Study of Molecular Quantum Similarity of Enantiomers of Amino Acids

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Molecular quantum similarity is evaluated for enantiomers in the case of molecules showing conformational flexibility, using our earlier proposed Boltzmann weighted similarity index. The conformers of the enantiomers of the amino acids alanine, asparagine, cysteine, leucine, serine, and valine were examined. Next to studying global indices, the evaluation of local similarity is carried out using our earlier proposed local similarity index based on the Hirshfeld partitioning, to further illustrate Mezey's holographic electron density theorem in chiral systems and to quantify dissimilarity of enantiomers.

1. Introduction

Similarity is a fundamental concept in chemistry and pharmacology.[1] In recent years, more and more quantitative molecular descriptors are becoming available and intense studies have been carried out looking for indices measuring molecular similarity based on these descriptors.[2] In line with the increasing importance of applying quantum mechanically based techniques to investigate the properties and reactions of molecules, quantum chemically based indices are getting more and more attention. In 1980, Carbó[3] proposed a similarity index based on the electron density which still now plays a fundamental role in similarity research.

When evaluating molecular similarity indices, one is immediately confronted with its dependence on the relative position of the molecules under consideration. The most simple way to deal with the translational problem is, for example, to work with coinciding centers of mass, centers of charge, and so forth. This however does not fix the relative orientation, nor will it invariably yield maximal similarity. On the other hand, optimizing the similarity index does not always guarantee that the chemically relevant information is obtained.

The fundamental role of the electron density in quantum molecular similarity (QMS) studies results in a close relationship between density functional theory,[4] especially conceptual DFT,[5] and quantum similarity.[3]

A lot of pharmacologically important molecules are chiral structures[6] leading upon interaction with a chiral partner to diastereoisomeric transition states, complexes, and reaction products with different energies and properties, which has enormous consequences for the difference in activity of chiral pharmaca. Via the use of computer-aided molecular design (CAMD), Richards et al.[7] demonstrated the existence of a quantitative structure activity relation (QSAR) between the potency ratio of two enantiomers—called the eudismic ratio (ER)[8]—and the "chiral coefficient" of the enantiomer pair. The ER is defined as the ratio of the potencies (affinities) of the more potent enantiomer (eutomer, Eu) and the less potent one (distomer, Dis). The chiral coefficient is a quantitative index of dissimilarity between enantiomers defined as "1 − molecular similarity index". Such a correlation permits the prediction, within a homologous series, of the ER of new pairs of enantiomers, which can be of great use for medicinal chemists (see below).

Here, the introduction of the concept of local chirality—instead of considering global chirality—can be of great importance as well. On the basis of symmetry arguments, in the literature, chirality was often considered as a binary black−white property: a molecule is either chiral or not chiral. Avnir and co-workers[9,10] extended the treatment of symmetry as a continuous molecular structural property considering chirality as a more continuous concept. The eudismic ratio can be seen as an application of chirality being a continuous property.[8] Pfeiffer states that a higher affinity of the eutomer yields a higher enantioselectivity of the enantiomers.[11] In eudismic analyses, the eudismic index EI = log(ER) is plotted versus pK_{Eu}, with K_{Eu} being the dissociation constant associated to the interaction with the receptor, to quantify the stereoselectivity of a given receptor toward a series of stereoisomeric substrates.[11−13] This plot turned out to give a linear regression with the slope quantifying the stereoselectivity of the receptor, namely, the eudismic affinity quotient (EAQ).[14] Within a homologous series of molecules, a plot of the ER versus the calculated dissimilarity can also be made. As a consequence, once the dissimilarity of an enatiomeric pair is calculated, the activity of these enantiomers can be predicted via the ER and the EI.

In more recent work,[15,16] we used global quantum molecular similarity indices (QMSI) in the case of enantiomers of the prototype chiral molecule, the halomethane CHFClBr, and of the amino acids alanine and leucine, all of them containing only one chiral center, which reflects the situation of many active compounds in pharmacology. We considered these systems for different reasons. Being the textbook example chiral molecule,[17] the halomethane CHFClBr was in a first phase an ideal test

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molecule to study the dissimilarity and local chirality of its enantiomers. Leucine and alanine, among the simplest "biomolecules", were then considered in order to investigate the relationship between their degree of chirality—and thus their dissimilarity—and their optical activity. In ref 15, we proposed a local similarity index based on the Hirshfeld partitioning technique[18] enabling us to evaluate (dis)similarity at the atomic level.

In the present paper, we study similarity for enantiomers in the case of an extended series of amino acids for which different conformers exist. To the best of our knowledge, this conformational aspect has only been considered in an introductory case study of the molecular quantum similarity of enantiomers of the amino acids alanine and serine[19] where a Boltzmann weighted similarity index was proposed in order to quantify the similarity of these sets of conformers of the amino acids with respect to the corresponding conformers of its enantiomer.

Next to using global indices, we evaluate local similarity using our previously[15] proposed local similarity index in order to further quantify Mezey's holographic electron density theorem[20] for chiral systems and to quantify the dissimilarity of enantiomers.

The aim of this paper is thus to study the link between the dissimilarity, optical activity, and holographic electron density theorem already pinpointed in ref 19. Mezey has presented introductory results in ref 21, which suggest a positive correlation between optical activity and dissimilarity, the latter not only at the asymmetric carbon. As in ref 19, the Boltzmann weighted similarity index proved to be a convenient and practical tool to study this link in a more fundamental level, both globally and locally.

Studying this link and next to using experimentally obtained values for the optical activity $[\alpha]_D$, we also calculated $[\alpha]_D$ for all conformers belonging to each amino acid after which a Boltzmann weighted optical activity value for each amino acid was created.

Furthermore and analogous to refs 15 and 19, in this paper, we study the effect on the value of similarity using either the electron density or the density difference function in the expression of the Carbó index and we consider two ways to align the molecules under consideration, namely, the backbone alignment and the topo-geometrical superposition approach (TGSA) (vide infra).

2. Theory and Computational Details

2.1. Similarity Indices. Molecular quantum similarity was introduced by Carbó.[3,22] He defined the Euclidean distance, ϵ_{AB}, between the electron densities, $\rho_A(\mathbf{r})$ and $\rho_B(\mathbf{r})$, of two molecules A and B as

$$\epsilon_{AB} = \int |\rho_A(\mathbf{r}) - \rho_B(\mathbf{r})|^2 \, d\mathbf{r} = \int \rho_A{}^2(\mathbf{r}) \, d\mathbf{r} + \int \rho_B{}^2(\mathbf{r}) \, d\mathbf{r} - 2\int \rho_A(\mathbf{r}) \, \rho_B(\mathbf{r}) \, d\mathbf{r} \quad (1)$$

Clearly, the more similar the two density functions are, the smaller ϵ_{AB}. Alternatively, a similarity index can be used, having a value bound between 0 and 1. The Carbó index is such a generalized cosine, given as

$$R_{AB} = \frac{\int \rho_A(\mathbf{r}) \, \rho_B(\mathbf{r}) \, d\mathbf{r}}{[(\int \rho_A{}^2(\mathbf{r}) \, d\mathbf{r})(\int \rho_B{}^2(\mathbf{r}) \, d\mathbf{r})]^{1/2}} = \frac{Z_{AB}}{\sqrt{Z_{AA} Z_{BB}}} \quad (2)$$

Higher similarity then corresponds to a higher value of R_{AB}. In eq 2, Z_{AB} is the overlap integral over the density functions of quantum objects A and B, often called the molecular quantum similarity measure (MQSM). Z_{AA} and Z_{BB} are called the molecular quantum self-similarity measures (MQSSM) of molecules A and B. R_{AB} was shown[23] to measure only the "shape similarity", meaning that homothecy relationships between density functions do not alter the similarity.[24]

Hodgkin and Richards proposed the index H_{AB}:[25]

$$H_{AB} = \frac{2\int \rho_A(\mathbf{r}) \, \rho_B(\mathbf{r}) \, d\mathbf{r}}{\int \rho_A{}^2(\mathbf{r}) \, d\mathbf{r} + \int \rho_B{}^2(\mathbf{r}) \, d\mathbf{r}} = \frac{2Z_{AB}}{Z_{AA} + Z_{BB}} \quad (3)$$

This index describes both the similarity of shape and extent of the electron distributions.[23] The Carbó index and the Hodgkin–Richards index are only two of a large set of indices that have been used in QMS.[22]

2.1.1. Global Similarity Indices for Enantiomers. As already pointed out in ref 15, one can write for the *R* and *S* enantiomers of a chiral molecule the Carbó index as

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

and also for enantiomers

$$H_{RS} = R_{RS} \quad (5)$$

To eliminate the dominant effect of the core electrons in the MQS analyses, one can also use the density difference, $\Delta\rho(\mathbf{r})$, instead of the global densities, $\rho(\mathbf{r})$, of the two molecules under consideration, as was shown in ref 15.

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

$$\Delta\rho_R(\mathbf{r}) = \rho_R(\mathbf{r}) - \rho_R^0(\mathbf{r}) \quad (6)$$

with $\rho_R^0(\mathbf{r})$ being the promolecular density of the *R* enantiomer, yielding for the numerator of the Carbó index the following expression:

$$Z_{RS} = \int \Delta\rho_R(\mathbf{r}) \, \Delta\rho_S(\mathbf{r}) \, d\mathbf{r} = \int (\rho_R(\mathbf{r}) - \rho_R^0(\mathbf{r}))(\rho_S(\mathbf{r}) - \rho_S^0(\mathbf{r})) \, d\mathbf{r} \quad (7)$$

It is immediately realized that Z_{RS} could possibly become negative because density differences are not positive definite. This could result in ambiguities in the similarity indices, and as a consequence in the chirality coefficient. However, our applications never revealed such a case, allowing the further use of the density difference.

2.1.2. Local Similarity Indices for Enantiomers. We proposed in ref 15 a conversion of the global Carbó index into a local index using the Hirshfeld partioning.[18] In this partitioning, the electron density at a point in space is divided into different atomic contributions on the basis of the "stockholder ratio". To that end, a promolecular density is introduced, corresponding in every point to the sum of the isolated atomic densities for the molecular geometry as in the actual molecule. The stockholder ratio in every point then corresponds to the relative contribution of an atom with respect to the total promolecular density. In the same vein, one can suggest a Hirshfeld-like

partitioning for the similarity integral, where the numerator Z_{RS} of the Carbó index becomes

$$Z_{RS}^{\text{local},C} = \int w_{C,R+S}\rho_R(\mathbf{r})\,\rho_S(\mathbf{r})\,d\mathbf{r} = \int \left(\frac{\rho_{C,R}^0(\mathbf{r}) + \rho_{C,S}^0(\mathbf{r})}{\sum_X \rho_{X,R}^0(\mathbf{r}) + \sum_Y \rho_{Y,S}^0(\mathbf{r})} \right) \rho_R(\mathbf{r})\,\rho_S(\mathbf{r})\,d\mathbf{r} \quad (8)$$

In the case of enantiomers, a strict one-to-one correlation can be drawn between every atom in *R* and an atom in the *S* enantiomer. For every atom, a $Z_{RS}^{\text{local},C}$ value can be defined, and the global similarity between both enantiomers again corresponds to the global MQSM, as required in the Hirshfeld approach. As a consequence, formula 8 corresponds to a possible definition of an atom condensed MQSM.

The self-similarities Z_{RR} and Z_{SS} can be written analogously in terms of atomic contributions:

$$Z_{RR}^{\text{local},C} = \int w_{C,R+R}\rho_R(\mathbf{r})\,\rho_R(\mathbf{r})\,d\mathbf{r} = \int \left(\frac{\rho_{C,R}^0(\mathbf{r}) + \rho_{C,R}^0(\mathbf{r})}{\sum_X \rho_{X,R}^0(\mathbf{r}) + \sum_X \rho_{X,R}^0(\mathbf{r})} \right) \rho_R(\mathbf{r})\,\rho_R(\mathbf{r})\,d\mathbf{r} = \int \left(\frac{\rho_{C,R}^0(\mathbf{r})}{\sum_X \rho_{X,R}^0(\mathbf{r})} \right) \rho_R(\mathbf{r})\,\rho_R(\mathbf{r})\,d\mathbf{r} \quad (9)$$

and the analogous expression for the *S* enantiomer.

Using eqs 8 and 9 in the expression of the Carbó index (eq 2), the global index is converted into a local analogue:

$$R_{RS}^{\text{local},C} = \frac{\int \left(\frac{\rho_{C,R}^0(\mathbf{r}) + \rho_{C,S}^0(\mathbf{r})}{\sum_X \rho_{X,R}^0(\mathbf{r}) + \sum_Y \rho_{Y,S}^0(\mathbf{r})} \right) \rho_R(\mathbf{r})\,\rho_S(\mathbf{r})\,d\mathbf{r}}{\left\{ \int \left(\frac{\rho_{C,R}^0(\mathbf{r})}{\sum_X \rho_{X,R}^0(\mathbf{r})} \right) \rho_R(\mathbf{r})\,\rho_R(\mathbf{r})\,d\mathbf{r} \right\}^{1/2} \left\{ \int \left(\frac{\rho_{C,S}^0(\mathbf{r})}{\sum_Y \rho_{Y,S}^0(\mathbf{r})} \right) \rho_S(\mathbf{r})\,\rho_S(\mathbf{r})\,d\mathbf{r} \right\}^{1/2}} \quad (10)$$

2.1.3. Global Similarity Indices for Series of Conformers of Enantiomers. In this work, we want to evaluate the molecular similarity of a set of conformers of the *R* enantiomer of a molecule with respect to the corresponding conformers of the *S* enantiomer of this molecule. We therefore use a Boltzmann weighted similarity index.

We denote the fraction of the conformers, p_i, with energy E_i above the energy of the lowest conformer as

$$p_i = \frac{n_i}{N} = \frac{e^{-E_i/kT}}{\sum_i e^{-E_i/kT}} \quad (11)$$

with *T* being the thermodynamic temperature and *k* the Boltzmann constant.

Using these fractions of the p_i, we can write the following expression for a Boltzmann weighted similarity index, ⟨SI⟩:

$$\langle \text{SI} \rangle = \sum_i (\text{SI})_i p_i = \frac{\sum_i (\text{SI})_i e^{-E_i/kT}}{\sum_i e^{-E_i/kT}} \quad (12)$$

describing the similarity of a set of conformers of a chiral molecule with respect to the corresponding conformers of its enantiomer and where for each conformer *i* the weight of the similarity index, $(\text{SI})_i$ (eq 2 or eq 10), contributes to the index, ⟨SI⟩, depending on the energy, E_i, of the conformer.

Analogously, one can, for a series of conformers belonging to one amino acid, write a Boltzmann weighted optical activity, $[\alpha]_D$, as

$$\langle [\alpha]_D \rangle = \sum_i ([\alpha]_D)_i p_i = \frac{\sum_i ([\alpha]_D)_i e^{-E_i/kT}}{\sum_i e^{-E_i/kT}} \quad (13)$$

2.2. Alignment of the Enantiomers. Several methods have already been proposed to establish a criterion on how molecules might be superposed in order to deal with the drawback of similarity indices, namely, their dependence on the relative orientation of the molecules under consideration. One of them is a procedure called the topo-geometrical superposition algorithm (TGSA)[26] based on comparisons of atom types and interatomic distances. Next to using this TGSA, we superimpose in this work the enantiomers by superimposing the asymmetric carbon atom and two of its directly bonded atoms. In the case of amino acids, the chiral carbon atom, the nitrogen, and the carbon of the carboxyl group were superimposed in this backbone alignment. This choice enables us—as opposed to the TGSA—to evaluate, next to global similarity, local similarity using the local similarity index (eq 10), to further investigate in a quantitative way the holographic electron density theorem for a large series of homologous molecules.

2.3. Computational Details. All charge densities used in this work were calculated using the Gaussian 03[27] program at the B3LYP/6-31G* level.[28,29] The conformers of the enantiomers were obtained using Spartan[30] and the Merck molecular modeling force field (MMFF).[31] At the same time, conformers were generated performing a stochastic search.[32]

To reduce the computational cost of the calculations incorporating all the sets of conformers of the amino acids (for the exact number of conformers belonging to each amino acid, we refer to section 3), the amino acids were considered only in their "neutral form", that is, with −COOH and $-NH_2$ termini, with their zwitterionic forms being left out of consideration. Therefore, we can already mention now that the comparison of the calculated optical activities, $[\alpha]_D$, with the experimental values measured in aqueous solution must be interpreted with caution.

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

TABLE 1: Boltzmann Weighted Global Similarity Index Using Total Densities and the Density Difference Function for Ala, Asp, Cys, Leu, Ser, and Val[a]

Using Total Densities		
	BB	TGSA
Ala	0.3908	0.6930
Asp	0.2408	0.4445
Cys	0.1072	0.1843
Leu	0.3075	0.3419
Ser	0.3050	0.5715
Val	0.3219	0.4485
Using the Density Difference Function		
	BB	TGSA
Ala	0.4633	0.5121
Asp	0.3178	0.4206
Cys	0.3953	0.4468
Leu	0.3407	0.4304
Ser	0.3521	0.4388
Val	0.3242	0.5889

[a] The alignment method (BB or TGSA) is indicated.

TABLE 2: Boltzmann Weighted Local Similarity Index for a Given Atom Type Using Total Densities and the Density Difference Function for Ala, Asp, Cys, Leu, Ser, and Val (Backbone (BB) Alignment)

Using Total Densities		
	C*	N
Ala	0.998 79	0.999 58
Asp	0.998 71	0.999 40
Cys	0.998 73	0.999 36
Leu	0.998 81	0.999 55
Ser	0.998 75	0.999 34
Val	0.998 74	0.999 45
Using the Density Difference Function		
	C*	N
Ala	0.921 10	0.764 92
Asp	0.906 60	0.669 02
Cys	0.914 16	0.640 45
Leu	0.923 23	0.752 44
Ser	0.927 78	0.628 87
Val	0.912 57	0.703 15

(GIAOs)[33] in the gas phase or in water using the polarizable continuum model (PCM).[34−36]

We used a highly efficient analytical implementation of the necessary integrals of the similarity indices by using the BRABO program package developed by Van Alsenoy et al.[37,38] and the program Artesimi.[39] The local index based on the Hirshfeld partitioning is implemented numerically in the program STOCK, part of the BRABO package mentioned earlier.

3. Results and Discussion

Where in ref 19 the conformers of the enantiomers of only two amino acids, alanine and serine were examined, in this paper, a series of amino acids, that is, homologous chiral molecules—alanine, asparagine, cysteine, leucine, serine, and valine—is considered.

These amino acids are chiral structures containing just one single asymmetric center but, as opposed to the CHFClBr case study presented in ref 15, show conformational flexibility. We therefore want to evaluate the (dis)similarity of the conformers of the *R* enantiomer with respect to the conformers of the *S* enantiomer of the amino acid under consideration.

The conformers of the amino acids alanine, asparagine, cysteine, leucine, serine, and valine, generated by the two methods described in section 2.3, were compared and followed by frequency calculations in order to confirm that all structures were local minima. Finally, a set of conformers was selected within an energy domain of 10 kcal mol^{-1} (yielding a Boltzmann factor of $e^{-E/kT} = 3.5 \times 10^{-8}$) above the lowest energy conformer, generating 9 conformers for alanine, 64 conformers for asparagine, 51 conformers for cysteine, 66 conformers for serine, and 21 conformers for valine.

3.1. Global Similarity. Looking at the top and bottom sections of Table 1, using total densities and the density difference function, respectively, we see that the TGSA alignment generates the highest similarity values. This could be expected, as the TGSA searches for the maximal topological overlap between the conformers. The backbone alignment generates—compared to the results obtained via the TGSA—the lowest similarity values, intuitively acceptable as this is one of the arbitrary alignments possible for amino acids, as also found in ref 19.

Comparing the similarity values between the top and bottom sections of Table 1 for the backbone alignment using total densities and density differences, respectively, the indices using the latter densities are yielding higher values of similarity. However, for the TGSA, no specific trend can be recognized now.

The fact that density differences are giving different and complementary information about the similarity of the systems has already been shown in refs 15 and 19.

3.2. Local Similarity. In the top and bottom sections of Table 2, the results for the Boltzmann weighted local similarity are given using total densities and density difference functions, respectively, considering the region around the chiral carbon atom and the nitrogen atom for the backbone alignment, where these two atoms are superimposed with the corresponding ones of their enantiomers.

From these results, it is seen that now the indices using total densities yield higher values of similarity indices as those using density difference functions. This points out that using density differences in the expressions of the indices, instead of using global densities, gives different and complementary information about the similarity of the systems because here the identical dominant contribution of the core electrons is eliminated. This indeed has already been shown in earlier work.[15,19]

Furthermore, it is remarkable that the local similarity indices are different from 1 for both the chiral carbon and for the originally nonchiral nitrogen atoms, with the deviation giving a good indication of the consequences of Mezey's holographic electron density theorem, which is stating that each region of a molecule contains the information about the whole system, in this case, about chirality.

In particular, comparing the values for the Boltzmann weighted similarity index using the density difference function (backbone alignment) in the bottom section of Table 1 with its local counterpart in the bottom section of Table 2, no trend can be found. The deviation from 1 for the local indices around the nitrogen atom indeed indicates that information about the asymmetry of a system, and thus chirality, can be found on other atomic centers in the system, in this case the nitrogen atom, and that not only the chiral centers carry information about chirality.

These results are in agreement with those from our previous work,[15,19] where the local asymmetry was quantified around the hydrogen atom directly bonded on the asymmetric carbon atom of the prototype chiral molecule CHFClBr and the amino acids Ala, Leu, and Ser.

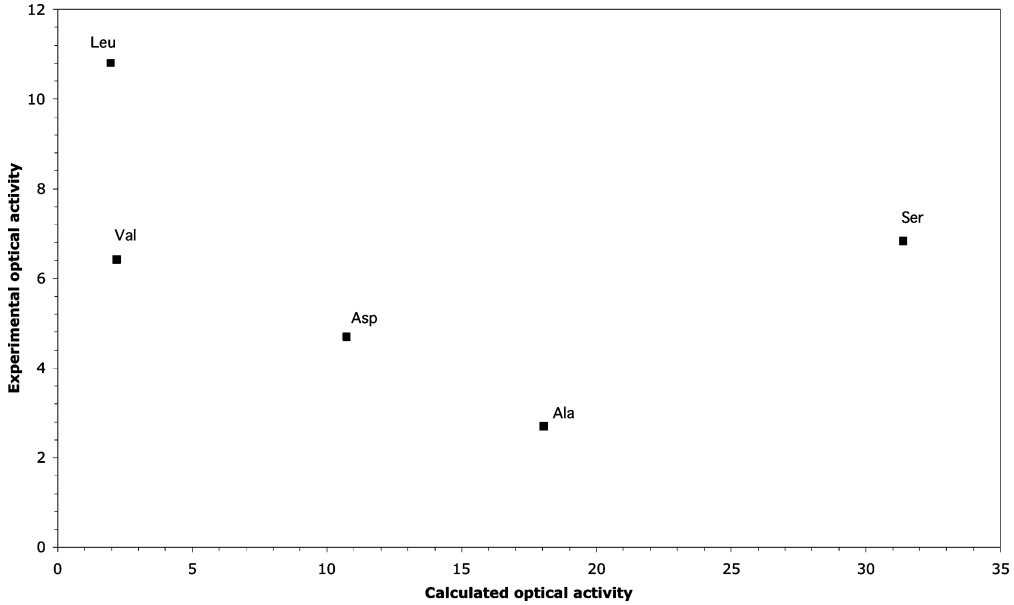

Figure 1. Experimental vs calculated optical activities for the series of amino acids.

For all amino acids using total densities, the highest similarity values (thus the smallest dissimilarity) are obtained for the region around the nitrogen atom, whereas, using density differences, this is the case for the region around the chiral carbon atom (showing the lowest dissimilarity now). This means that the nitrogen atom is asymmetric even though according to the textbook rules (cf. four different substituents) this should not be the case, in agreement with the preliminary results in ref 19.

Closer inspection shows that these effects are prominent in some conformers where an asymmetric environment is created due to H-bonding involving the N-atom. This conformational induction of asymmetry on a previously symmetric center was already pointed out by one of the present authors[40] in the case of possible chirality of tetrahedral carbon atoms with two substituents of identical constitution, for example, the α-carbon of glycine in the helical form of the dipeptide *N*-acetyl-*N*′-methylglycylamide.

This effect superimposes on the one seen in ref 15 for CHFClBr where a conformationally independent phenomenon of propagation of chirality away from an asymmetric center was found (e.g., on the H-atom and the Br-atom) in accordance with the holographic electron density theorem. The latter effect is expected to fade upon increasing distance from the asymmetric center, whereas the conformationally induced effect may, on the contrary, show importance for centers situated at larger distances from the asymmetric atom.

Anyhow, as for all conformers—also those in which the above-mentioned conformational effect might be expected to be nonexistent—the similarity index at the N-atom was smaller than 1.

3.3. Relationship between the Dissimilarity and the Optical Activity of L- and D-Amino Acids. The link between the dissimilarity and the optical activity was advocated by Mezey[20] and discussed in our previous work.[15,19] As mentioned in the Introduction, Mezey et al. has presented results in ref 21, which suggest a positive correlation between optical activity and dissimilarity, the latter not only at the asymmetric carbon.

Chiral molecules showing high absolute values of optical activity are expected to be very dissimilar, thus yielding low values of similarity indices and vice versa.

TABLE 3: Optical Activity of Amino Acids[a]

	A	B	C
Ala	16.54	18.06	2.7
Asp	3.63	10.73	4.7
Cys	33.20	30.01	–
Leu	1.98	1.98	10.8
Ser	28.21	31.38	6.8
Val	2.20	2.20	6.4

[a] Column A: absolute values of Boltzmann weighted $[\alpha]_D$ calculated in the gas phase. Column B: absolute values of Boltzmann weighted $[\alpha]_D$ calculated with the PCM (aqueous solvent). Column C: measured experimentally $[\alpha]_D$ at the sodium D-line in water.

In ref 19, the Boltzmann weighted similarity index proved to be a convenient and practical tool to study this link in a more fundamental level, both globally and locally.

As already pinpointed in section 2.3, indeed, no specific correlation can be found between the values of the calculated optical activities, $[\alpha]_D$, and the experimental values measured in aqueous solution (Figure 1), which could be expected, since, for the calculated values, the neutral forms of the amino acids were considered, whereas, measuring the experimental optical activities in aqueous solution, the amino acids are essentially present in their zwitterionic forms or in ionized forms.

Table 3 gives the absolute values of the Boltzmann weighted optical activity, $[\alpha]_D$, calculated in the gas phase, calculated with the PCM and $[\alpha]_D$ measured experimentally at the sodium D-line. A good correlation ($r^2 = 0.9383$) can be found between the Boltzmann weighted optical activities calculated in the gas phase versus those calculated with PCM, whereas no trend can be seen between the calculated optical activities and the one measured experimentally, although using the same methodology on series of substituted allenes this latter evaluation gave a good correlation.[41] The reason no trend can be found here can be due to the reason stated above.

Taking a look at Figure 2 (backbone alignment), giving the global Boltzmann weighted similarity index using total densities versus the optical activity calculated in the gas phase, prudence is called for when stating that amino acids with higher similarity—thus low dissimilarity—between their enantiomers yield lower $[\alpha]_D$ values, as intuitively expected. The same caution has to be taken into account when evaluating the global

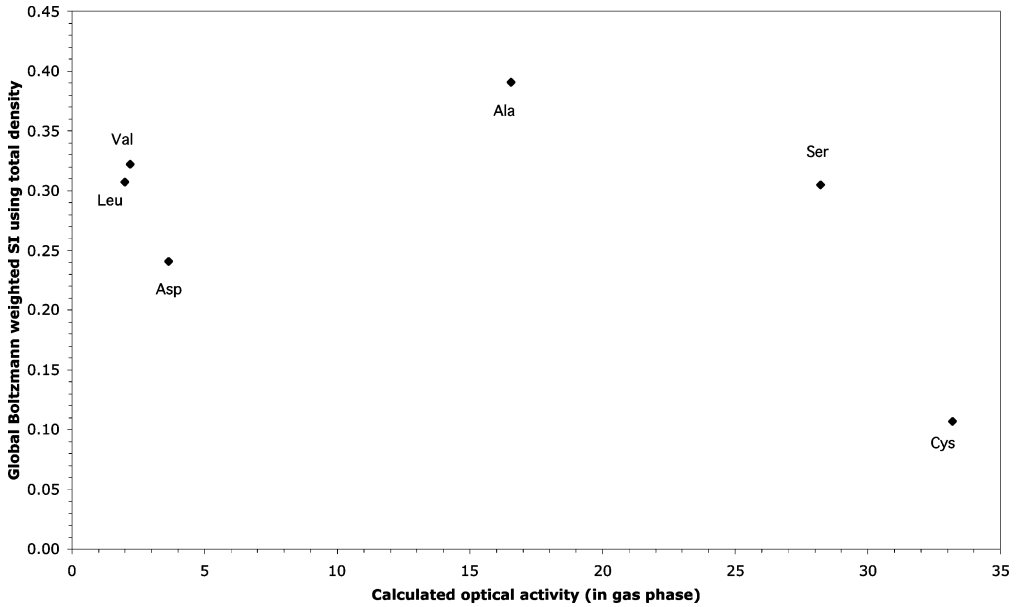

Figure 2. Backbone alignment: global Boltzmann weighted SI using the total density vs calculated optical activity (in the gas phase).

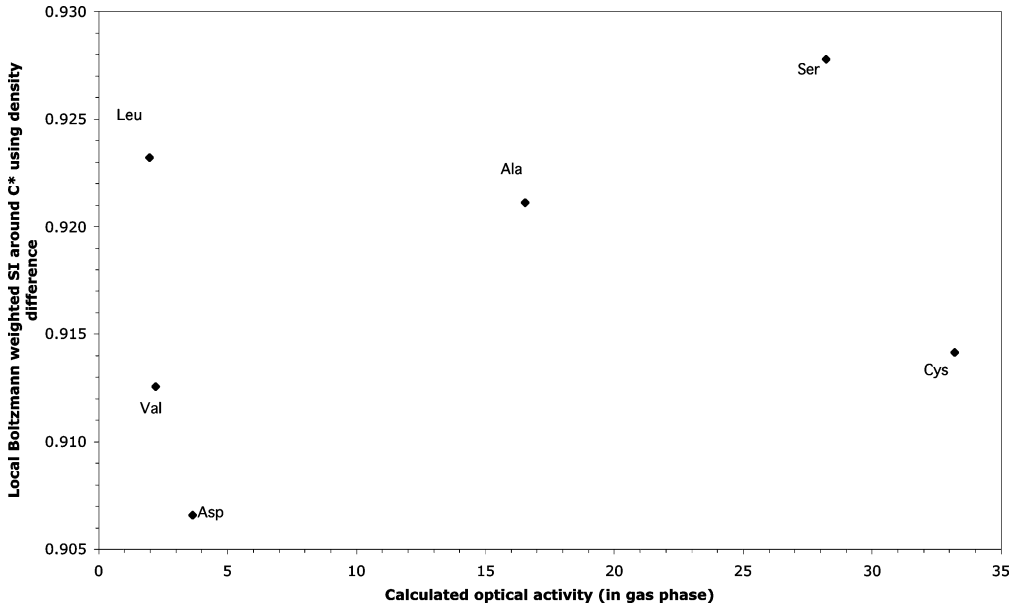

Figure 3. Local Boltzmann weighted SI around C* using the density difference function vs calculated optical activity (in the gas phase).

Boltzmann weighted similarity index using total densities versus the optical activity calculated incorporating the PCM and the experimentally yielded $[\alpha]_D$, respectively.

Using the density difference function, also, no specific trends are shown between dissimilarity and the optical activity calculated in the gas phase, the one calculated incorporating the PCM, and the experimentally measured optical rotatory power.

The same prudence is in order for the similarity results using the TGSA alignment using both total densities and density difference functions.

Analogous to Figure 2, we plotted (for the backbone alignment) the local Boltzmann weighted similarity index using total densities/density difference functions around the chiral carbon atom and the originally nonchiral nitrogen atom versus the optical activities, $[\alpha]_D$, calculated in the gas phase, incorporating the PCM and the experimental $[\alpha]_D$. Figure 3 is shown as an example of such a plot of the local Boltzmann weighted similarity index around the chiral carbon atom using the density difference function versus the calculated optical activity in the gas phase.

From all of these results, we see that no specific trend between dissimilarity and optical activity is shown for local similarity around the carbon atom or around the nitrogen atom.

4. Conclusions

Molecular quantum similarity was evaluated for enantiomers in the case of molecules showing conformational flexibility, using our earlier proposed Boltzmann weighted similarity index. The conformers of the enantiomers of the amino acids alanine, asparagine, cysteine, leucine, serine, and valine were examined.

For a given conformer, the highest values of global similarity indices are generated using the TGSA alignment procedure which could be expected as the TGSA searches for the maximal topological overlap between the conformers.

Furthermore, the results show the complementary information obtained by studying global and local (dis)similarity using both the electron density function and density differences.

The local approach of studying similarity reveals a conformationally dependent induction of asymmetry on an originally symmetric center, an effect which can be important even for centers situated at large distances from the chiral center. This effect superimposes previous numerical evidence we proposed for a conformationally independent phenomenon of propagation of chirality away from the asymmetric center in accordance with the *holographic electron density theorem*. For conformers where the conformationally dependent effect might not be expected to exist, the results in this paper show further numerical support of this theorem.

From the results of the series of amino acids under consideration, it is also shown that prudence is called for in stating that a positive correlation exists between the dissimilarity—both global and local—between the corresponding conformers of two enantiomers with their optical activity.

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