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Two-point contact chiral distinction—a theoretical appraisal†

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***Ab initio* calculations reveal chiral distinction in two-point contact CHFClBr dimers, with chiral distinction energy of 1.5 kJ mol^{-1} between the *SR* and *SS* dimers fully optimized at the MP2/6-311++G** level.**

Chiral molecules are pervasive in the Universe.[1] They are of fundamental interest in all fields of chemistry and have received much attention in areas such as pharmaceuticals where properties related to their chiral nature can have profound impact.[2] While indistinguishable in achiral environments, the enantiomers of a chiral molecule may have different properties in chiral environments.[3] Discussions on the mechanism of chiral distinction[4] in different systems have considered from one to four points on each of the interacting molecules.[5–7] This has resulted in an apparent ambiguity in understanding the geometric basis for chiral distinction.[6] We have previously underscored[7] the distinction between contact points and interactions (points) in an effort to establish a framework for elucidating chiral distinction principles. The basic requirements of defining a chiral object dictate that a minimum of four points on each molecule are involved in the interactions required for chiral distinction in three-dimensional space.[7] However, contact points may be defined on a chemically intuitive basis, as the sources of primary interaction between the molecules. An important distinction is that the actual assignment of the contact points in a given system is generally subjective, whereas the interactions are rooted in physical principles.[7c] As an illustrative case, one may consider the interaction between a pair of pyramidal objects: in spite of the fact that the four vertices of each pyramid are involved in chiral distinction, the proximal contact may be vertex-vertex (1–1), vertex–edge (1–2), edge–edge (2–2), edge–face (2–3) *etc*. Complexes of chiral molecules are often described in terms which are tantamount to the present definition of contact points, but are discussed in the sense of interactions. Recently a hetero-chiral dimer of butan-2-ol has been identified by microwave spectroscopy and analyzed on the basis of *ab initio* computations.[8] We have used the classical prototype of a chiral molecule, CHFClBr,[9] to address the basic issue of contact points and chiral distinction. We present results of *ab initio* computations on a dimer in an edge–edge orientation which unambiguously illustrates chiral distinction even at this near minimal two-point contact!

We have first carried out full geometry optimization of CHFClBr at the Hartree–Fock level using a variety of basis sets.[10] Full geometry optimization was done at the MP2/6-311++G** level as well. Computations at the various levels showed that the H atom possesses a strong positive charge whereas the F atom possesses the strongest negative charge.† This prompted us to consider a two-point contact model for the CHFClBr dimer involving two H···F interactions.

Full geometry optimization was carried out on the *SR* and *SS* dimers at the HF level using the different basis sets as before.† Frequency calculations confirmed that the optimized geometries were genuine energy minima. MP2 energies of these geometries were computed followed by full geometry optimization at the MP2/6-311++G** level (Fig. 1). In the latter case however, a frequency calculation could not be performed due to the prohibitively large computer time needed. The optimized *SR* dimer has C_i symmetry at all levels of calculation. The *SS* dimer generally has C_1 symmetry, but becomes nearly C_2 symmetric with higher basis sets. Each dimer has two close H···F primary interactions, 248.5 pm in *SR* and 240.1 pm in *SS*, considerably shorter than the sum of the van der Waals radii, 255 pm.[11] The C···F distances, 299.9 pm in *SR* and 309.0 pm in *SS*, are also less than the sum of the van der Waals radii, 311 pm. All other intermolecular atom–atom contacts are greater than the respective sum of the van der Waals radii. We define the stabilization energy for the *SR* and *SS* dimers as :

$$\Delta E_{SR} = E_{SR} - E_{\mathrm{S}} - E_{\mathrm{R}}\ ;\ \Delta E_{SS} = E_{SS} - 2E_{S} \qquad (1)$$

The systems studied here lead to appreciable basis set superposition error (BSSE). The stabilization energy corrected for the BSSE using the counterpoise correction method is :

$$\begin{aligned}\Delta E_{SR}{}^{\mathrm{CC}} &= E_{SR} - E_{(S)R} - E_{S(R)};\\ \Delta E_{SS}{}^{\mathrm{CC}} &= E_{SS} - E_{(S)S} - E_{S(S)}\end{aligned} \qquad (2)$$

In eqns. (1) and (2), *R*, *S* stand for the atoms (nuclei, electrons and basis functions) of the corresponding enantiomers and (*R*), (*S*) for the ghost basis functions of the enantiomers used in the counterpoise correction calculations. Table 1 provides the stabilization energies of the dimers.

The counterpoise correction reduces the dimerization energies. Indeed, the magnitude of the counterpoise correction can even exceed the dimerization energy as in the case of the 6-31G** calculation of the *SS* dimer. In all cases except the

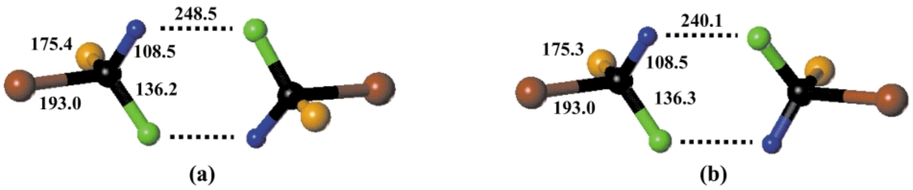

Fig. 1 MP2/6-311++G** optimized geometries of the (a) *SR* (C_i symmetry) and (b) *SS* (near C_2 symmetry) CHFClBr dimers. The atoms are colored, C; black, H; blue, F; green, Cl; orange and Br; brown; the H···F contacts are shown by broken lines; significant distances in pm are indicated.

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† Electronic supplementary information (ESI) available: atomic charges on CHFClBr and energies of the monomer and *SR* and *SS* dimers calculated at various levels and typical optimized geometries. See http://www.rsc.org/suppdata/cc/b2/b205346b/

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Table 1 Stabilization energies (kJ mol^{-1}) of *SR* and *SS* dimers without and with counterpoise correction for BSSE

	HF				MP2 at HF optimized geometry [at MP2 optimized geometry]			
	ΔE		ΔE^{CC}		ΔE		ΔE^{CC}	
Basis set	*SR*	*SS*	*SR*	*SS*	*SR*	*SS*	*SR*	*SS*
6-31G**	−9.565	−14.276	−2.707	+2.042	−18.004	−27.702	−5.853	−5.694
6-311G**	−9.757	−9.590	−4.046	−4.067	−16.623	−16.393	−6.033	−6.100
6-31++G**	−25.280	−24.510	−1.322	−2.155	−38.786	−37.823	−7.058	−7.924
6-311++G**	−8.134	−7.979	−4.958	−4.966	−18.159 [−20.631]	−18.012 [−20.079]	−7.410 [−6.017]	−7.368 [−7.485]

above one, the dimerization is found to be stabilizing. The stabilization may be attributed to the two strong H···F interactions present in these structures.

The chiral distinction energy for the dimers may be defined without and with counterpoise correction for BSSE:

$$\Delta\Delta E_{(SR-SS)} = \Delta E_{SR} - \Delta E_{SS};\quad \Delta\Delta E_{(SR-SS)}{}^{CC} = \Delta E_{SR}{}^{CC} - \Delta E_{SS}{}^{CC} \tag{3}$$

It is seen from Table 2 that for most of the cases considered, the counterpoise correction reverses the sign of $\Delta\Delta E$ suggesting that the prediction of the more stable dimer between the *SR* and *SS* is sensitive to the methodology. Thus the counterpoise correction affects both the sign and magnitude of the predicted chiral distinction energy. The contribution of the counterpoise correction to the chiral distinction energy always exceeds the corrected value and generally exceeds the uncorrected value in magnitude and may be even twice as large, as in the cases of the HF/6-31G** and HF/6-31++G** calculations. The variation in the counterpoise corrected results for different basis sets is larger at the HF level than at the MP2 level. Nevertheless, the variations from one basis set to the other generally parallel each other at both the levels. The only exception is at the 6-311++G** level, where the corrected chiral distinction energies are nearly zero. The MP2 level geometry optimization was carried out only with the highest basis set used in this study (6-311++G**); it led to a chiral distinction energy of 1.5 kJ mol^{-1} after counterpoise correction. Comparison to the same calculation using the HF optimized geometry (−0.04 kJ mol^{-1}) shows that the effect of the geometry can also be large enough to affect both the sign and magnitude of the chiral distinction energy.

The present computational investigation illustrates clearly that the basic tenet of chiral distinction is exhibited in a two-point contact model at the various computational levels employed. The quantitative and qualitative results are sensitive to the basis set, geometry and the level of computation used. At the most accurate level studied, MP2/6-311++G**, the chiral distinction is less than 1 kcal mol^{-1}. Nevertheless, these dimers with two-point contact orientations, which emphasize the attractive electrostatic interactions between the H and F atoms, reveal the impact of chiral distinction exerted through the remote influence of the Cl and Br atoms. We emphasize that the results presented herein do not attempt to predict the more stable of the two (*SS* and *SR*) complexes. The variations in sign and magnitude of the energy differences obtained clearly indicate that such a prediction is beyond the scope of this study. Rather, the objective is to show the intrinsic energetic inequivalence between the two complexes, even for a two-point contact arrangement. The results presented are therefore computational models to test this contention. Moreover, even in the present two-point contact example, with each of the computational methods presented, there is no observed cancellation of terms leading to an equivalence in the interaction energies of the *SS* and *SR* dimers.

Table 2 Chiral distinction energies (kJ mol^{-1}) without and with counterpoise correction for BSSE

	HF		MP2 at HF [MP2] optimized geometry	
Basis set	$\Delta\Delta E$	$\Delta\Delta E^{CC}$	$\Delta\Delta E$	$\Delta\Delta E^{CC}$
6-31G**	+4.711	−4.749	+9.703	−0.159
6-311G**	−0.172	+0.021	−0.234	+0.067
6-31++G**	−0.766	+0.828	−0.962	+0.866
6-311++G**	−0.155	+0.008	−0.146 [−0.552]	−0.042 [+1.469]

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