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Theoretical study of peptide model dimers. Homo versus heterochiral complexes

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Abstract

The study of possible chiral recognition of a series of peptide models (For-Gly-NH_2, For-Ala-NH_2 and four of their fluoro substituted derivatives) has been carried out by means of DFT calculations. Homo (L,L) and heterochiral (L,D) dimers formed by hydrogen bond (HB) complexation have been considered. Initially, the conformational preferences of the monomers have been calculated and used to generate all the possible homo and heterochiral dimers. The energetic results show that in most cases, the β monomers are the most stable while in the dimers, the γ−γ complexes show the strongest interaction energies. In three of the four chiral cases studied, a heterochiral dimer is the most stable one. In addition, the electron density and nuclear shielding of the complexes have been studied.

Keywords: Peptide; Chiral recognition; DFT calculations

1. Introduction

In the last years, an increasing number of articles devoted to the chiral self-recognition of small molecules have been published. Gas phase studies of the dimers of small molecules such as 2-butanol [1] and glycidol [2] have been carried out. Protonated octamers of serine are formed exclusively from enantiomerically pure mixtures according to electrospray ionisation experiments [3]. Spectroscopic tools have been used in supersonic beams to study the energetics of enantiomeric discrimination [4]. An example of chiral amplification of oligopeptides on the water surface due to differences in the two-dimensional packing arrangements has recently been reported [5]. The induction of chirality due to vortices has been described for porphyrin aggregation [6]. The different mechanisms proposed for the natural selection of a unique enantiomeric form of the aminoacids in biology have recently been reviewed by Cintas [7].

Several theoretical articles have addressed the problem of chiral self-recognition as in the case of a series of α-aminoalcohols [8] or different compounds that present axial chirality [9]. The study of the diastereomeric interaction between a chiral system and the two enantiomeric forms of another molecule has been carried out for simple ethers, oxirane derivatives and hydrogen peroxide [10]. The interaction of 2-naphtyl-1-ethanol with chiral and non-chiral alcohols has been studied experimentally and theoretically [11]. A recent publication reports the study of cooperative network in β-sheet models, both parallel and antiparallel, using DFT methods [12]. The results show that the antiparallel disposition is favoured over the parallel one in the model used and that no co-operativity is found as the strand increases in terms of enthalpy in both cases.

In the present article, a family of peptide models (Scheme 1) has been chosen as a suitable set to study the chiral recognition in peptides by means of hybrid HF-DFT, B3LYP, methods. Besides the publications already quoted [3,5,7,12], the self-recognition of amino acids and peptides is important in theoretical biology [13], in crystallography of racemic amino acids [14], and in chromatography. The analysis of proteinogenic and non-natural amino acids by chromatography using amino acids, small peptides or proteins as stationary phases [15] is based on the kind of interactions we will describe in this paper.

Initially, the conformational preferences of the monomers have been explored. Then, all the potential dimers of the mentioned monomers have been studied for both

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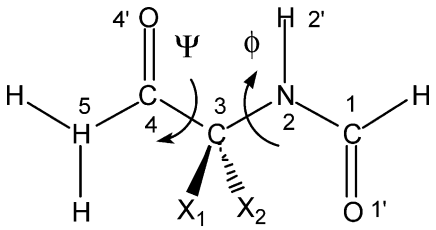


X_1	X_2
H	H
F	F
F	H
CH_3	H
CH_3	F
CF_3	H

Scheme 1.

the homo and heterochiral dimers. The electron density of the complexes has been investigated by means of the Atoms In Molecules (AIM) methodology. In addition, the effect of the complexation on the chemical shielding has been calculated using the GIAO method. Fluorine (or trifluoromethyl) derivatives were selected as models of larger groups with electron withdrawing properties.

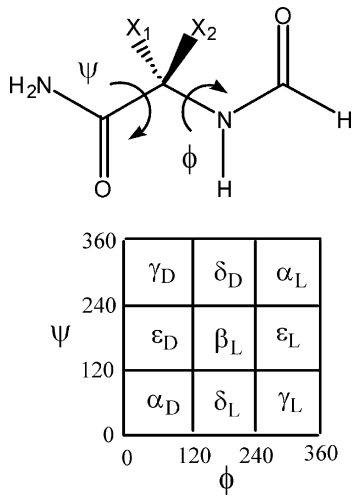
From these six monomers, not taking into account conformations, 24 homo dimers can be formed (for instance HH/HH or CF_3H/CF_3H). Excluding non-chiral monomers (HH and FF), eight homochiral (the same enantiomer, L:L) and eight heterochiral (the two monomers of different chirality, L:D) complexes can be built up.

2. Methods

Based on the values of the ψ and ϕ angles, which characterise the conformation of the protein backbone, nine different regions have been defined corresponding to three minima for each rotational angle [16]. The nomenclature used to define the configurations of the monomers (α_L, α_D, β_L, γ_L, γ_D, δ_L, δ_D, ε_L and ε_D) is the one proposed in Ref. [16] (Scheme 2). In addition, the chirality of the aminoacid has been denoted by adding an L or D letter prior to the configuration; for instance L-α_D denotes an aminoacid with L chirality and α_D configuration.

For the non-chiral aminoacids, the number of unique configurations is reduced to five since four of them can be generated as mirror images of the unique ones [17]. However, this degeneracy is broken when the structures are included in a chiral environment.

The geometries of the monomers have been optimised starting with standard ψ and ϕ angles for the nine potential regions in the case of the chiral monomers and five for the non-chiral ones. The minimised structures have been analysed and those duplicated have been discarded.

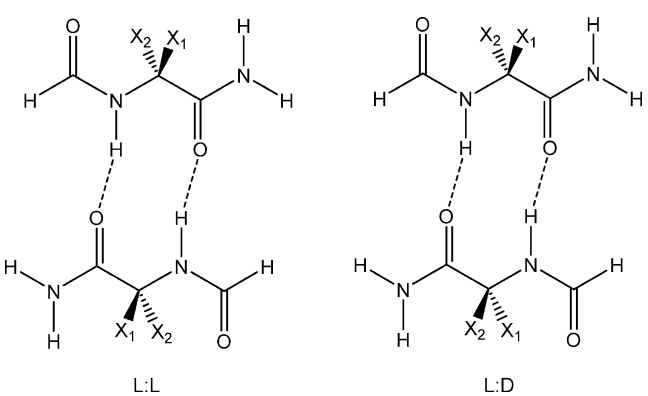


Scheme 2.

All the possible homo and heterochiral dimers have been built as combination of the minima structures obtained for the monomers with a simultaneous double CO···HN hydrogen bond (Scheme 2). Initially, the geometries have been optimised without allowing the ψ and ϕ angles of each monomer to relax. This geometry has been used in a further optimisation without any constraint (Scheme 3).

All the initial geometrical explorations of the monomers and dimers have been carried out with the hybrid HF-DFT (B3LYP) [18] method and the 6-31 + G** basis set [19] within the GAUSSIAN-98 program package [20]. Further optimisations have been carried out at the B3LYP/6-311 + G** level for selected cases. These levels of calculations have been shown, in previous studies of HB complexes, to provide similar results to those of the corresponding MP2 calculations with the same basis set [9]. The interaction energy has been corrected of the inherent Basis Set Superposition Error (BSSE) using the full counterpoise method proposed by Boys and Bernardi [21].

The electron density of the complexes calculated at the B3LYP/6-31 + G** level has been analysed using the AIM methodology [22] and the AIMPAC package [23]. Finally, the absolute chemical shieldings of the monomers



Scheme 3.

and dimers (σ in ppm) have been calculated using the GIAO method [24] at the B3LYP/6-31 + G** level.

3. Results and discussion

3.1. Energetic aspects

For the monomers, the relative energy and conformational characteristics of the minima are gathered in Table 1. Interesting is the fact that the total number of conformations found for these monomers is reduced to 3 or 4 in the non-chiral systems and between 5 and 6 in the chiral ones. The results obtained with the B3LYP/6-31 + G** and B3LYP/6-311 + G** methods are almost identical with the exception of the relative stability of the γ_L and β_L conformers of alanine (isoenergetic with the smallest base while with the largest one, their relative energies are 0.0 and 3.6 kJ/mol, respectively). The results obtained here for For-Ala-NH_2 and For-Gly-NH_2 (For- stands for formyl) are almost identical to a recent report by Perczel and Császár [25] who studied those systems at the B3LYP/6-311++G** computational level.

The β_L conformation is the most stable one for all cases except for glycine and alanine where it shows a relative energy of 0.4 and 3.6 kJ/mol, respectively. The presence of fluorine atoms as X_1 or X_2 substituents tends to destabilise the γ and δ conformations and favours the presence of ε and α ones that are absent in the rest of the cases. The intramolecular HB formed in each case is responsible for these tendencies. While the γ and δ conformations present an intramolecular HB that is disrupted by the presence of fluorine atoms at X_1 and X_2, new HBs are formed in the ε and α conformation, stabilising their relative energies.

Since the barriers between conformers are small, in the process of optimisation of the dimers, those corresponding to high-energy monomers disappear, due the driving force of the HBs formed in the process. Thus, the number of minima found for the dimers ranges from 4 to 7 considering only the homochiral dimers and can be twice if the homo and heterochiral ones are taken into account. A total number of 45 unique dimers have been obtained for the six systems studied here.

The relative energy and the interaction energy of the calculated dimers are reported in Table 2. The dimers formed by the β_L monomers correspond to a simplified model of an antiparallel β-sheet that has been shown in glycine strand models to be more stable than the parallel one [12]. The results obtained at the B3LYP/6-31 + G**

Table 1
Optimised ψ and ϕ (°) of the monomers at B3LYP/6-31 + G** and B3LYP/6-311 + G** (in parenthesis) levels

X_1/X_2	ψ	ϕ	E_{rel} (kJ/mol)	Nomenclature
H/H	180.0 (180.0)	180.0 (180.0)	0.42 (0.38)	β
H/H	65.1 (65.7)	−81.3 (−81.4)	0.00 (0.00)	γ
H/H	−18.8 (−18.5)	112.9 (113.3)	7.78 (7.78)	δ
F/F	180.0 (180.0)	180.0 (180.0)	0.00 (0.00)	β
F/F	72.5 (73.4)	−69.8 (−69.7)	6.57 (6.32)	γ
F/F	131.7 (131.2)	−50.4 (−50.2)	5.40 (4.69)	ε
F/F	44.92 (46.7)	53.81 (52.3)	23.05 (22.01)	α
H/F	−162.2 (−162.1)	−150.0 (−149.7)	0.00 (0.00)	β_L
H/F	−83.3 (–)	65.3 (–)	15.52 (–)	γ_D
H/F	75.8 (75.9)	−88.0 (−88.3)	17.78 (17.78)	γ_L
H/F	−126.8 (−126.0)	51.5 (48.3)	12.18 (11.05)	ε_D
H/F	43.7 (44.6)	53.3 (52.9)	35.61 (34.23)	α_D
H/F	42.4 (47.7)	−143.0 (−143.2)	22.59 (21.76)	α_L
H/CH_3	163.4 (163.6)	−157.0 (−156.7)	0.00 (3.39)	β_L
H/CH_3	−55.0 (−55.5)	72.4 (72.4)	5.65 (8.95)	γ_D
H/CH_3	72.3 (73.4)	−82.5 (−82.6)	0.00 (0.00)	γ_L
H/CH_3	−41.3 (−41.5)	−168.8 (−168.7)	22.43 (25.27)	δ_D
H/CH_3	15.7 (15.5)	−113.9 (−114.3)	7.11 (10.25)	δ_L
F/CH_3	153.4 (152.7)	175.4 (174.7)	0.00 (0.00)	β_L
F/CH_3	−60.3 (−61.2)	74.2 (74.1)	13.35 (13.43)	γ_D
F/CH_3	−34.1 (−36.2)	158.8 (161.3)	27.49 (26.78)	δ_D
F/CH_3	124.3 (124.4)	−47.2 (−47.0)	1.72 (0.88)	ε_L
F/CH_3	−38.4 (−39.5)	−55.6 (−55.2)	25.98 (25.06)	α_L
H/CF_3	170.0 (169.9)	−133.2 (−132.0)	0.00 (0.00)	β_L
H/CF_3	−59.8 (−62.2)	60.4 (60.3)	17.61 (17.82)	γ_D
H/CF_3	78.0 (79.0)	−86.8 (−87.1)	7.41 (7.82)	γ_L
H/CF_3	−76.4 (−75.5)	−123.8 (−123.3)	19.33 (19.04)	δ_D
H/CF_3	13.9 (14.1)	−123.7 (−122.5)	16.32 (16.48)	α_L

The relative energy (kJ/mol) to the most stable conformation in each case is also given.

Table 2
Relative and corrected interaction energy (kJ/mol) of the homo and heterochiral dimers at the B3LYP/6-31 + G** (B3LYP/6-311 + G** in parenthesis)

X_1/X_2	Configuration of the monomers	Relative energy	E_{I+BSSE}[a]
H/H	β_L, β_L	38.49	−27.41
H/H	γ_D, γ_D	2.72 (2.43)	−62.01 (−57.03)
H/H	γ_D, γ_L	0.00 (**0.00**)	−64.64 (−63.22)
H/H	δ_D, δ_D	24.94	−39.81
F/F	β_L, β_L	23.85	−29.46
F/F	γ_D, γ_D	9.00	−56.61
F/F	γ_D, γ_L	0.00 (0.00)	−65.06 (−63.51)
F/F	ε_D, ε_D	6.19 (5.73)	−56.40 (−54.68)
F/F	ε_D, ε_L	4.94 (4.23)	−58.03 (−56.36)
H/F	L-β_L, L-β_L	13.14	−25.77
H/F	L-γ_D, L-γ_D	14.60	−55.10
H/F	L-γ_D, L-γ_L	5.69	−65.86
H/F	L-γ_L, L-γ_L	11.09	−62.72
H/F	L-ε_D, L-ε_D	3.05 (3.22)	−59.41 (−57.40)
H/F	L-ε_D, L-γ_D	8.91	−57.20
H/F	L-ε_D, L-γ_L	2.93 (3.77)	−65.14 (−63.51)
H/F	L-γ_L, D-ε_D	1.21 (2.01)	−66.73 (−65.31)
H/F	L-β_L, D-β_L	0.00 (**0.00**)	−38.70 (−38.91)
H/F	L-γ_D, D-γ_D	7.36	−62.13
H/F	L-ε_D, D-γ_D	1.21 (2.05)	−64.52 (−58.16)
H/F	L-γ_D, D-γ_L	6.19	−65.48
H/F	L-γ_L, D-γ_L	5.94	−67.61
H/CH_3	L-β_L, L-β_L	33.14	−28.16
H/CH_3	L-γ_L, L-γ_L	4.64	−55.94
H/CH_3	L-γ_D, L-γ_D	12.55	−59.37
H/CH_3	L-γ_D, L-γ_L	4.60 (4.73)	−61.71 (−53.85)
H/CH_3	L-β_L, D-β_L	36.78	−24.60
H/CH_3	L-γ_L, D-γ_D	7.99	−58.32
H/CH_3	L-γ_L, D-γ_L	0.00 (**0.00**)	−60.58 (−52.55)
H/CH_3	L-γ_D, D-γ_D	9.04	−62.72
F/CH_3	L-β_L, L-β_L	14.98	−29.20
F/CH_3	L-ε_L, L-γ_D	3.35	−54.85
F/CH_3	L-ε_L, L-ε_L	0.00 (**0.00**)	−46.86 (−45.27)
F/CH_3	L-γ_D, L-γ_D	17.66	−52.34
F/CH_3	L-β_L, D-β_L	11.59	−32.55
F/CH_3	L-γ_D, D-γ_D	6.02	−63.22
F/CH_3	L-ε_L, D-ε_L	0.59 (0.42)	−46.57 (−45.15)
H/CF_3	L-β_L, L-β_L	10.84 (10.00)	−33.18 (−33.39)
H/CF_3	L-γ_D, L-γ_D	26.11	−53.26
H/CF_3	L-γ_L, L-γ_L	16.86	−41.88
H/CF_3	L-γ_D, L-γ_L	10.13 (10.46)	−58.32 (−57.32)
H/CF_3	L-β_L, D-β_L	15.61	−29.29
H/CF_3	L-γ_L, D-γ_D	13.35	−55.35
H/CF_3	L-γ_L, D-γ_L	0.00 (**0.00**)	−57.45 (−56.82)
H/CF_3	L-γ_D, D-γ_D	20.00	−59.08

[a] Calculated with respect to the conformations of minimum energy of the isolated monomers that form the dimer.

and B3LYP/6-311 + G** levels are very similar, as in the case of the monomers, and qualitatively identical.

The interaction energy of the dimers (4th column of Table 2) clearly shows that the γ conformers are the most suitable to form two simultaneous HBs with interaction energies of −58 kJ/mol approximately for the dimers calculated here. In several cases, the interaction energies are higher than 65 kJ/mol, corresponding to over 32.5 kJ/mol for each HB, which is above those obtained for amides acting as HB acceptor or donors [26]. In contrast, the β conformers are the ones with the lowest interaction energies with only −29 kJ/mol approximately. The dimers formed by ε monomers present intermediate interaction energies. Thus, the relative stability of the dimers is a compromise between those of the starting monomers and the interaction energy. Considering independently the homo and heterochiral dimers, in six cases the most stable dimers are formed by γ monomers, in two cases by ε ones and in one case a mixture of γ and ε and in another one by a dimer of β monomers. In general, the most stable dimers correspond to those in which analogous groups are located above and below the average plane formed by the new HBs. Thus in the homodimers, the most stable configuration corresponds in several cases to γ_L/γ_D configurations, while in heterodimers it is formed by the same configuration with opposite chirality as L-γ_L/D-γ_L.

Regarding the preferences of the homo versus the heterodimers (see 3rd column of Table 2), in three of the four chiral cases, one of the hetero dispositions is the most favourable, in agreement with previous reports that show similar results in gas phase calculations [8,9]. The only case where the homochiral disposition is favoured corresponds to the α-fluoroalanine derivative ($X_1/X_2 = CH_3/F$) where an additional stabilising interaction is observed between the π-clouds of the formylamino groups at the opposite ends of both monomers. The preference of the aminoacids to form heterochiral complexes has been found in the formation of nanotubes with cyclic peptides [27] and in the 2D crystalline structures of oligopeptides; this can explain the enrichment of the most abundant homochiral sequence [5].

The differences in energy found for the heterochiral dimers vs. the homochiral ones (between 2.9 and 10.1 kJ/mol) should lead to very different populations of the given dimers; thus, it should be possible to observe these differences with a variety of standard techniques. In this sense, the homo and heterochiral dimers of *N*-acetylvaline *tert*-butyl ester [28] and dihydroquinones [29] have been observed by NMR spectroscopy.

3.2. Geometries

The geometrical parameters of the HBs present in the dimers are reported in Table 3. The HB distances range between 1.84 and 2.10 Å and the N–H···O angles between 179 and 132°. In general, the shortest HBs correspond to the more linear ones (Fig. 1), i.e. as the interaction becomes longer, the HB angle tends to be less linear. Similar tendencies have already been described for systematic studies of HB in structural databases [30,31].

An examination of Fig. 1 allows to postulate the existence of two sub-sets of points: a less populated upper

Table 3
Geometrical characteristic of the complexes calculated at the B3LYP/6-31 + G** level (distances in Å and angles in °)

X_1/X_2	Configuration of the monomers	HB distance	HB angle
H/H	β_L, β_L	2.049	152
H/H	γ_D, γ_D	1.900	165.6
H/H	γ_D, γ_L	1.893	161.7
H/H	δ_D, δ_D	2.100	132.2
F/F	β_L, β_L	2.036	150.1
F/F	γ_D, γ_D	1.924	157.2
F/F	γ_D, γ_L	1.866	172.0
F/F	ε_D, ε_D	1.906	160.5
F/F	ε_D, ε_L	1.894	165.4
H/F	L-β_L, L-β_L	2.063	147.3
H/F	L-γ_D, L-γ_D	1.962	154.3
H/F	L-γ_D, L-γ_L	1.845, 1.947	176.3, 153.6
H/F	L-γ_L, L-γ_L	1.907	161.4
H/F	L-ε_D, L-ε_D	1.905	164.5
H/F	L-ε_D, L-γ_D	1.888, 1.970	167.4, 150.6
H/F	L-ε_D, L-γ_L	1.852, 1.971	170.9, 152.5
H/F	L-γ_L, D-ε_D	1.836, 1.958	178.5, 154.1
H/F	L-β_L, D-β_L	2.004	149.4
H/F	L-γ_D, D-γ_D	1.963	154.3
H/F	L-ε_D, D-γ_D	1.836, 1.957	178.2, 154.2
H/F	L-γ_D, D-γ_L	1.902	160.6
H/F	L-γ_L, D-γ_L	1.860	170.1
H/CH_3	L-β_L, L-β_L	2.033	152.5
H/CH_3	L-γ_L, L-γ_L	1.963	161.6
H/CH_3	L-γ_D, L-γ_D	1.932	161.1
H/CH_3	L-γ_D, L-γ_L	1.909, 1.938	171.9, 156.8
H/CH_3	L-β_L, D-β_L	2.094	147.4
H/CH_3	L-γ_L, D-γ_D	1.959, 1.940	153.7, 163.2
H/CH_3	L-γ_L, D-γ_L	1.926	170.4
H/CH_3	L-γ_D, D-γ_D	1.911	160.76
F/CH_3	L-β_L, L-β_L	2.032	155.5
F/CH_3	L-ε_L, L-γ_D	1.901, 2.019	164.7, 160.5
F/CH_3	L-ε_L, L-ε_L	1.997	157.3
F/CH_3	L-γ_D, L-γ_D	1.990	152.7
F/CH_3	L-β_L, D-β_L	1.988	158.3
F/CH_3	L-γ_D, D-γ_D	1.888	174.1
F/CH_3	L-ε_L, D-ε_L	1.989	158.4
H/CF_3	L-β_L, L-β_L	1.929	168.9
H/CF_3	L-γ_D, L-γ_D	1.952	155.6
H/CF_3	L-γ_L, L-γ_L	1.982	161.02
H/CF_3	L-γ_D, L-γ_L	1.869, 2.029	172.9, 146.2
H/CF_3	L-β_L, D-β_L	2.099	140.5
H/CF_3	L-γ_L, D-γ_D	1.895, 1.992	164.0, 149.8
H/CF_3	L-γ_L, D-γ_L	1.899	174.9
H/CF_3	L-γ_D, D-γ_D	1.935	155.1

set (white squares) and a more populated lower set (black squares). The upper part corresponds to structures that, for the same HB distance are more straight (by about 8°). The lower part corresponds to complexes with additional interactions between the atoms attached to the C_α that disrupt the HB or a CO···H dispositions far from the one corresponding to the interaction of the hydrogen atom with the lone pair of the CO group. In general, most compounds

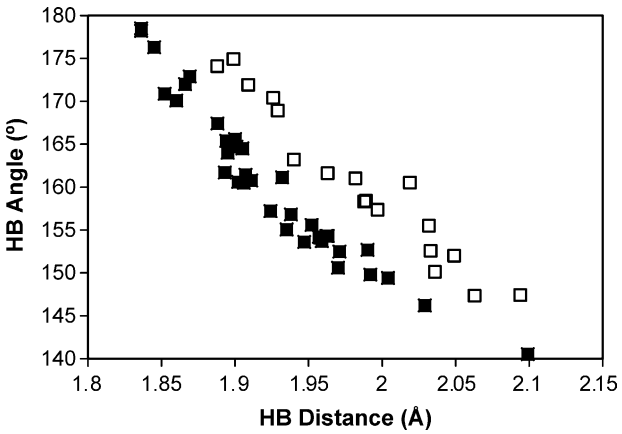


Fig. 1. NH···O angle versus H···O distance in the HB formed. The black and white squares are explained in the text.

of the upper set of structures correspond to compounds with $X = CH_3$ and β_L conformations.

In the same way, a rough tendency is observed between the average HB distance and the interaction energy (Fig. 2). A linear correlation between those parameters with a correlation coefficient of 0.91 can be obtained not considering an outlier point, indicated in Fig. 2 as an open square.

The outlier point corresponds to the L-β_L:L-β_L dimer of the trifluoromethyl-alanine derivative that presents the largest distortion energy (4.73 kJ/mol for each of the monomers) of all the complexes studied here.

Obviously, a linear relationship is an acceptable approximation only for a limited variation of the HB distance, like that of Fig. 2. A general curve should show a Morse behaviour as previously shown for other HB systems [32,33]. For longer distances, the interaction energy should tend to zero and for shorter ones to increase rapidly. The 43 points of Fig. 2 can be adjusted to a sigmoid curve, $E_{I+BSSE} = \{k[1 + \exp b(\text{HB distance} - c)]\} + d$, with $k = 38.6 \pm 3.3$, $b = -(40.9 \pm 8.2)$, $c = 1.990 \pm 0.006$, $d = -(63.5 \pm 1.4)$, $r^2 = 0.92$.

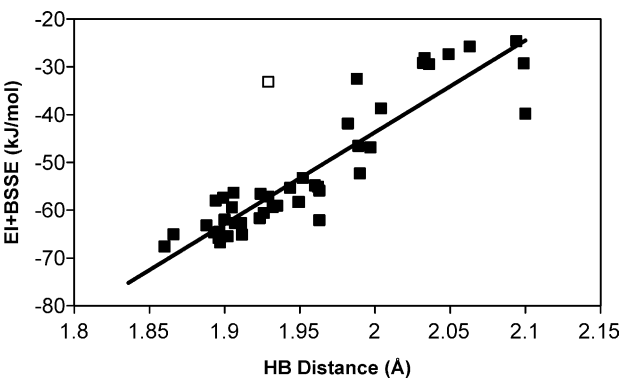


Fig. 2. Interaction energy versus the average bond distance. The fitted linear correlation corresponds to $E_{I+BSSE} = -428 + 192 \times (\text{HB distance})$, $r^2 = 0.83$, $n = 44$. The open point square has not been considered in the regression.

3.3. Analysis of the electron density

The analysis of the electron density shows bond critical points (bcp) in the new formed HBs as well as a ring critical point. The values of the electron density at the HB bcp are small and the corresponding Laplacians are positive and small as expected for these HBs. Although the HB distances vary in a narrow range (1.85–2.1 Å), the exponential correlations between the electron density and its Laplacian at the bcp versus the HB distance provide a better correlation coefficient than the linear ones (Fig. 3). For larger HB ranges, it has been shown that it corresponds clearly to exponential relationships [34].

As in previous articles, the presence of additional bcp's provides a clue to understand the effect of these contacts in the stabilisation of the dimers [8,9,35]. While the presence of a bcp has been proposed to indicate a stabilising interaction [36], it can disrupt other stronger interactions, lealing to a partial destabilisation of the complex. This seems to be present in the cases studied here, since the absolute minima does not present additional bcp (Table 4). In all cases, the small values of the electron density and its Laplacian indicate that the contacts correspond to van der Waals interactions. In several cases, weak hydrogen bonds are formed between the fluorine atoms and $C_\alpha H$ moieties, in agreement with reports that indicate that the latter acts as HB donor in protein structures [37]. The presence of a $\pi-\pi$ interaction is observed in the most stable dimers of α-fluoroalanine derivative ($X_1/X_2 = CH_3/F$) reversing the general tendency of greater stability of the heterochiral dimers.

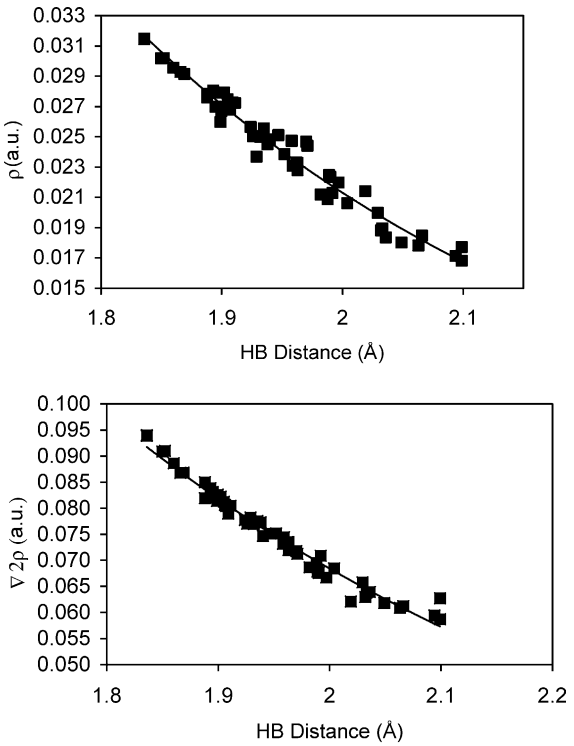


Fig. 3. Electron density and Laplacian of the electron density versus the HB distance. The fitted curve are: $\rho_{BCP} = 2.65\exp(-2.41 \times \text{HB distance})$, $r^2 = 0.96$, $n = 56$ and $\nabla^2\rho_{BCP} = 2.44\exp(-1.79 \times \text{HB distance})$, $r^2 = 0.97$, $n = 56$.

Table 4
Properties (a.u.), electron density ρ and its Laplacian $\nabla^2\rho$, of the additional bcp found in the dimers calculated at the B3LYP/6-31 + G** level

X_1/X_2	Configuration of the monomers	ρ	$\nabla^2\rho$	Atoms	Distance
H/H	γ_D, γ_D	0.003	0.010	C_α**H**···**H**C_α	2.63
F/F	γ_D, γ_D	0.008	0.038	C_α**F**···**F**C_α	2.81
F/F	ε_D, ε_D	0.004	0.020	C_α**F**···**F**C_α	3.15
H/F	L-γ_D, L-γ_D	0.005	0.017	C_α**H**···**H**C_α	2.36
H/F	L-γ_L, L-γ_L	0.006	0.031	C_α**F**···**F**C_α	2.93
H/F	L-γ_L, D-ε_D	0.008	0.033	C_α**F**···**H**C_α	2.48
H/F	L-γ_D, D-γ_D	0.009	0.037	C_α**F**···**H**C_α	2.38
H/F	L-ε_D, D-ε_D	0.008	0.033	C_α**F**···**H**C_α	2.48
H/F	L-ε_D, D-γ_D	0.008	0.033	C_α**F**···**H**C_α	2.47
H/CH_3	L-γ_L, L-γ_L	0.006	0.021	C**H**$_3$···**H**$_3$C	2.21
H/CH_3	L-γ_D, L-γ_D	0.005	0.019	C_α**H**···**H**C_α	2.31
H/CH_3	L-γ_L, D-γ_D	0.007	0.013	C**H**$_3$···**H**C_α	2.27
F/CH_3	L-γ_L, L-γ_L	0.008	0.027	C**H**$_3$···**H**$_3$C	2.09
F/CH_3	L-ε_L, L-ε_L	0.007	0.023	C**H**$_3$···**H**$_3$C	2.16
		0.004	0.014	$\pi-\pi$	
F/CH_3	L-γ_D, L-γ_D	0.008	0.038	C_α**F**···**F**C_α	2.81
H/CF_3	L-γ_D, L-γ_D	0.005	0.017	C_α**H**···**H**C_α	2.33
H/CF_3	L-γ_L, L-γ_L	0.008	0.041	C**F**$_3$···**F**$_3$C	2.70
H/CF_3	L-γ_L, L-γ_D	0.009	0.037	C**F**$_3$···**H**C_α	2.34

3.4. NMR chemical shifts

The NMR of proteins is important both for the determination of their structure and for methodological aspects: the progress of NMR spectroscopy owes much to its application to biomolecules [38,39]. One important aspect is the effect of N–H···O=C HBs on the NMR parameters (δ and J) [40,41]. The most important effects on the chemical shieldings due to the complexation are reported in the Supporting Information. The chemical shielding of the monomers clearly show a clustering of the values as a function of the conformation of the aminoacids as has been shown previously by Perczel and Császár [25]. In the dimers, the formation of the HBs produce a shielding of the oxygen that acts as HB acceptor and a deshielding in the hydrogen atom up to 42 and −4 ppm, respectively. In addition, a deshielding of the all the nuclei of the peptide backbone is observed in the complexes, with the exception of the C_α carbons which show positive and negative variations.

In general, those complexes showing the largest interaction energies present the most significant nuclear shielding variations. This is in agreement with previous reports concerning simpler related complexes that have shown a linear relationship between the HB interaction and the deshielding of the hydrogen involved in the HB [42].

The present results are of interest for comparison with large peptides where a single configuration predominates and the difference between the isolated and the HB system can be

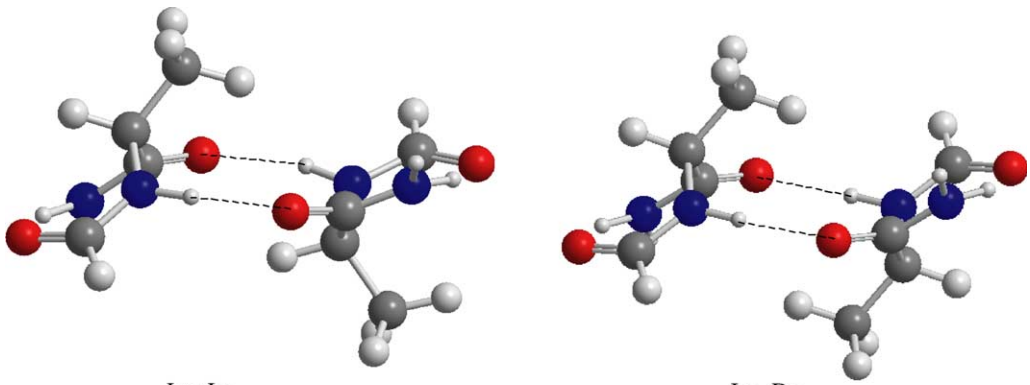


Fig. 4. Optimised geometries of the minimum complexes of the homo ($L\gamma_L$:$L\gamma_D$) and heterochiral ($L\gamma_L$:$D\gamma_L$) dimers of the alanine derivative.

measured. In small peptides, a large number of conformations are present at room temperature and the chemical shielding of each nuclei corresponds to the numerical integration over the energy profile of the molecule.

In what concerns chiral recognition, we have selected below the case of alanine dimers, the homochiral $L\gamma_L$, $L\gamma_D$ and the heterochiral $L\gamma_L$, $D\gamma_L$ represented in Fig. 4.

A comparison of the GIAO calculated absolute shieldings (σ, ppm) for the same conformation of the monomer, the $L\gamma_L$, shows significant effect for the atoms involved in the HB (see Scheme 1 for numbering): N(2) 1.00, H(2′) 0.53, C(4) 0.66 and O(4′) −21.95 ppm. These diastereotopic differences are large enough to be used to discriminate interactions between aminoacids in a peptide.

4. Conclusions

A theoretical study of the dimerization of a peptide model has been carried out using DFT, B3LYP/6-31 + G** and B3LYP/6-311 + G** levels. Initially, the conformational preferences of the monomers have been studied, characterising all the minima. Those minima have been used for all the potential dimers, homo and heterochiral ones. During the energy optimisation, the final number of complexes has been reduced significantly because the small barrier that separates them is overcome by the formation of two simultaneous HBs.

The geometrical characteristics of the HB bonds formed indicate that those with shorter distances present a more linear disposition. In addition, a rough linear correlation can be obtained between the average HB distance and the interaction energy.

Three of the four chiral systems studied show energetic preference for the heterochiral dimer. The only case with homochiral preference ($X_1/X_2 = CH_3/F$) presents an extra stabilising interaction that explains its different behaviour.

The analysis of the electron density shows bond critical points in all the HBs formed. Exponential relationships have been found between the electron density and its Laplacian at the bond critical point versus the HB distance. In addition, other new bond critical points have been found that can explain the relative energy of the corresponding dimers.

Finally, the nuclear chemical shielding of the monomers and dimers has been calculated and compared. The largest variation corresponds to the two atoms directly involved in the HB, with a large deshielding of the hydrogen and a shielding of the oxygen that acts as HB donor. Another significant effect is the deshielding of all NMR signals corresponding to the atoms of the protein backbone due to the formation of the complexes. In what concerns chiral recognition, significant effects have been found.

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