a directly bonded hydrogen or halogen atom coinciding. This brings us to nine different alignments for each enantiomer couple.

Also, a comparison of these Kullback−Leibler information deficiencies with Carbó similarity indices and Avnir CCM will be discussed and related to optical rotation values.

3.1. Sum of Local Information Deficiency. The results of the sum over all atoms of the local information deficiency (eq 10), is shown in part A of Figure 1 for the six different alignments of the molecule CHFClBr, and in part B of Figure 1 for the nine different alignments of the *RR*/*SS* enantiomer couple of the molecule CHFCl−CHFCl. For every alignment, the sum of the nuclear charges of the coinciding atoms is considered. In this case, the sum of the nuclear charges of the coinciding atoms can be considered as proportional to the sum of the substituent volumes, whose diversity might be expected to be related to the chirality.[54] We notice that in both figures the information deficiency correlates surprisingly well with the sum of the nuclear charges of the coinciding atoms, showing a decreasing linear correlation. When the heaviest substituents coincide (coinciding atoms C*, Br, and Cl in part A of Figure 1 and atoms C1*, C2* and both Cl atoms in part B of Figure 1), the sum of the local information deficiencies is small, indicating that the difference in information between the *R* and the *S* enantiomer (or the *RR* and the *SS* enantiomer for the ethane molecule), aligned this way, is small. Interpreted in an information theory framework, we say that the *R* enantiomer contains a lot of information about the *S* enantiomer. Thus, a small value of the information deficiency leads to the most similar alignment. A similar linear correlation is regained for all five considered halomethanes and for the four considered enantiomer couples of the substituted ethanes.

The results for the sum of the local information deficiency over all atoms in parts A and B of Figure 1 can be compared to Carbó's global quantum similarity results, which may be found in part A of Figure 2 for the CHFClBr halomethane and in part B of Figure 2 for the *RR*/*SS* enantiomer couple of the CHFCl−CHFCl ethane (as already published earlier). In part A of Figure 2, we differentiate two subsets of values, three very high similarity values for alignments where the bromine atoms are coinciding, and three very low values when these heavy atoms are not coinciding. Within both subsets the values differ little. The same trend can be seen in part B of Figure 2, showing higher values whenever heavier atoms are coinciding. The SI is most sensitive to the relative position of the heavy atoms, and is almost indifferent to that of the lighter atoms.

The results in Figure 1 may be related to the conclusions drawn for the Carbó SI, where the overlap integral in the SI (**11**) showed higher values when the atoms were coinciding, with the largest values when the heaviest atoms are superimposed. High similarity values correspond to low information deficiency values for coinciding atoms, and analogous, small overlap integrals appear when atoms are not centered on the same position, corresponding to large entropy values. One notices that the information deficiency evolves more gradually and more linear, making it more appealing than the QSI, as the basis of a chirality measure.

3.2. Division into Coinciding/Noncoinciding Atoms and Global/Mixing Entropy. The sum of the local entropies over all atoms can be divided, as seen in Figure 1A for CHFClBr, into a contribution designated to the coinciding atoms, shown also in Figure 3, and a contribution due to the noncoinciding atoms. The identification of these two terms reveals, as expected, that the largest part of the entropy can be assigned to the noncoinciding atoms. The values of the noncoinciding atoms are actually that large that the finer details in the information of the coinciding atoms, as seen in Figure 3, are masked completely. The difference in magnitude is striking, although comprehensible, in the sense that atomic contributions centered on the same position are much more alike, yielding a smaller difference in information. This result reflects the importance of the relative orientation of both molecules. Note that the entropy values are most dependent on the lightest coinciding atom, in this case the halogen atom, pulling the entropy down. The second ordering goes along with the second lightest coinciding atom, and so forth.

As demonstrated in eq 10, the sum of the local information deficiency contains a contribution that can be interpreted as an entropy of mixing. The global entropy and the mixing entropy, constituting the sum of atomic entropies, do not separately reveal information of chemical interest. Moreover, we experienced that the global Carbó SI results compare much better to the sum of local entropies, that is, taking into account the mixing term, than to simply the global entropy. This mixing term is characteristic for molecules and obviously does not appear for isolated atoms, emphasizing the importance of the mixing entropy for molecular density functions.[37,38]

3.3. Local Information Deficiency of the Carbon atom. In this work, we aimed for one single value characterizing the chirality of a molecule, in other words, a value independent of the alignment of both enantiomers. Therefore we looked at the local information deficiency for each atom separately, taking for instance the local information deficiency of the asymmetric carbon atom in CHFClBr plotted against the sum of the nuclear charges of the coinciding atoms. As depicted in Figure 4, we find results still depending on the relative orientation of both molecules. Notice that the same tendencies are present as in Figure 3. Also when looking at the local information deficiency of both carbon atoms in molecules CHFCl-CHFCl or CHFCl−CHFBr, the same trends are found. To achieve a single value for each molecule, different options are possible.

We may take the arithmetic mean of the six alignments of this local carbon entropy and plot it against the sum of the nuclear charges of all atoms. In this case, we obtain a single value for each molecule because in the chosen BB alignment the asymmetric carbon atoms are always coinciding.

Another possibility is to consider only the alignment resulting in the highest similarity value, the best score alignment. As expected, this is the alignment where the carbon atom and the two heaviest substituents are coinciding (e.g., carbon, chlorine, and bromine for the CHFClBr molecule). These mean values and highest similarity alignments are both plotted in part A of Figure 5 and show a linear correlation with a negative slope.

A third solution to obtain a single value for each molecule is to use the QSSA, aligning the molecules so that the resulting molecular similarity is maximized, instead of the BB alignment. A closer look at this alignment reveals that this maximal similarity value is obtained when the three heaviest atoms of both enantiomers coincide; so in the case of the CHFClBr molecule, the atoms fluorine, chlorine, and bromine will be coinciding. Plotting these results against the sum of the nuclear charges of all atoms, also a good linear correlation is found with a negative slope. These values are much larger than the values seen in Figure 5, which is essentially due to the fact that the carbon atoms are now no longer coinciding.

To a certain extent, a comparison can be made between these local entropy results of the carbon atom and the results in Figure 1. The entropy values become smaller as heavier atoms or molecules are considered. A major difference between both figures is that Figure 1 contains intramolecular information about all six alignments, whereas Figure 5 considers intermolecular information of all five molecules.

We propose these local entropy values of the carbon atom (Figure 5) as a measure of chirality, more precisely the difference in information between the *R* and the *S* enantiomer reveals the chirality of the system quantitatively.

3.4. Local Information Deficiency of Substituents. For the (coinciding) substituents, a similar negative slope is found, as shown in Figure 6, with the difference that the values of all nonchiral substituents are much smaller than the values of the asymmetric carbon atom. This was to be expected because the asymmetric carbon atom being the chiral atom, it should contain the dominant information about the chirality of the molecule. When looking at the local Carbó similarity index on the other hand, the asymmetric carbon atom did not show the smallest similarity value. Although the average local entropy values of the substituents in Figure 6 are small, they are still significant and different from zero (order of magnitude between 4×10^{-7} and 5×10^{-5}). One recognizes this as a numerical illustration of Mezey's holographic electron density theorem, stating that molecular regions contain all of the information about the whole system. In this case, the nonasymmetric substituents contain information about the chiral electron distribution in both enantiomers.

Looking at the different values for each alignment separately − so before we take the average, we clearly see for all substituents and for all molecules that values are much smaller when the considered atoms are coinciding. We are talking about 3 up to 6 orders of magnitude smaller. This is in line with intuition because the atomic electron density overlap is much bigger for coinciding atoms.

3.5. Continuous Chirality Measure CCM. As already mentioned in section 2.1, also the very popular chirality measure of Avnir et al.[1] has been calculated for our molecules. The first step in this approach is to find the nearest configuration of points $\{\hat{P}_i\}_{i=1}^{n}$ that has an improper element of symmetry, in other words the closest achiral structure. The tool used for this is termed the *folding/unfolding procedure*, and is based on the method of constructing a symmetric object.

For the halomethane molecules, the closest achiral structure is a structure where all atoms are located in a plane, centered around the carbon atom. The substituted ethanes possessing at least four different types of substituents, so the ethanes without a possible meso compound (CHFCl−CHFBr in our case), also result in a planar structure. The closest achiral molecule of the *RR*/*SS* enantiomers of the ethanes having only three different types of substituents (CHFCl−CHFCl) is a bipyramid-type structure with both hydrogen atoms at the apex sites. The meso compounds (so the *RS*/*SR* enantiomers) result in a bipyramid-like figure possessing an inversion center.

The results for the halomethanes are shown in Table 1, where can be seen that not much difference is seen for our five molecules, all *S* (chiral) values lying between 17.3 and 22.8 on a scale of 0 to 100.

Ten different substituted ethanes (of the type CXYZ−CX′Y′Z′ with X, Y, Z, X′, Y′, Z′ = H, F, Cl, or Br) are considered in Figure 7, showing values of *S*(chiral) = 0 for the four meso compounds, as expected, and small values for the *RR*/*SS* enantiomers of these molecules, confirming that these molecules are less chiral than the other considered ethanes. The other ethanes show only small differences between them.

Comparing the CCM values with information theory, we found for the latter results a better correlation, consistent with the fact that information theory is an electron density based chirality measure. The information theory also has the advantage of being able to compute local values and does not necessitate searching for the closest achiral structure. The orientation problem using the BB alignment can easily be overcome by choosing the best score alignment or the QSSA alignment.

3.6. Optical Rotation. In Table 2, the results of the absolute value of the optical rotation $[\alpha]_D$ for the *S* enantiomer of the five different halomethanes are shown. We find an overall decreasing optical rotation (absolute value) as function of the sum of the nuclear charges over all atoms when looking at the halomethanes possessing the iodine atom (all molecules except CHFClBr). This is in agreement with the average local carbon entropies (Figure 5) because a decreasing slope for the entropy corresponds to an increasing slope for the similarity and a decreasing slope for the optical rotation, although no empirical link is found between the information deficiency and the optical rotation. Note that also when looking at Avnir's CCM values, no correlation can be found with the optical rotation.

7. Conclusions

In this work, we report the calculation of an information theory based quantum similarity measure (QSM), the Kullback−Leibler information deficiency. It was evaluated for enantiomers in the case of molecules possessing a single asymmetric carbon atom, namely five chiral halomethane pairs with as substituents hydrogen, fluorine, chlorine, bromine, and iodine, with each of these being superposed in six different alignments. An extension to molecules with two asymmetric carbon atoms has been presented for two halogen substituted ethanes. This QSM was studied globally, considering therefore the sum over all atoms of the local contributions, as well as locally.

The sum over all atoms of the local information deficiency decreases linearly with the nuclear charge of the coinciding atoms, the biggest contribution being due to the noncoinciding atoms.

The values for the substituents are considerably smaller (but not zero) than the values of the central carbon atom, corresponding with the chemical intuition of a first-order effect on the central asymmetric carbon atom versus the second-order effect on the nonasymmetric substituents.

The whole of the results are a numerical illustration of Mezey's holographic electron density theorem with an intuitively appealing division of the strength of propagation of the atomic chirality from an asymmetric carbon atom throughout the molecule.

The local entropy of the carbon atom, averaged over the different alignments or taking the best score alignment or using the QSSA alignment, is proposed as a measure of chirality, more precisely the difference in information between the *R* and the *S* enantiomer turns out to be a quantitative measure of the chirality of the system.

Comparison with the optical rotation shows that the degree of chirality emerging from information deficiency is only partially recovered in the optical rotation.

Acknowledgment. We thank Prof. Avnir (Hebrew University of Jerusalem) and his Ph.D. student Chaim Dryzun for the useful help on the visualization of the output structure of their CCM program. The authors acknowledge also the reviewers for their constructive remarks. P.G. wishes to thank the Free University of Brussels (VUB) for a generous computer grant and the Fund for Scientific Research-Flanders (FWO - Vlaanderen) for continuous support. Research funded by a Ph.D. grant of the Institute for the Promotion of Innovation through Science and Technology in Flanders (IWT-Vlaanderen).

References and Notes

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

(2) Alvarez, S.; Alemany, P.; Avnir, D. *Chem. Soc. Rev.* **2005**, *34*, 313, and references cited therein.

(3) Petitjean, M. C. R. *Acad. Sci. Paris, Chimie/Chemistry* **2001**, *4*, 331.

(4) Petitjean, M. *Entropy* **2003**, *5*, 271.

(5) Carbó, R.; Arnau, M.; Leyda, L. *Int. J. Quantum Chem.* **1980**, *17*, 1185.

(6) Hodgkin, E. E.; Richards, W. G. *Int. J. Quantum Chem.* **1987**, *14*, 105.

(7) Rouvray D. H. In *Topics in Current Chemistry*; Sen, K., Ed.; Springer-Verlag: Berlin Heidelberg, 1995; Vol. 173I, p 1.

(8) Parr, R. G.; Yang, W. In *Density-Functional Theory of Atoms and Molecules*; Oxford University Press: New York, Clarendon Press: Oxford, **1989**.

(9) Parr, R. G.; Yang, W. *Annu. Rev. Phys. Chem.* **1995**, *46*, 701.

(10) Chermette, H. *J. Comput. Chem.* **1999**, *20*, 129.

(11) Geerlings, P.; De Proft, F.; Langenaeker, W. *Chem. Rev.* **2003**, *103*, 1793.

(12) Geerlings, P.; Boon, G.; Van Alsenoy, C.; De Proft, F. *Int. J. Quantum Chem.* **2005**, *101*, 722.

(13) Boon, G.; Van Alsenoy, C.; De Proft, F.; Bultinck, P.; Geerlings, P. *J. Phys. Chem. A* **2003**, *107*, 11120.

(14) Janssens, S.; Van Alsenoy, C.; Geerlings, P. *J. Phys. Chem. A* **2007**, *111*, 3143–3151.

(15) Janssens, S.; Boon, G.; Geerlings, P. *J. Phys. Chem. A* **2006**, *110*, 9267.

(16) Boon, G.; De Proft, F.; Langenaeker, W.; Geerlings, P. *Chem. Phys. Lett.* **1998**, *295*, 122.

(17) Boon, G.; Langenaeker, W.; De Proft, F.; De Winter, H.; Tollenaere, J. P.; Geerlings, P. *J. Phys. Chem. A* **2001**, *105*, 8805.

(18) Borgoo, A.; Torrent-Sucarrat, M.; De Proft, F.; Geerlings, P. *J. Chem. Phys.* **2007**, *126*, 23.

(19) Kullback, S.; Leibler, R. A. *Ann. Math. Stat.* **1951**, *22*, 79.

(20) For a review, see: Gadre, S. In *Reviews of Modern Quantum Chemistry*; Sen, K. D., Ed.; World Scientific: Singapore, 2002; Vol. 1, p 108.

(21) Gadre, S. R.; Kulkarni, S. A.; Shrivastava, I. H. *Chem. Phys. Lett.* **1990**, *166*, 445.

(22) Gadre, S. R.; Sears, S. B.; Chakravorty, S. J.; Bendale, R. D. *Phys. Rev. A* **1985**, *32*, 2602.

(23) Nagy, A.; Parr, R. G. *Int. J. Quantum Chem.* **1996**, *58*, 323.

(24) Nalewajski, R. F.; Parr, R. G. *Proc. Natl. Acad. Sci. USA* **2000**, *97*, 8879.

(25) Hirshfeld, F. L. *Theor. Chim. Acta* **1977**, *44*, 129.

(26) Borgoo, A.; Godefroid, M.; Sen, K. D.; De Proft, F.; Geerlings, P. *Chem. Phys. Lett.* **2004**, *399*, 363.

(27) Borgoo, A.; Godefroid, M.; Indelicato, P.; De Proft, F.; Geerlings, P. *J. Chem. Phys.* **2007**, *126*, 44102.

(28) De Proft, F.; Geerlings, P. *J. Phys. Chem. A* **1997**, *101*, 5344.

(29) Ayers, P. W. *Proc. Natl. Acad. Sci. U.S.A.* **2000**, *97*, 1959.

(30) De Proft, F.; Ayers, P. W.; Sen, K. D.; Geerlings, P. *J. Chem. Phys.* **2004**, *120*, 9969.

(31) Sen, K. D.; De Proft, F.; Borgoo, A.; Geerlings, P. *Chem. Phys. Lett.* **2005**, *410*, 70.

(32) Shannon, C. E. *Bell Syst. Tech. J.* **1948**, *27*, 379.

(33) Kullback, S. In *Information Theory and Statistics*; Wiley: New York, 1959.

(34) Parr, R. G.; Bartolotti, L. J. *J. Phys. Chem.* **1983**, *87*, 2810.

(35) Ayers, P. W.; De Proft, F.; Geerlings, P. *Phys. Rev. A* **2007**, *75*, 12508.

(36) Mezey, P. G. *Mol. Phys.* **1999**, *96*, 169.

(37) Parr, R. G.; Ayers, P. W.; Nalewajski, R. F. *J. Phys. Chem. A* **2005**, *109*, 3957.

(38) Ayers, P. W. *Theor. Chem. Acc.* **2006**, *115*, 370.

(39) Solà, M.; Mestres, J.; Oliva, J.; Duran, M.; Carbò-Dorca, R. *Int. J. Quantum Chem.* **1996**, *58*, 361.

(40) Gironés, X.; Robert, D.; Carbó-Dorca, R. *J. Comput. Chem.* **2001**, *22*, 255.

(41) Constans, P.; Carbó-Dorca, R. *J. Chem. Inf. Comput. Sci.* **1995**, *35*, 1046.

(42) Constans, P.; Amat, L.; Carbó-Dorca, R. *J. Comput. Chem.* **1997**, *18*, 826.

(43) Amat, L.; Carbó-Dorca, R. *Int. J. Quantum Chem.* **2002**, *87*, 59.

(44) Bultinck, P.; Carbó-Dorca, R.; Van Alsenoy, C. *J. Chem. Inf. Comput. Sci.* **2003**, *43*, 1208.

(45) Bultinck, P.; Kuppens, T.; Gironés, X.; Carbó-Dorca, R. *J. Chem. Inf. Comput. Sci.* **2003**, *43*, 1143.

(46) Mezey, P. G.; Ponec, R.; Amat, L.; Carbó-Dorca, R. *Enantiomer* **1999**, *4*, 371.

(47) Boon, G.; Van Alsenoy, C.; De Proft, F.; Bultinck, P.; Geerlings, P. *J. Phys. Chem. A* **2006**, *110*, 5114.

(48) Stephens, P. J.; Devlin, F. J.; Cheeseman, J. R.; Frisch, M. J.; Mennucci, B.; Tomasi, J. *Tetrahedron: Asymmetry* **2000**, *11*, 2443.

(49) Frisch, M. J. ; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Montgomery,Jr., J. A.; Vreven, T.; Kudin, K. N. ; Burant, J. C.; Millam, J. M.; Iyengar, S. S.; Tomasi, J.; Barone, V.; Mennucci, B.; Cossi, M.; Scalmani, G.; Rega, N.; Petersson, G. A.; Nakatsuji, H.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y. ; Kitao, O.; Nakai, H.; Klene, M.; Li, X.; Knox, J. E.; Hratchian, H. P.; Cross, J. B.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Yazyev, O.; Austin, A. J.; Cammi, R.; Pomelli, C.; Ochterski, J. W.; Ayala, P. Y.; Morokuma, K.; Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Zakrzewski, V. G.; Dapprich, S.; Daniels, A. D.; Strain, M. C.; Farkas, O.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Ortiz, J. V.; Cui, Q.; Baboul, A. G.; Clifford, S.; Cioslowski, J.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Challacombe, M.; Gill, P. M. W.; Johnson, B.; Chen, W.; Wong, M. W.; Gonzalez, C.; and Pople, J. A. *Gaussian 03*, Rev. B.03; Gaussian, Inc.: Pittsburgh PA, 2003.

(50) Becke, A. D. *J. Chem. Phys.* **1993**, *98*, 5648.

(51) Lee, C.; Yang, W.; Parr, R. G. *Phys. Rev. B* **1988**, *37*, 785.

(52) Rousseau, B.; Peeters, A.; Van Alsenoy, C. *Chem. Phys. Lett.* **2000**, *324*, 189.

(53) Van Alsenoy, C.; Peeters, A. *J. Mol. Struct. (Theochem)* **1993**, *105*, 19.

(54) Meyer, A. Y.; Avnir, D. *Struct. Chem.* **1991**, *2*, 475.

JP711895T