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Effect of fluoro substituents and central atom nature on chiral derivatives of bisdiphenylborates and isoelectronic structures

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Abstract—A DFT study of the geometrical, electronic, and energetic parameters of homo- and heterochiral complexes of fluoro derivatives of diphenylborate and isoelectronic structures where the central atom has been substituted by carbon and nitrogen has been carried out. The results have allowed correlation of the relative energies (hetero- minus homochiral complex) versus the presence of fluorine in the different positions on the aromatic rings and the presence of different central atoms. Other correlations between geometrical parameters and the relative energy have also been found. Some of the predictions have been confirmed with the calculation of new derivatives.
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1. Introduction

Although intimately related, the cases of chiral recognition (a chiral molecule A discriminates between the two chiral forms, *R* or *S*, of a molecule B) and chiral self-recognition (two enantiomers of the same molecule A) should be distinguished. When discussing chiral recognition and chiral self-recognition, it is useful to consider two aspects: the quantitative and the qualitative. The first refers to the magnitude and the second to the sign (in the general case, which enantiomer of B, the *R* or the *S* is preferred, and in self-recognition, which of the homo- or the heterodimer is most stable).

This bimodal logic could be avoided by considering only three states (Scheme 1, note that the interaction being diastereomeric, the difference in energy, E_{rel}, can be very

Large and positive
Small
Large and negative

Scheme 1.

weak but not null). It is easier to discuss the problem in two parts by means of Scheme 1.

1.1. Magnitude (large vs small)

The magnitude of E_{rel} depends on:

(1) The proximity of the two moieties. It is obvious that moving away the two halves of the complex will decrease the chiral discrimination, which will tend asymptotically to 0 at infinite distance.
(2) The degree of chirality of each moiety. It is evident that a methyl group (–CHDT) will be less efficient in inducing recognition than, for instance, a substituent with heteroatoms. The problem of quantifying chirality has been examined by different authors.[1]
(3) The rigidity of the complex. This aspect is not relevant in calculations since the minimum is rigid by definition (experimentally, this is related to the number, 1, 2 or 3, of contacts—usually hydrogen bonds—linking the chiral molecules).

### 1.2. Sign (positive vs negative)

To simplify the problem, let us consider the case of self-recognition (homo- vs heterochiral) and ask ourselves why is it so difficult to predict (or explain) the sign of the interaction? The stability of the complex is the sum of a series of terms relating both moieties: steric, electronic, and orbital effects. These effects are transmitted

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either through space or through bonds (covalent as well as hydrogen bonds or metal bonds).

1.3. Phase effects

All this is true only for the gas phase. In condensed phases, the problem has one additional dimension: the environment. In solution, the polarity of the solvent should favor the more polar complex that in many self-recognition complexes corresponds to the *RR* one since there is an inversion center in the *RS* complex and thus is devoid of dipole moment. This problem has been studied in the hydrogen-bonded complexes of the R–OOH (R = H and CH$_3$) dimers[2] and in the self-recognition of α-aminoalcohols.[3] For specific solvent effects, like HBs between the complex and the solvent, it is expected that the relative energy ($E_{rel} = E_{RS} - E_{RR}$) will be modified in a more complex way, either increased or decreased.

We have devoted some effort to the study of these matters,[3–8] and we herein report the results obtained with a series of compounds with the aim of understanding the effect of the distance on the sign and magnitude of the self-recognition effect. We have selected three isoelectronic systems represented below (Y = O). It should be noted that the biphenyl structure possesses axial chirality. The fluorine substituents are present four times in the complexes, thus 3-F is the 3,3′,3″,3‴-tetrafluoro derivative.

X = B$^-$, C, N$^+$
Y = O, CH$_2$
For **Y** = O, **X** = B$^-$ (**1-7**), C (**8-14**), N$^+$ (**15-21**)
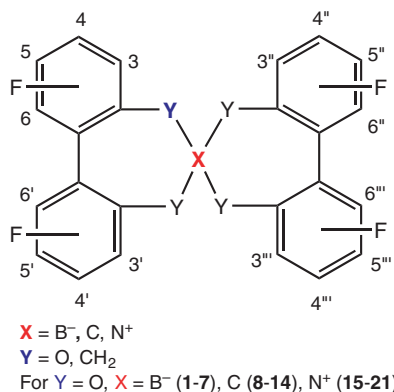
Amongst these compounds, the most studied are the borates (X = B$^-$, Y = O). For instance, the unsubstituted compound **1**, bis[(1,1′-biphenyl)-2,2′-diolate-O,O′]-borate or bis(2,2′-dihydroxydiphenyl) spiroborate, related to Meulenhoff's acid, has been reported many times in the literature.[9] The corresponding binaphthyl derivatives are important compounds, which have been used for the resolution of racemic binaphthol.[10] Although not studied in this work, the quaternary ammonium salts (X = N$^+$, Y = CH$_2$, also binaphthyl derivatives) are useful asymmetric transfer-phase catalysts.[11] Chiral boron derivatives, like **22**, have been described as bacterial quorum-sensing signals.[12] The nonbiphenyl spiro *ortho*-carbonates (X = C, Y = O, derivatives of methanetetrol) are compounds of industrial relevance,[13] but the

derivatives of tetrahydroxynitrogen(1^+) (X = N$^+$, Y = O) are unknown and only the parent compound, H$_4$NO$_4{}^+$, can be found in a theoretical study.[14]

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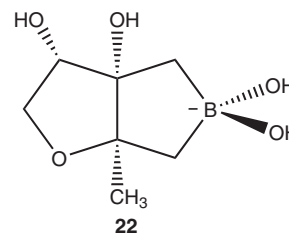
1.4. Methods

The complexes were optimized using the Gaussian-98 package[15] at the B3LYP/6-31G* computational level.[16,17] D_2 and S_4 symmetries have been assumed for all the homo- and heterochiral complexes, respectively. The minimum nature of the structures has been confirmed in all the cases by frequency calculations. The electron density was analyzed using the atoms in molecules methodology[18] and the AIMPAC package.[19]

2. Results and discussion

The relative energies of complexes are given in Table 1. Test calculations on the parent compounds with a larger basis set (B3LYP/6-311 + G**) showed similar results in the relative energies to those reported in Table 1 (1.15, −1.45 and −3.43 kcal/mol for X = B **1**, C **8**, and N **15**, respectively). The general trend of these values indicates

Table 1. Relative energy (kcal/mol) of the complexes calculated at the B3LYP/6-31G* computational level

Compound	X	Fluoro substitution[a]	E_{rel}[b]
1	B$^-$	—	0.45
2	B$^-$	3F	1.85
3	B$^-$	4F	0.29
4	B$^-$	5F	0.17
5	B$^-$	6F	0.30
6	B$^-$	3F6F	1.90
7	B$^-$	3F4F5F6F	1.68
8	C	—	−1.20
9	C	3F	0.49
10	C	4F	−1.28
11	C	5F	−1.61
12	C	6F	−1.62
13	C	3F6F	−0.07
14	C	3F4F5F6F	−0.39
15	N$^+$	—	−2.56
16	N$^+$	3F	−1.74
17	N$^+$	4F	−2.51
18	N$^+$	5F	−2.91
19	N$^+$	6F	−3.07
20	N$^+$	3F6F	−2.36
21	N$^+$	3F4F5F6F	−2.33

[a] All the aromatic rings are identically substituted and thus, for instance, 3F corresponds to the 3,3′,3″,3‴-tetrafluoro derivative.
[b] Positive values indicate that the homochiral complex is more stable than the heterochiral one.

that with boron, the homochiral complexes are more stable, while the opposite is true for the nitrogen containing ones and the ones with carbon represent a border case. It is significant that the same analysis can be carried out using the charge of the complexes.

Assuming that the effect of the central atom as well as the fluoro substitution in the different positions of the aromatic ring are additive, a presence/absence equation can be proposed to explain the relative energies. The coefficient of the 4F substitution is not significant and thus it has been removed from the equation. The fitted equation provides a square fitting coefficient (r^2) of 0.98, a standard deviation of 0.28 kcal/mol and the coefficients gathered in Table 2. This equation predicts the relative energy as a sum of the characteristics present on a given complex, for instance the relative energy of the complex with X = B$^-$ and fluorine atoms in position 3 **2**, (3F) is predicted to be 0.59 + 1.34 = 1.83 kcal/mol, which compares nicely to the DFT calculations (1.85 kcal/mol). These results indicate that the X = B$^-$ and the fluoro substitution in position 3 (3F) energetically favor the homochiral complex.

Table 2. Coefficients of a presence/absence equation to explain the E_{rel} (kcal/mol)

Parameter	Coefficient	Standard error
X = B$^-$	0.59	0.13
X = C	−1.18	0.13
X = N$^+$	−2.86	0.13
3F	1.34	0.14
5F	−0.26	0.14
6F	−0.32	0.14

The optimized geometries of the homo- and heterochiral complexes of **1** and **2** are shown in Figure 1 as representative of all the complexes studied herein. The disposition of the biphenyl moieties are approximately in parallel planes in the homochiral complexes while they are perpendicular in the heterochiral ones.

A selection of geometrical characteristics of the complexes studied is shown in Table 3. The X–O distances are longer in the complexes with X = B and shorter for X = C, being intermediate for X = N (in average the values are 1.471, 1.395, and 1.413 Å, respectively). These variations clearly show the effect of the charge on the complexes that reverse the expected bond length for X = C and N. In all the pairs studied here, the X–O distance is shorter for the heterochiral complex than the homochiral one. The differences increase when going from X = B$^-$ to C and then to N$^+$ and with the fluoro substitution, the largest difference being 0.012 Å for the perfluoro derivative of X = N$^+$, **21**.

A plot of E_{rel} versus Δd (d being the O–X distance in Å, $\Delta d = d_{homo} - d_{hetero}$) is reported in Figure 2. Graphically, two groups of compounds can be distinguished depending on the presence or absence of a F atom at the position 3 (i.e., 3,3′,3″,3‴; note in the preceding table, the 1.34 ± 0.14 effect of 3-F). Although the linear hypothesis is a good assumption, clearly each family of three points
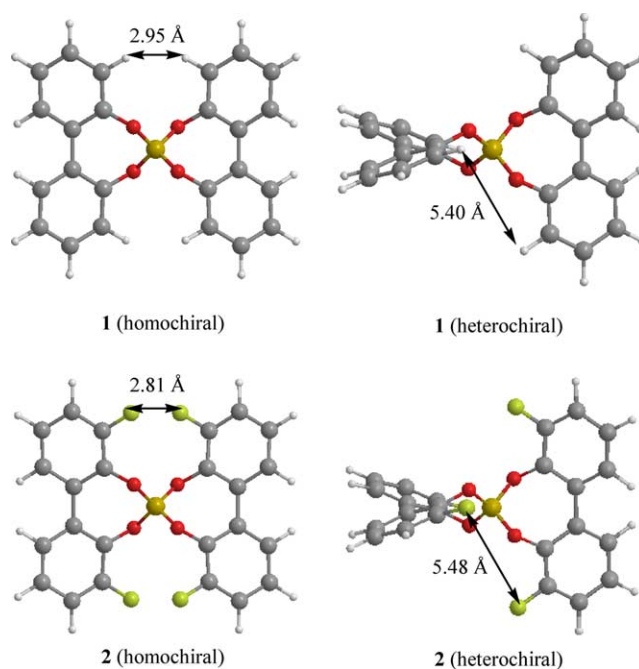
Figure 1. Optimized geometries (B3LYP/6-31G*) of the homo- and heterochiral complexes of **1** and **2**. The distance between the 3 and 3″ substituents are shown.

corresponds to an exponential decay. Adjusting them to equation $E_{rel} = a + b \ln(\Delta d)$, leads to $a = -9.1$, $b = -1.56$ ($n = 9$, $r^2 = 0.96$) for 3-F and to $a = -8.7$, $b = -1.22$ ($n = 9$, $r^2 = 0.98$) for 3-H (when $\Delta d = 1$, $E_{rel} = a$). This means that when the geometries of the homo- and heterochiral complexes, as defined by the Δd distance, are very similar the homochiral complex is the more stable. This stability increases considerably when there is a 3-F substituent in agreement with the linear regression shown previously. Then, the more different the geometries, the more stable the heterochiral complex, being dominant for all the ammonium complexes.

The C2C1C1′C2′ dihedral angle that defines the rotation of the biphenyl system decreases regularly from X = B$^-$ to N$^+$. In this case, the presence of fluorine atoms in position 6 (6F) produces an increment of this parameter between 2° and 3° when compared to the rest of the complexes of the same family as an indication of repulsive forces due to the presence of fluorine atoms at that position.

Several factors modulate the distance between the substituents in 3–3″ in the homochiral complexes: (i) the central atom plays the more important role, decreasing when going from the boron complexes the nitrogen ones independently if the substituent in these positions are hydrogen or fluorine atoms. (ii) The fluorine substitution at the 6 position produce a shortening of the 3–3″ distance in the three families studied. (iii) The substitution in position 3 produce a shortening of this distance in the case of the boron derivatives and a lengthening in the other two families. It seems as in the first case (X = B) the two fluorine atoms tend to form a

Table 3. Selection of the geometrical characteristic (Å and °) of the complexes studied calculated at the B3LYP/6-31G* computational level
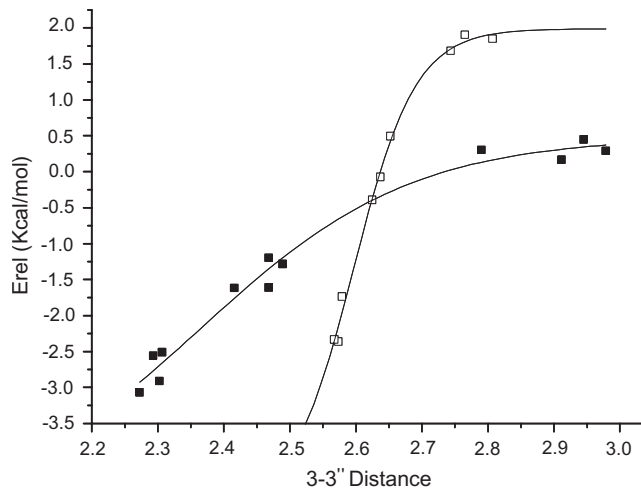
X	Fluoro substitution	X–O distance		C2C1C1'C2' angle		3–3'' Distance	
		Homo	Hetero	Homo	Hetero	Homo	Hetero
1 B⁻	—	1.4715	1.4710	40.4	40.1	2.945	5.401
2 B⁻	3F	1.4708	1.4702	40.5	40.2	2.807	5.484
3 B⁻	4F	1.4712	1.4705	40.8	40.6	2.979	5.441
4 B⁻	5F	1.4711	1.4706	40.0	39.8	2.912	5.383
5 B⁻	6F	1.4730	1.4724	43.7	43.4	2.790	5.347
6 B⁻	3F6F	1.4725	1.4716	43.8	43.5	2.765	5.433
7 B⁻	3F4F5F6F	1.4722	1.4710	43.6	43.4	2.744	5.439
8 C	—	1.3960	1.3934	38.0	37.8	2.468	5.140
9 C	3F	1.3964	1.3933	37.7	37.6	2.652	5.199
10 C	4F	1.3961	1.3933	38.1	38.1	2.489	5.179
11 C	5F	1.3962	1.3934	37.6	37.6	2.468	5.143
12 C	6F	1.3975	1.3945	40.8	40.3	2.416	5.114
13 C	3F6F	1.3980	1.3943	39.9	39.9	2.637	5.173
14 C	3F4F5F6F	1.3981	1.3943	40.1	39.5	2.625	5.187
15 N⁺	—	1.4119	1.4049	36.9	36.8	2.293	5.051
16 N⁺	3F	1.4181	1.4090	36.4	36.3	2.579	5.058
17 N⁺	4F	1.4121	1.4053	36.8	36.8	2.307	5.086
18 N⁺	5F	1.4153	1.4083	36.7	36.6	2.303	5.061
19 N⁺	6F	1.4143	1.4072	39.6	40.3	2.273	5.024
20 N⁺	3F6F	1.4211	1.4105	39.2	38.1	2.573	5.050
21 N⁺	3F4F5F6F	1.4256	1.4137	38.2	37.48	2.567	5.071
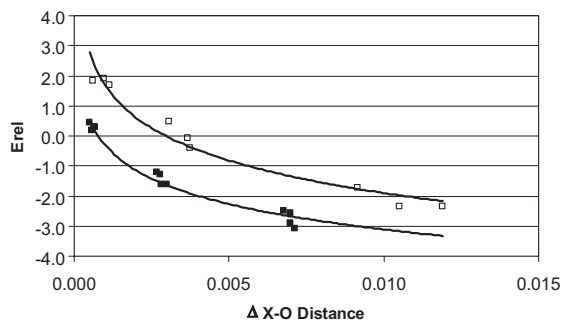
Figure 2. E_{rel} (kcal/mol) versus the variation of the X–O distance (Å) in each pair of complexes. Open square stands for complexes with fluorine in position-3 and black squares for those with hydrogen.

Figure 3. E_{rel} (kcal/mol) versus distance of the substituents in 3–3'' (Å) in the homochiral complex with the open squares are indicated the 3F substituted complexes and with black squares the 3H ones. The fitted curves are only tentative.

van der Waals interaction while in the second (X = C and N) they tend to minimize steric and electronic repulsions.

The 3–3'' distance in the homochiral complexes has been plotted versus the relative energy of the corresponding pair in Figure 3. This figure clearly shows that complexes fluorinated in position 3 favor more rapidly the heterochiral complex (negative E_{rel}) as the distance becomes shorter than those with hydrogen in these positions. This is expected due to the different steric and electronic characteristics of these two atoms. In addition, it allows us to predict that the moieties with a larger sized group in this position should increase the energy gap between the homo- and heterochiral complexes in favor of the last one.

The AIM analysis shows in all the homochiral complexes a bond critical point between the substituents in 3 and 3'' (due to the symmetry of the complexes another one is located between 3' and 3'''). The small and positive values of the density, ρ_{BCP}, and Laplacian, $\nabla^2\rho_{BCP}$,

at the bond critical point indicate that they correspond to closed shell interaction as those found in hydrogen bonds and van der Waals complexes. The linear correlations with the negative slope found between ρ of the homochiral system and the E_{rel} of the complexes (r^2 of 0.97 and 0.94 for the complexes with hydrogen and fluorine atoms in position 3, respectively) confirms, that as the interaction between the substituents in position 3 becomes stronger, it favors the heterochiral complex.

In addition, exponential relationships between the interaction distance and the values of ρ and $\nabla^2\rho$ have been obtained (Fig. 4). Similar relationships have been found for other closed shell interactions.[20] The presence of this
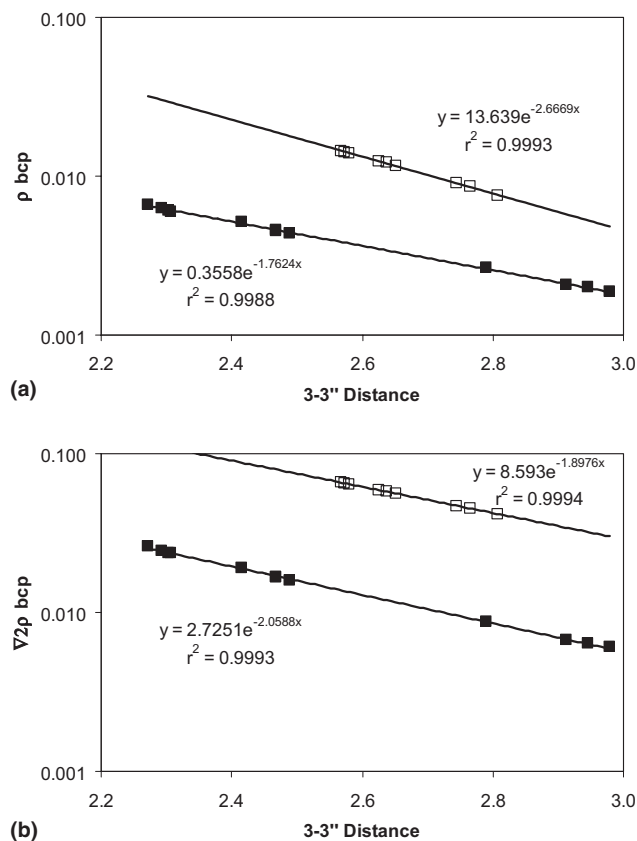
Figure 4. (a) Electron density at the bond critical point, ρ_{BCP} (logarithmic scale) versus the interatomic distance. (b) Laplacian of the electron density at the bond critical point, $\nabla^2\rho_{BCP}$, (logarithmic scale) versus the interatomic distance. Open squares represent the complexes with fluorine in position 3 and the black squares those with hydrogen in these positions.

kind of BCP between fluorine atoms has been correlated for other systems with the values of the experimental coupling constants across the space.[21]

2.1. Predictions

The effect of larger groups at position 3 of the biphenyl group has been evaluated calculating the corresponding 3-chloro and the binaphthyl derivatives shown in Figure 5. The results are shown in Table 4. The results clearly show in both cases how the heterochiral complexes are favored up to 12 kcal/mol in the cases when the central atoms are nitrogen.

Table 4. Relative energy (kcal/mol) of the new complexes considered (kcal/mol)

X	Substitution	E_{rel}
B^-	3-Cl[a]	−2.24
C	3-Cl[a]	−7.96
N^+	3-Cl[a]	−12.88
B^-	See Figure 5	−2.36
C	See Figure 5	−7.71
N^+	See Figure 5	−12.31

[a] 3-Cl stands for (3,3′,3″,3‴ tetrachloro derivatives).
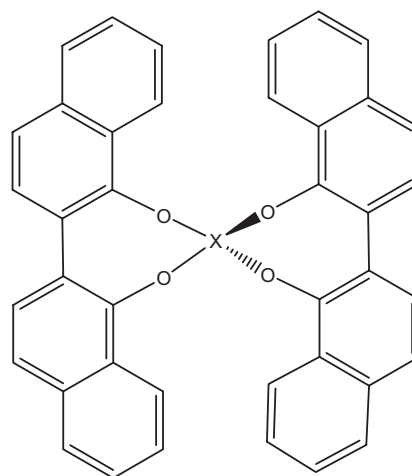
Figure 5. Calculated binaphthyl derivatives.

3. Conclusions

A theoretical study by means of the B3LYP/6-31G* DFT method has been carried out on the relative stability of the biphenyl derivatives of borates and isoelectronic structures where the central boron atom has been substituted by carbon or nitrogen. The relative energy of the homochiral complex versus the heterochiral one has been linearly correlated with the central atom and the fluorine substitution on the different positions of the aromatic ring.

The variation on the X–O bond distance between each given pair of structures (homo- and heterochiral ones) shows an exponential relationship with the relative energy. Also, the interatomic distances in the homochiral complexes in the substituents in position 3–3″ show a relationship with the relative energy, which indicates that larger groups should favor the heterochiral structures. This hypothesis has been confirmed by calculation of the chloro and binaphthyl derivatives. The electron density and its Laplacian in the BCP found between the substituents in positions 3–3″ correlate exponentially with the interatomic distances.

Acknowledgements

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