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Molecular Quantum Similarity and Chirality: Enantiomers with Two Asymmetric Centra

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Molecular quantum similarity is evaluated for enantiomers possessing two asymmetric carbon atoms, namely halogen substituted ethanes. This study is an extension of previous work performed on molecules with a single asymmetric carbon atom and molecules possessing a chiral axis. Global similarity and its local counterpart based on the Hirshfeld partitioning are evaluated. By these means we quantify the dissimilarity of enantiomers and illustrate Mezey's holographic electron density theorem in chiral systems. Furthermore, the relation between the optical activity and the dissimilarity is studied. Special attention is drawn to the meso compounds, since these isomers enable us to examine local chirality in an achiral system.

1. Introduction

Similarity is a fundamental concept in a variety of molecular sciences. It is a paradigm in chemistry that similar molecules react in a similar way.[1] In order to classify, interpret, or predict the physiological activity of molecules in pharmacology, for example, this relation requires experimental or theoretical "measurements" of molecular similarity.

The quantum molecular similarity index (QMSI) based on the electron density proposed by Carbó,[2] now almost 25 years ago, is the prototype of such an index and continues to play a fundamental role in present day similarity research. These indices describe the global similarity of the total system. It can, however, be important to have an idea about the local similarity of certain regions of the systems under consideration. Therefore, a local analogue of the global similarity index, based on the Hirshfeld partitioning technique,[3] has been proposed.[4] This local index will also be used for numerical tests on Mezey's holographic electron density theorem.[5]

Due to the fundamental role of the electron density in the QMSI, a close linkage exists between density functional theory,[6] conceptual DFT,[7−10] and quantum similarity.[11] So, besides the electron density itself, these indices can also be used in combination with various other reactivity descriptors (e.g., Fukui function $f(\mathbf{r})$, local softness[12,13]).

An interesting application of similarity analysis is the case of enantiomers, receiving not much attention in the literature so far besides the work performed within our own research group. Some simplifications can be made when dealing with enantiomers due to the identical connectivity of both molecules.

At this point, one can ask if there is a connection between the difference in behavior of enantiomers and their degree of chirality.

Chirality is mostly considered as a discrete, black and white property. A molecule is either chiral or not chiral. However, Avnir et al.[14,15] and Petitjean[16] extended and evaluated the treatment of symmetry as a continuous molecular structural property to chirality, saying that one molecule can be more or less chiral (compared to another one).

In this work, we indeed assume that the degree of chirality is linked to the (dis)similarity of two enantiomers, reducing the problem to how to quantify molecular similarity in the case of enantiomers.

Previously within our research group, QMSI was used in the case of enantiomers of molecules containing a single chiral center[4,17,18] and molecules possessing a chiral axis.[19] As an extension, we opted in the present study to examine enantiomers possessing two asymmetric carbon centra, namely halogen substituted ethanes of the type $XYZC{-}CX'Y'Z'$ with X, Y, Z, X′, Y′, Z′ = H, F, Cl, or Br, providing us 10 different molecules to investigate. This substitution pattern is analogous with the previously examined halomethane CHFClBr by Boon et al.[4] and substituted allenes $XHC{=}C{=}CX'H$ with X = F, Cl, or Br.[19]

One of the reasons for our interest in this extension to molecules with two asymmetric carbon centra is the possibility of meso compounds. These isomers enable us to examine local chirality in achiral systems. The systems under consideration also show conformational flexibility, a problem already accounted for when studying amino acids.[17,18] In order to quantify the similarity of these sets of conformers of ethanes with respect to the corresponding conformers of its enantiomer, a Boltzmann weighted similarity index was proposed.[18]

Next to studying global and local similarity indices by means of the total electron density and the density difference, the second aim of this paper is to compare the computed (dis)similarity with the specific rotation $[\alpha]_D$. Mezey et al.[20] presented introductory results on amino acids, which suggest a positive correlation between optical activity and dissimilarity, the latter not only at the asymmetric carbon, but the results were obtained in a relatively highly approximate scheme. In ref 17, the Boltzmann weighted similarity index proved to be a convenient and practical tool to study this link, both globally and locally.

2. Theoretical Basis and Computational Details

2.1. Similarity Indices. As mentioned in the Introduction, Carbó[2,21] was the first to define the molecular quantum similarity

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TABLE 1: Boltzmann Weighted Global Similarity Indices for Halogen Substituted Ethanes of the Type XYZC−CX′Y′Z′ with X, Y, Z, X′, Y′, Z′ = H, F, Cl, or Br[a]

XYZ X′Y′Z′	1A	1B	1C	1D
HFCl HFCl	0.3569	0.4523	0.3569	0.4521
HFCl HFBr	0.3380	0.3507	0.3379	0.3499
HFCl HClBr	0.3488	0.3597	0.3465	0.3567
HFCl FClBr	0.3489	0.3589	0.3467	0.3573
HFBr HFBr	0.3359	0.3423	0.3359	0.3414
HFBr HClBr	0.3419	0.3471	0.3407	0.3460
HFBr FClBr	0.3424	0.3473	0.3412	0.3461
HClBr HClBr	0.3499	0.3520	0.3473	0.3475
HClBr FClBr	0.3487	0.3490	0.3502	0.3515
FClBr FClBr	0.3508	0.3514	0.3494	0.3484

[a] A, B, C, and D represent global similarity indices for *RR*/*SS* enantiomers using the total density (A) and the density difference (B) and for *RS*/*SR* enantiomers using the total density (C) and the density difference (D).

index R_{AB} between two molecules A and B on the basis of their electron densities $\rho_{\mathrm{A}}(\mathbf{r})$ and $\rho_{\mathrm{B}}(\mathbf{r})$. He introduced a generalized cosine expression, the so-called Carbó index R_{AB}, written as

$$R_{\mathrm{AB}} = \frac{\int \rho_{\mathrm{A}}(\mathbf{r})\rho_{\mathrm{B}}(\mathbf{r})\,\mathrm{d}\mathbf{r}}{[(\int \rho_{\mathrm{A}}{}^{2}(\mathbf{r})\,\mathrm{d}\mathbf{r})(\int \rho_{\mathrm{B}}{}^{2}(\mathbf{r})\,\mathrm{d}\mathbf{r})]^{1/2}} = \frac{Z_{\mathrm{AB}}}{\sqrt{Z_{\mathrm{AA}}Z_{\mathrm{BB}}}} \tag{1}$$

having a value bound between 0 and 1. In eq 1, Z_{AB} is the overlap integral between the electron densities $\rho(\mathbf{r})$'s of molecules A and B, often called the molecular quantum similarity measure (MQSM). Z_{AA} and Z_{BB} are the molecular quantum self-similarity measures (MQSSMs) of molecules A and B.

Introducing the shape function $\sigma(\mathbf{r})$ defined as the density per particle[22]

$$\sigma(\mathbf{r}) = \frac{\rho(\mathbf{r})}{N} \tag{2}$$

one can easily see that R_{AB} depends only on the shape function, in line with recent work in the literature on the fundamental nature of this function as carrier of information.[23−26]

2.1.1. Global Similarity Indices for Enantiomers. As already pointed out in ref 4, one can write for the *R* and *S* enantiomers of a chiral molecule

$$N_R = N_S = \int \rho_R(\mathbf{r})\,\mathrm{d}\mathbf{r} = \int \rho_S(\mathbf{r})\,\mathrm{d}\mathbf{r} \tag{3}$$

with N_R and N_S the total number of electrons of enantiomers *R* and *S*, respectively.

This yields, for an enantiomeric pair, the following expression for the Carbó index:

$$R_{RS} = \frac{\int \rho_R(\mathbf{r})\rho_S(\mathbf{r})\,\mathrm{d}\mathbf{r}}{[(\int \rho_R{}^{2}(\mathbf{r})\,\mathrm{d}\mathbf{r})\,(\int \rho_S{}^{2}(\mathbf{r})\,\mathrm{d}\mathbf{r})]^{1/2}} = \frac{\int \rho_R(\mathbf{r})\rho_S(\mathbf{r})\,\mathrm{d}\mathbf{r}}{[(\int \rho_R{}^{2}(\mathbf{r})\,\mathrm{d}\mathbf{r})^{2}]^{1/2}} = \frac{\int \rho_R(\mathbf{r})\rho_S(\mathbf{r})\,\mathrm{d}\mathbf{r}}{\int \rho_R{}^{2}(\mathbf{r})\,\mathrm{d}\mathbf{r}} \tag{4}$$

In order to eliminate the dominant effect of the core electrons in the MQS analyses, one can use the density differences $\Delta\rho(\mathbf{r})$,[4] functions well-known to represent bonding characteristics

TABLE 2: Global Similarity Values for *RR*/*SS* Enantiomers Using the Total Density for Different Alignments and Their Average for All Three Conformations[a]

		alignments						
		coinciding substituents			similarity values			
XYZ X′Y′Z′	conformations	1	2	3	1	2	3	average
HFCl HFCl	1	H+H	F+Cl	Cl+F	0.0418	0.5145	0.5145	0.3569
	2	H+F	F+H	Cl+Cl	0.0867	0.0868	0.8971	0.3569
	3	H+Cl	F+F	Cl+H	0.4695	0.1319	0.4695	0.3570
HFCl HFBr	1	H+H	F+Br	Cl+F	0.0083	0.9053	0.1003	0.3380
	2	H+F	F+H	Cl+Br	0.0169	0.0170	0.9799	0.3379
	3	H+Br	F+F	Cl+H	0.8965	0.0257	0.0917	0.3380
HFCl HClBr	1	H+H	F+Br	Cl+Cl	0.0453	0.8425	0.1627	0.3502
	2	H+Cl	F+H	Cl+Br	0.0851	0.0375	0.9119	0.3449
	3	H+Br	F+Cl	Cl+H	0.8342	0.0933	0.1207	0.3494
HFCl FClBr	1	H+F	F+Cl	Cl+Br	0.0393	0.0936	0.9046	0.3458
	2	H+Cl	F+Br	Cl+F	0.0856	0.8358	0.1289	0.3501
	3	H+Br	F+F	Cl+Cl	0.8278	0.0597	0.1625	0.3500
HFBr HFBr	1	H+H	F+Br	Br+F	0.0047	0.5016	0.5016	0.3359
	2	H+F	F+H	Br+Br	0.0094	0.0094	0.9889	0.3359
	3	H+Br	F+F	Br+H	0.4968	0.0143	0.4968	0.3359
HFBr HClBr	1	H+H	F+Br	Br+Cl	0.0249	0.4816	0.5213	0.3426
	2	H+Cl	F+H	Br+Br	0.0487	0.0198	0.9496	0.3394
	3	H+Br	F+Cl	Br+H	0.4769	0.0533	0.4964	0.3422
HFBr FClBr	1	H+F	F+Cl	Br+Br	0.0206	0.0537	0.9453	0.3399
	2	H+Cl	F+Br	Br+F	0.0492	0.4798	0.5001	0.3430
	3	H+Br	F+F	Br+Cl	0.4752	0.0344	0.5193	0.3430
HClBr HClBr	1	H+H	Cl+Br	Br+Cl	0.0506	0.5014	0.5014	0.3511
	2	H+Cl	Cl+H	Br+Br	0.0629	0.0629	0.9134	0.3464
	3	H+Br	Cl+Cl	Br+H	0.4731	0.0894	0.4731	0.3452
HClBr FClBr	1	H+F	Cl+Cl	Br+Br	0.0467	0.0897	0.9094	0.3486
	2	H+Cl	Cl+Br	Br+F	0.0687	0.4995	0.4781	0.3488
	3	H+Br	Cl+F	Br+Cl	0.4761	0.0711	0.4995	0.3489
FClBr FClBr	1	F+F	Cl+Br	Br+Cl	0.0577	0.4977	0.4977	0.3510
	2	F+Cl	Cl+F	Br+Br	0.0693	0.0693	0.9053	0.3480
	3	F+Br	Cl+Cl	Br+F	0.4800	0.0899	0.4800	0.3500

[a] For the coinciding substituents, the first ones are the substituents on C1 and the second ones on C2.

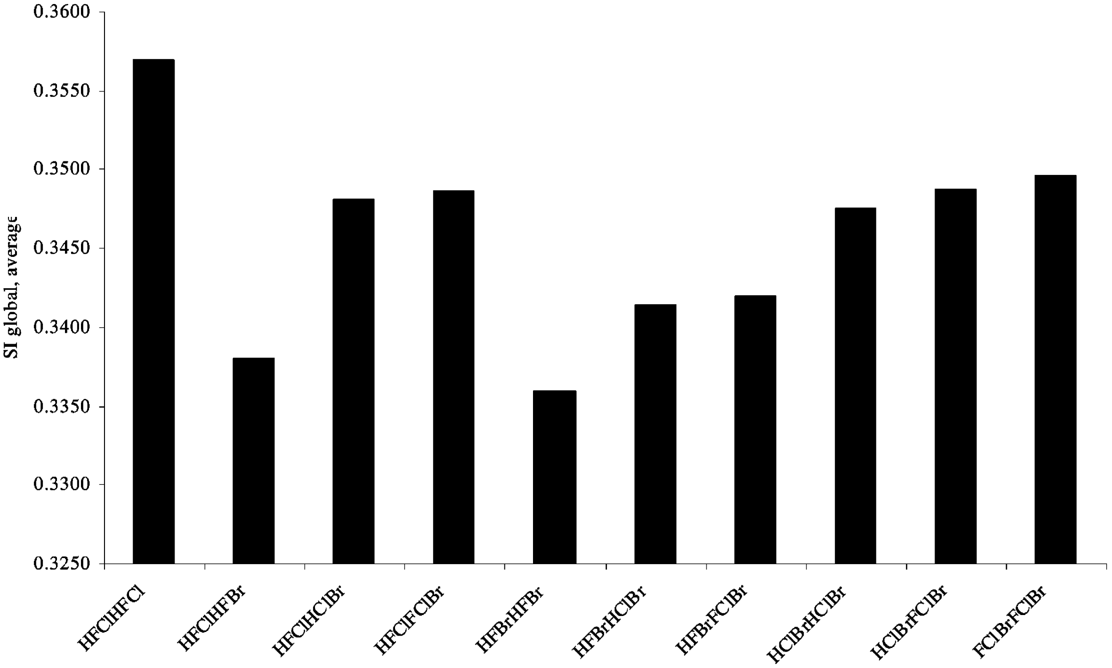

Figure 1. Global SI for *RR*/*SS* enantiomers using the total density. Average values of the 3 alignments and 3 conformations.

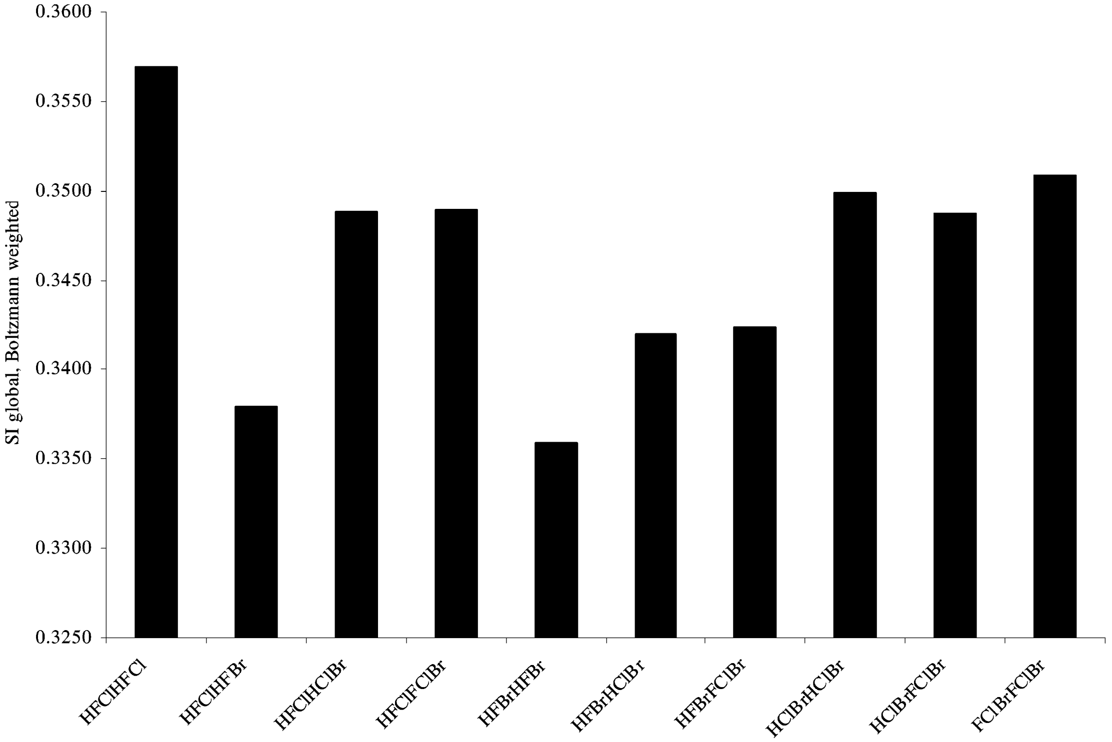

Figure 2. Global SI for *RR*/*SS* enantiomers using the total density. Boltzmann weighted index of averaged alignments for the 3 conformations.

in molecules, instead of the total densities $\rho(\mathbf{r})$ of the two molecules under consideration.

The density difference function $\Delta\rho_R(\mathbf{r})$ of the *R* enantiomer is defined as

$$\Delta\rho_R(\mathbf{r}) = \rho_R(\mathbf{r}) - \rho_R^0(\mathbf{r}) \tag{5}$$

with $\rho_R^0(\mathbf{r})$ the promolecular density of the *R* enantiomer.

2.1.2. Local Similarity Indices for Enantiomers. As a consequence of Mezey's holographic electron density theorem,[5] molecular regions (for example, atomic regions around chiral or nonchiral atoms) contain all the information about the system, thus also about its chirality. In this work, we put numerical testing of the consequences of this theorem into practice by concentrating on atomic regions using Hirshfeld partitioning,[3] which partitions the total electron density $\rho(\mathbf{r})$ of a molecule in atomic contributions $\rho_A(\mathbf{r})$ according to

$$\rho_A(\mathbf{r}) = w_A(\mathbf{r})\rho(\mathbf{r}) \tag{6}$$

with

$$w_A(\mathbf{r}) = \frac{\rho_A^0(\mathbf{r})}{\sum_X \rho_X^0(\mathbf{r})} \tag{7}$$

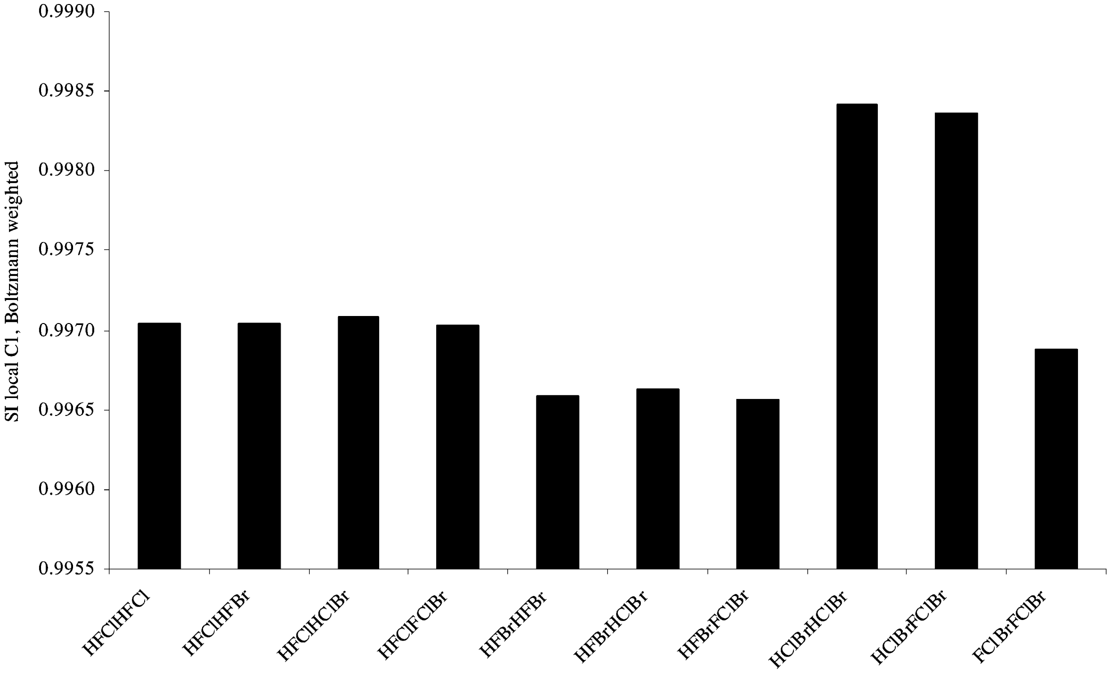

Figure 3. Boltzmann weighted local SI for carbon atom C1 of *RR*/*SS* enantiomers using the total density.

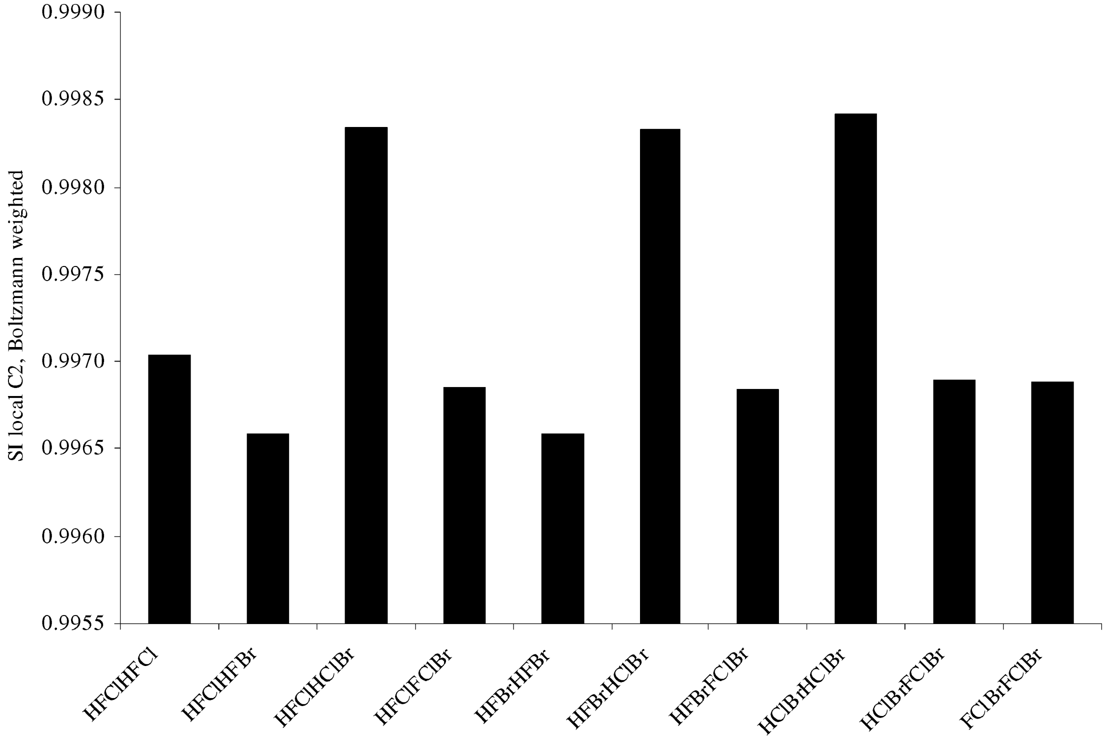

Figure 4. Boltzmann weighted local SI for carbon atom C2 of *RR*/*SS* enantiomers using the total density.

Here $\rho^0_{\mathrm{A}}(\mathbf{r})$ is the electron density of the isolated atom A and $\sum_X \rho^0_X(\mathbf{r})$ is the density built from the superposition of the densities of the isolated atoms placed on the same positions as in the molecule itself, the "promolecular density". The sum of all weight coefficients $w_{\mathrm{A}}(\mathbf{r})$ is, by construction, equal to 1.

With the *R* and *S* enantiomers of a chiral molecule, the contribution of a given atom, for example, an asymmetric carbon atom, to the total electron density $\rho_R(\mathbf{r})$ of the *R* enantiomer can be written as

$$\rho_{\mathrm{C},R}(\mathbf{r}) = w_{\mathrm{C},R}(\mathbf{r})\rho_R(\mathbf{r}) \tag{8}$$

with

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

and analogously for the contribution of the asymmetric carbon atom to the total electron density $\rho_S(\mathbf{r})$ of the *S* enantiomer.

In the numerical calculation of the overlap integral $\int \rho_R(\mathbf{r})\rho_S(\mathbf{r})\,\mathrm{d}\mathbf{r}$, the integrand $\rho_R(\mathbf{r})\rho_S(\mathbf{r})$ is evaluated on a combined grid of the aligned enantiomers. The contribution of one particular

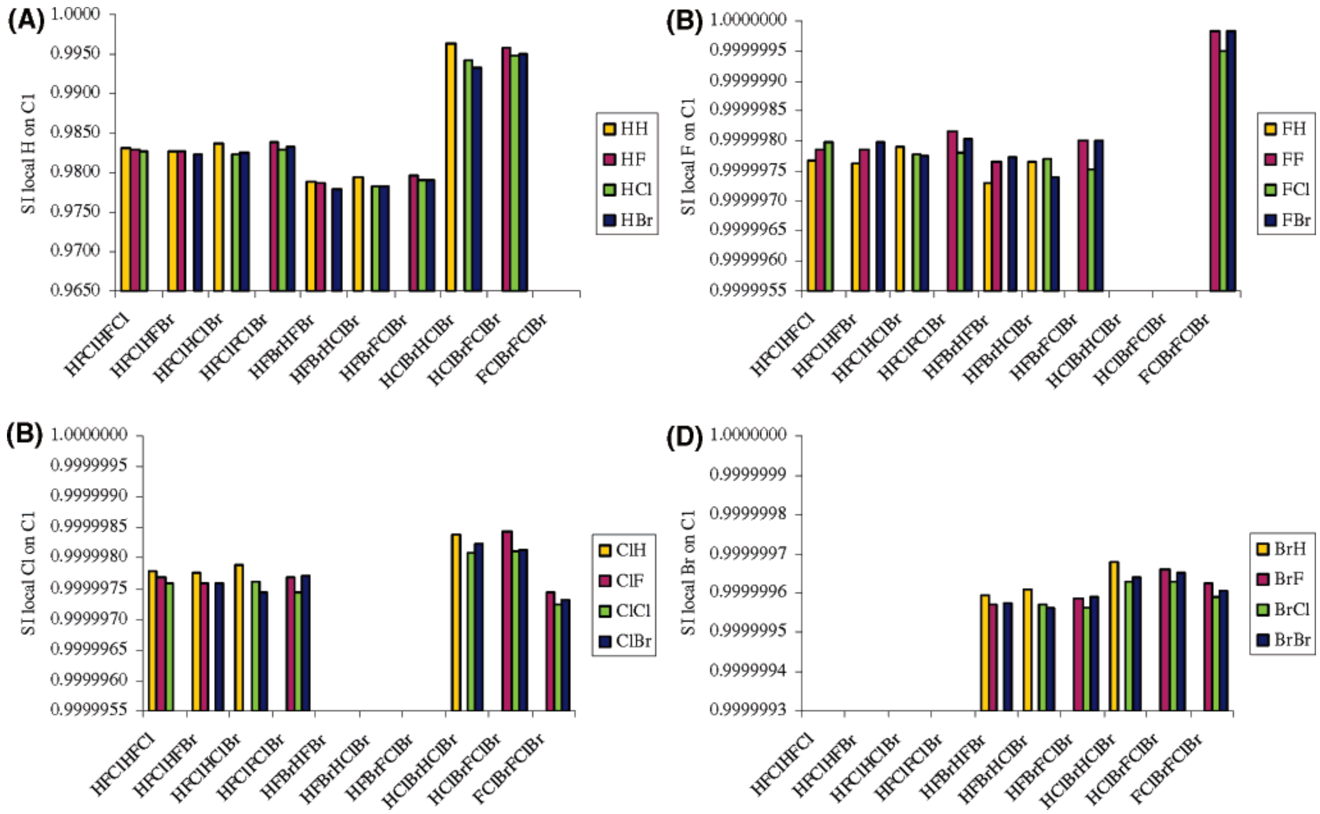

Figure 5. Boltzmann weighted local SI for the coinciding substituents on C1 of *RR*/*SS* enantiomers using the total density: (A) coinciding substituents H on C1; (B) coinciding substituents F on C1; (C) coinciding substituents Cl on C1; (D) coinciding substituents Br on C1.

kind of atom of the grid, e.g., an asymmetric carbon atom C, to the total integral thus needs the consideration of two contributions, the carbon atom in the *R* enantiomer and the atom in the *S* enantiomer.

As such, the contribution of the asymmetric carbon atom to the product $\rho_R(\mathbf{r})\rho_S(\mathbf{r})$, as proposed earlier by Boon et al.,[4] is written as

$$\rho_{\mathrm{C},R+S}(\mathbf{r}) = w_{\mathrm{C},R+S}(\mathbf{r})\rho_R(\mathbf{r})\rho_S(\mathbf{r}) \qquad (10)$$

with

$$w_{\mathrm{C},R+S}(\mathbf{r}) = \frac{\rho^0_{\mathrm{C},R}(\mathbf{r}) + \rho^0_{\mathrm{C},S}(\mathbf{r})}{\sum_X \rho^0_{X,R}(\mathbf{r}) + \sum_Y \rho^0_{Y,S}(\mathbf{r})} \qquad (11)$$

where $\sum_X \rho^0_{X,R}(\mathbf{r}) + \sum_Y \rho^0_{Y,S}(\mathbf{r})$ is the total promolecular density of the two enantiomers with their asymmetric carbon atoms superimposed.

The integral of equation 10 provides us the numerator Z_{RS} of the Carbó index.

The self-similarities Z_{RR} and Z_{SS} can be written analogously in terms of atomic contributions, which provides us the denominator of the Carbó index.

Introducing these Hirshfeld partitioned expressions in the original Carbó index (eq 4), we can convert the global index into a local analogue $R_{RS}^{\mathrm{local,C}}$.

2.1.3. Global Similarity Indices for Series of Conformers of Enantiomers. In this work, we aim at evaluating the average behavior of large numbers of molecules in our similarity study of conformers of enantiomers, saying that for example the *R* enantiomer of a particular molecule behaves as the average of all the conformers of this enantiomer. In order to carry out the study of similarity of enantiomers, dealing with all their conformers, a Boltzmann weighted similarity index ⟨SI⟩ can be useful:

$$\langle \mathrm{SI} \rangle = \sum_i (\mathrm{SI})_i p_i = \frac{\sum_i (\mathrm{SI})_i e^{-Ei/kT}}{\sum_i e^{-Ei/kT}} \qquad (12)$$

In this expression, p_i is the fraction of the conformers with energy E_i above the energy of the lowest conformer, T is the thermodynamic temperature, and k the Boltzmann constant. For each conformer i the weight of the similarity index $(\mathrm{SI})_i$ contributes to the index ⟨SI⟩ depending on the energy E_i of the conformer. The Boltzmann weighted similarity index describes the similarity of a set of conformers of a chiral molecule with respect to the corresponding conformers of its enantiomer.

Analogously, one can, for a series of conformers belonging to one chiral molecule, write a Boltzmann weighted optical activity $[\alpha]_\mathrm{D}$ as

$$\langle [\alpha]_\mathrm{D} \rangle = \sum_i ([\alpha]_\mathrm{D})_i p_i = \frac{\sum_i ([\alpha]_\mathrm{D})_i e^{-Ei/kT}}{\sum_i e^{-Ei/kT}} \qquad (13)$$

2.2. Relative Orientation of the Enantiomers. An important drawback of the molecular similarity indices is their dependence on the relative orientation of the molecules under consideration. The most simple way to deal with the translational problem is to work with coinciding centers of mass, centers of charge, etc. However, this does not fix the relative orientation or will not

TABLE 3: Boltzmann Weighted Optical Activity ($\langle\alpha\rangle$) for *RR*/*SS* and *RS*/*SR* Enantiomers Using the Total Density[a]

		α (deg)		energy (au)	
XYZ X′Y′Z′	conformations	*RR*	*RS*	*RR*	*RS*
HFCl HFCl	1	68.46	0.06	−1197.4685	−1197.4704
	2	−56.94	73.70	−1197.4681	−1197.4669
	3	−62.05	−73.67	−1197.4675	−1197.4669
	$\langle\alpha\rangle$	3.4819	0.0583		
HFCl HFBr	1	67.26	−4.22	−3308.9770	−3308.9790
	2	−52.89	76.98	−3308.9770	−3308.9756
	3	−66.25	−71.29	−3308.9763	−3308.9758
	$\langle\alpha\rangle$	−7.7948	−4.2847		
HFCl HClBr	1	58.48	46.78	−3669.3379	−3669.3381
	2	−87.68	22.63	−3669.3370	−3669.3357
	3	−20.09	−87.90	−3669.3359	−3669.3371
	$\langle\alpha\rangle$	15.8028	13.2036		
HFCl FClBr	1	16.85	34.45	−3768.5634	−3768.5630
	2	15.08	−47.88	−3768.5621	−3768.5642
	3	−52.39	−8.84	−3768.5643	−3768.5624
	$\langle\alpha\rangle$	−30.2500	−28.3427		
HFBr HFBr	1	72.09	0.01	−5420.4861	−5420.4878
	2	−52.38	82.25	−5420.4861	−5420.4851
	3	−79.20	−82.19	−5420.4858	−5420.4851
	$\langle\alpha\rangle$	−14.7623	0.0120		
HFBr HClBr	1	69.66	55.00	−5780.8471	−5780.8469
	2	−97.57	23.58	−5780.8460	−5780.8453
	3	−30.46	−101.83	−5780.8456	−5780.8464
	$\langle\alpha\rangle$	24.1626	0.1087		
HFBr FClBr	1	22.20	41.59	−5880.0726	−5880.0727
	2	17.67	−52.12	−5880.0716	−5880.0734
	3	−60.13	−16.17	−5880.0738	−5880.0720
	$\langle\alpha\rangle$	−38.5589	−20.2974		
HClBr HClBr	1	30.63	0.00	−6141.2060	−6141.2057
	2	−106.37	81.75	−6141.2035	−6141.2042
	3	33.42	−81.66	−6141.2045	−6141.2042
	$\langle\alpha\rangle$	23.5414	0.0123		
HClBr FClBr	1	−8.80	25.73	−6240.4313	−6240.4317
	2	59.41	−69.52	−6240.4303	−6240.4299
	3	−57.01	26.39	−6240.4306	−6240.4306
	$\langle\alpha\rangle$	−7.9942	16.0818		
FClBr FClBr	1	−17.93	−0.01	−6339.6577	−6339.6572
	2	41.95	−36.62	−6339.6549	−6339.6552
	3	−13.17	36.53	−6339.6549	−6339.6552
	$\langle\alpha\rangle$	−15.0482	−0.0165		

[a] For coinciding substituents of conformations, see Table 2.

invariably yield maximal similarity. On the other hand, obtaining chemically relevant information is not guaranteed by an optimized similarity index.

Several methods have already been proposed to establish a criterion on how molecules might be superposed: for example, alignments according to common physicochemical features, or topological and geometrical features (TGSA[27]), or alignment of the molecules so that the resulting molecular similarity is maximized (QSSA[28−32]).

The method used in this paper is the so-called backbone alignment (BB). In the case of our substituted ethanes, we superimpose both backbone asymmetric carbon atoms and on each of these carbon atoms a directly bonded hydrogen or halogen atom of both enantiomers under consideration, yielding 3 different alignments for each enantiomer couple. This choice enables us, as opposed to TGSA and QSSA, to evaluate not only global similarity, but also local similarity measures, and for the asymmetric carbon atoms as well as for the non-asymmetric substituents. This local approach allows us to investigate the holographic electron density theorem in a quantitative way.

2.3. Computational Details. All electron densities and optical rotations used in this work were calculated in a DFT approach using the GAUSSIAN 03[33] program at the B3LYP/6-31G* level.[34,35] Optimizations of all molecules were done with all three dihedral angles fixed at 180° as a constraint. We opted to concentrate on the 3 possible staggered conformations of a given enantiomer, being the lowest energy conformers, and we compared these with the corresponding conformers of its mirror image.

As a solution to the time-consuming three-dimensional integrations, we used a highly efficient analytical implementation of the necessary integrals of the similarity indices, namely the BRABO program package developed by one of the authors.[36,37] The local Carbó index based on the Hirshfeld partitioning is implemented numerically in the program STOCK, part of this BRABO package.[36,37]

3. Results and Discussion

In our study, four types of similarity indices are considered, namely global and local similarity indices using the total density or the density difference, which will be discussed in the following section.

As already mentioned in section 2.3, 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 backbone carbon atoms and two substituents coinciding. This brings us to nine different alignments for each of the 10 molecules.

3.1. Global Similarity. The results for the calculation of the Boltzmann weighted global similarity index using the total

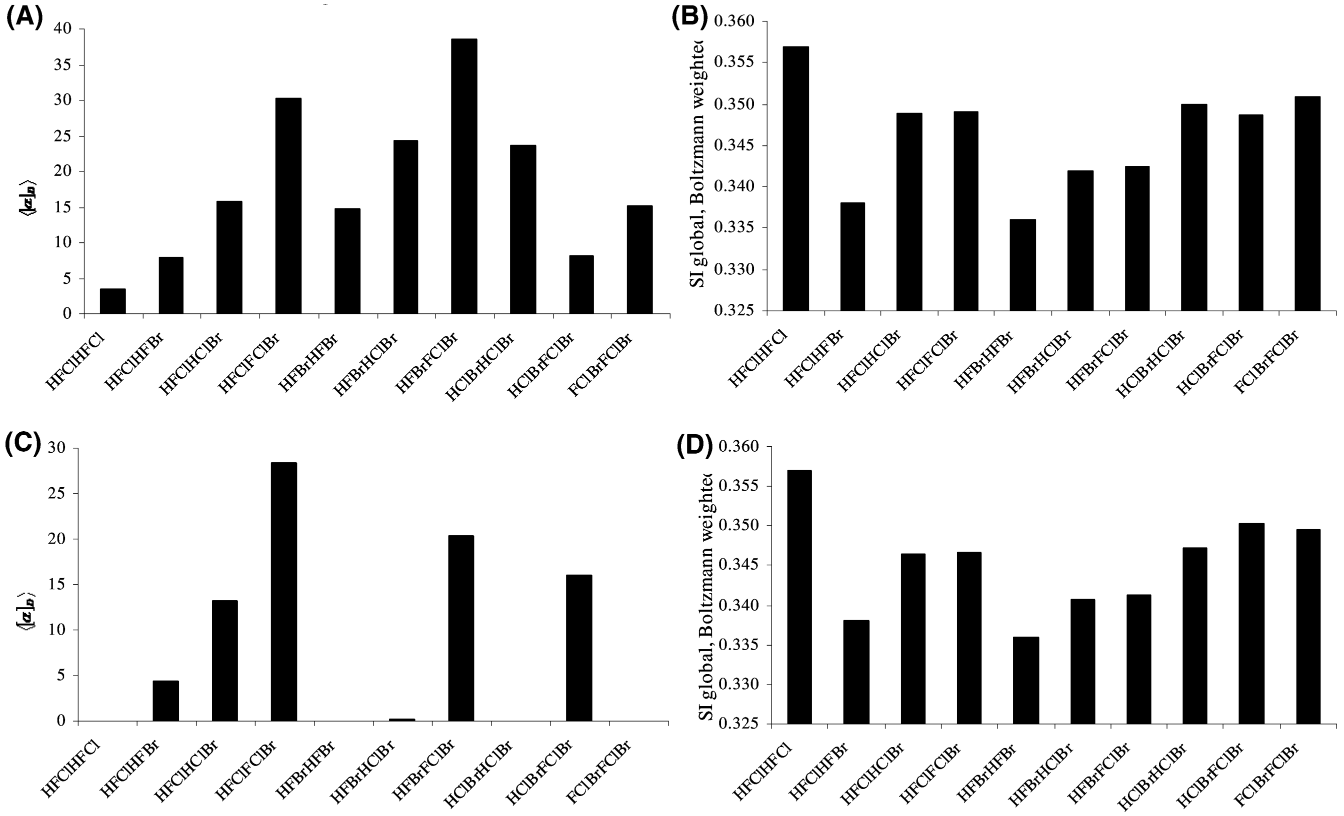

Figure 6. Boltzmann weighted optical rotation compared with the global Boltzmann weighted similarity index using the total density: (A) Boltzmann weighted optical rotation for *RR*/*SS* enantiomers; (B) global Boltzmann weighted similarity index for *RR*/*SS* enantiomers; (C) Boltzmann weighted optical rotation for *RS*/*SR* enantiomers; (D) global Boltzmann weighted similarity index for *RS*/*SR* enantiomers.

density and the density difference, for *RR*/*SS* and *RS*/*SR* enantiomers, are shown in Table 1.

Table 2 shows the global similarity values for *RR*/*SS* enantiomers using the total density, for different alignments, and their average for all three conformations. In Table 2, we notice that the global similarity is highly dependent on the heavy halogens. When these atoms are at a large distance from each other, they tear the value of the global similarity down, while when the lighter atoms are at a large distance from each other their effect is negligible in comparison with the then coinciding heavy atoms. This trend is in line with our earlier results on the halogen disubstituted allenes.[19]

When we compare the values in column 1B in Table 1 with the values in column 1D, using the density difference, no clear-cut trend could be found in the latter densities, showing that density differences give different and complementary information about the similarity of the system, confirming again earlier results.

In Figure 1, the similarity index was calculated as the average value of the similarities of the 3 different alignments and the 3 conformers. These values show little variation because they mediate, but we still find some pattern, the first ordering going along with the number of bromine atoms (varying from 0 bromine atoms in HFClC−CHFCl to 2 bromine atoms). The second ordering goes along with the number of chlorine atoms, and the third one parallels the number of fluorine atoms. These results, which are in line with the results in our study on allenes, indicate that larger atoms will dominate smaller atoms in electron based similarity measures.

The same trend, although a little less pronounced, can be found in Figure 2, where the average of the 3 alignments is calculated, taking then the Boltzmann weighted similarity index of these averaged alignments for the 3 conformers. The reason for losing the beautiful pattern when using Boltzmann weighted similarity indices might be attributed to the fact that they are based on very subtle differences in energy, typically 0.002 au, while average values are less sensitive.

3.2. Local Similarity. In Figures 3, 4, and 5A−D, the results are shown for the local similarities, considering atoms C1, C2, H, F, Cl, and Br, respectively.

It is remarkable that all local similarity indices are different from unity not only for the chiral carbon atoms, but also for the nonchiral substituents. This deviation quantifies the consequences of Mezey's holographic electron density theorem, stating that each region of a molecule contains information about the whole system, in this case, about chirality.

From Figures 3 and 4, which show the local similarity indices on atoms C1 and C2 using the total density, it can be seen that the similarity values are very similar when the substituents on the considered carbon atom are equal. This implies that the indices are most dependent on the first binding partner, so the β-substituent on the carbon atom.

For the similarity values of the substituents, we only consider these alignments where two substituents of a molecule coincide with the corresponding substituents of its enantiomers. Figure 5A−D yields the similarities of, respectively, substituents H, F, Cl, and Br on carbon atom C1 for *RR*/*SS* enantiomers. A comparison of these figures displays the largest similarity values in Figure 5D for the bromine atom and the smallest values in Figure 5A for the hydrogen atom, stating again that heavier substituents have larger similarity values. Within one figure, the effect of the second coinciding substituent, so the substituent on C2, can be seen to be negligible due to the large distance of this substituent from the considering substituent on C1.

These similarity values are found to be analogous for the substituents on carbon atom C2.

These results are all in line with earlier work on the halomethane CHFClBr,[4] on a series of simple amino acids[17,18] and on the substituted allenes.[19]

The meso compounds among the *RS* type molecules give us a chance to examine local chirality in an achiral system. Let us consider the HFClC−CHFCl molecule as a case study, looking particularly at the asymmetric carbon atom C1. The local similarity value of this carbon atom using the total density is very similar in the meso compound (the *RS* type molecule) and in the *RR*/*SS* enantiomers, namely 0.997033 and 0.997036, respectively, which is within the error of numerical integration. So due to a value differing from unity for the carbon atom C1, we have local dissimilarity in both types of molecules, and thus local chirality. Although, due to the presence of a symmetry plane or an inversion center, global chirality is vanishing.

When considering the optical rotation of the HFClC−CHFCl molecule on the other hand, for the meso compound a value of zero is found, except for round-off errors, as it should because it is achiral, while the *RR*/*SS* enantiomers are chiral molecules and have values of +3.48° (*RR*) or −3.48° (*SS*).

3.3. Relation between Dissimilarity and Optical Rotation. Supposing that the optical activity, as quantified in a standardized way by the specific rotation $[\alpha]_D$, is an experimentally accessible quantity for the degree of chirality of a molecule and also assuming that the dissimilarity between enantiomers describes their chirality, one can expect a link between the dissimilarity and the optical activity of enantiomers, as was previously shown by Mezey.[5]

As mentioned in section 2.1.3., for a series of conformers belonging to one chiral molecule, a Boltzmann weighted optical activity $\langle[\alpha]_D\rangle$ is used, the results of which are found in Table 3.

Special attention needs to be drawn to the meso compounds, which are not chiral anymore due to an internal plane of symmetry or a center of inversion, and consequently do not show optical activity. In Table 3 it can indeed be seen that for the meso compounds the values of the three conformers mediate to a value of $\langle[\alpha]_D\rangle$ equal to zero.

A comparison of the Boltzmann weighted global similarity values using the total density with the Boltzmann weighted optical rotation $\langle[\alpha]_D\rangle$ is given in Figure 6A,B for the *RR*/*SS* enantiomers, and Figure 6C,D for the *RS*/*SR* enantiomers.

For the meso compounds among the *RS* type molecules, it is clear that the global similarity values are very comparable to the values for the corresponding *RR* molecules, while the optical rotation values are zero, as they should be, in the former case, whereas the *RR* type molecules do show optical activity.

Unfortunately, no specific trends between the dissimilarity and the optical activity are shown.

4. Conclusions

A contribution to the study of molecular quantum similarity was made in this work. It was evaluated for enantiomers in the case of halogen substituted ethanes, molecules possessing two asymmetric carbon atoms. Due to their conformational flexibility, a Boltzmann weighted similarity index has been used.

For molecules of the type XYZC−CX′Y′Z′ with X, Y, Z, X′, Y′, Z′ = H, F, Cl, or Br, global and local similarities were studied using total densities and density differences, all carrying different and complementary information.

The global dissimilarity turns out to be strongly influenced by the positioning of the heavy halogens. We see a pattern which is in line with the chemical intuition that larger atoms dominate smaller atoms in electron based similarity measures.

The local similarity, based on the Hirshfeld partitioning, illustrates Mezey's holographic electron density theorem. The local similarity indices on the carbon atoms are most dependent on the first binding partner. Looking at the values for the substituents, we again find that heavier substituents have larger similarity values. The meso compounds among the *RS* type molecules show local chirality in an achiral system.

The optical activity can be considered as an indicator of global chirality of the whole molecule. In the case of the meso compounds the optical activity values of the three conformers mediate to a value of $\langle[\alpha]_D\rangle$ equal to zero, as they should.

Comparing the Boltzmann weighted global similarity with the Boltzmann weighted optical rotation shows that prudence needs to be taken when stating a positive correlation between both.

This method can easily be extended to enantiomers with more than two asymmetric carbon atoms, for which we can proceed in the same way by superposing the backbone carbon atoms. In the case of molecules with three asymmetric carbon atoms, the outmost carbon atoms C1 and C3 are the analogues of the atoms C1 and C2 from the molecules with two asymmetric carbon atoms. The middlemost atom C2 is fixed due to the backbone alignment, while the outmost atoms C1 and C3 can rotate, yielding still nine different superposition possibilities.

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