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Self-Discrimination of Enantiomers in Hydrogen-Bonded Dimers

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Abstract: The homochiral and heterochiral hydrogen-bonded (HB) dimers of a set of small model molecules (α-amino alcohols) have been studied by means of ab initio methods. The gas-phase calculations have been carried out with the hybrid HF/DFT B3LYP method and the 6-311++G** basis set. The electron density of the complexes has been analyzed using the atoms in molecules (AIM) methodology, which allows characterization of the HB interactions and additional intermolecular contacts. To take into account the water solvation effect, the polarized continuum model (PCM) method has been used to evaluate the ΔG_{solv}. The gas-phase results show that the heterochiral dimers are the most stable ones for each case studied, while in solution for several cases, the relative stability is reversed and the homochiral dimers become more stable. The AIM analysis shows the typical bond critical points characteristic of the HB and additional bond critical points denoting, in this case, destabilization of intermolecular interaction as $CF_3\cdots F_3C$ and $CH_3\cdots H_3C$ contacts.

Introduction

Enantiodifferentiation through hydrogen-bonded complexes is of paramount importance. It is present in liquid chromatographic separation of enantiomers by hydrogen bond associations,[1] in supramolecular chemistry (self-assemblies),[2] in the application of chiral additives such as Pirkle's alcohol in NMR,[3] and in the recognition of biomolecules (nucleic acids, peptides).[4] A particularly significant aspect is the crystallization of racemic compounds either as racemates or as conglomerates.[5] If the crystal growth is governed by thermodynamic factors, then, following Kitaigorodsky, the most compact structure will be obtained.[6] On the other hand, if the process is kinetically controlled, the most stable dimer will be formed; if this dimer is the *RS* (*SR*), the racemate will be obtained, but if it is the *RR* (*SS*), a conglomerate will result.[7] An analysis of the different forces involved in the discrimination process has been reviewed by Craig and Mellor.[8]

A comprehensive survey of the literature concerning this problem is not possible in the space devoted to this Introduction, and a detailed description of most of the methods used for stereoisomer discrimination can be found in the book by Eliel and Wilen.[9] Nevertheless, some significant papers will be noted. Horeau and Guetté[10] have reviewed the diastereomeric interactions between identical and opposite enantiomers in the liquid state. They conclude that the differences in energy are too weak to modify the optical composition of a mixture by distillation. Shiraiwa et al.[11] have described the optical resolution by preferential crystallization of DL-thiazolidine-4-carboxylic acid (**1**) (Figure 1). This amino acid crystallizes as a conglomerate.

Harger has reported the discrimination by ^{1}H NMR of both enantiomers of alkylphenylphosphinic amides (**2**)[12] (a problem closely related to phosphinic acids dimerization.[13] The homodimer (*RR* or *SS*) and the heterodimer (*RS* ≡ *SR*) give different signals in NMR.

Hara et al. have described the self-induced nonequivalence in the association of D- and L-amino acid derivatives.[14] In the case of *N*-acetylvaline *tert*-butyl ester (**3**) they propose the structure reported in Figure 1 for the homochiral (L−L) dimer interlinked via bidentate $N{-}H\cdots O{=}C$ ester hydrogen bonds.

Wynberg et al. explored the difference of reactivity between mixtures with different enantionemic excess: in the extreme cases, pure enantiomers vs racemic.[15]

Finally, Giordano et al.[16] have described the case of compound (**4**), a 1,5-benzothiazepine, and pointed out that enantiomers and racemates show identical NMR spectra only at high dilution.

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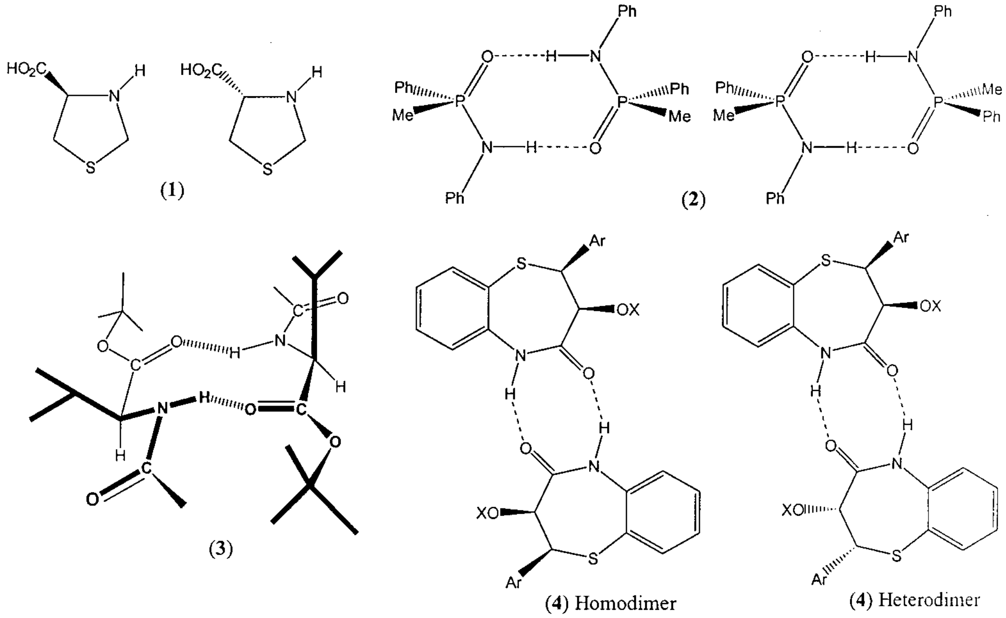
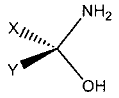


Figure 1. Some examples of enantiodifferentiations.



X = Y = H, F, CH_3, CF_3

X/Y = H/F, H/CH_3, H/CF_3, F/CH_3, CH_3/CF_3

Figure 2. Schematic representation of the monomers considered.

In the present study we explored the relative stability of the dimers formed by a series of chiral and nonchiral model compounds (Figure 2). The α-amino alcohols selected shown a HB donor (OH group) and a HB acceptor center (NH_2 group). Only those configurations with a simultaneous double HB have been explored. The effect of solvation has been taken into account using the polarized continuum model (PCM).

Methods

All the homodimers of the compounds shown in Figure 3 with a double HB has been considered. The configurations studied can be divided into pseudochair and pseudoboats (C and B), in analogy with the disposition of the cyclohexane.

The geometry of the complexes has been fully optimized starting from different spatial configurations with the Gaussian-98 package.[17] The 6-31G* and 6-311++G** basis sets[18,19] have been used at the hybrid HF-DFT, B3LYP,[20] computational level.

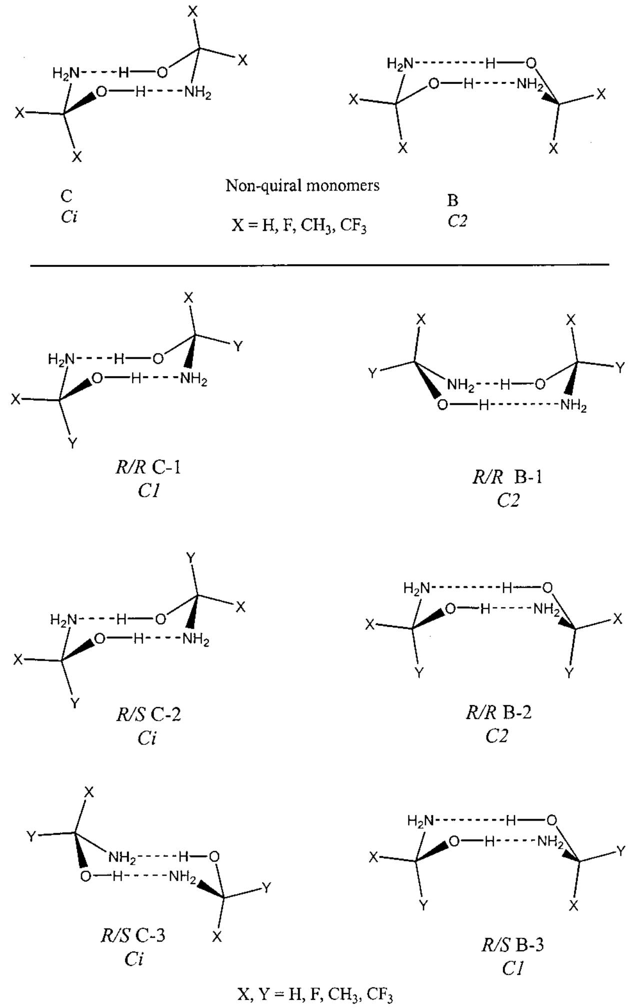


Figure 3. Schematic representation of the configuration studied. The chirality and symmetry of each case are indicated.

The inherent basis set superposition error (BSSE) of the energy has been evaluated using the full counterpoise method proposed by Boys and Bernardi.[21] Thus, the uncorrected E_I and corrected interaction

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Table 1. Interaction Energy E_I, Corrected Interaction Energy E_{I+BSSE}, and Relative Energy E_{rel} (kcal/mol) of the Dimers Studied at the B3LYP/6-311++G** Level

substituents X/Y	chirality and confign	E_I	E_{I+BSSE}	E_{rel}
H/H	C	−12.10	−10.84	0.00
H/H	B	−11.56	−10.31	0.53
F/F	C	−13.79	−12.26	0.00
F/F	B	−12.89	−11.37	0.89
CH_3/CH_3	C	−11.14	−9.96	0.00
CH_3/CH_3	B	−10.12	−9.04	0.92
CF_3/CF_3	C	−11.87	−9.70	0.00
CF_3/CF_3	B	−9.53	−7.61	2.09
F/H	R/R C-1	−11.45	−10.13	1.54
F/H	R/R B-1	−10.04	−8.73	2.94
F/H	R/R B-2	−11.55	−10.25	1.42
F/H	R/S C-2	−10.38	−9.09	2.58
F/H	R/S C-3	−13.02	−11.67	0.00
F/H	R/S B-3	−11.96	−10.60	1.07
H/CH_3	R/R C-1	−11.47	−10.15	0.72
H/CH_3	R/R B-1	−11.75	−10.44	0.43
H/CH_3	R/R B-2	−9.71	−8.68	2.19
H/CH_3	R/S C-2	−12.16	−10.87	0.00
H/CH_3	R/S C-3	−10.69	−9.56	1.31
H/CH_3	R/S B-3	−11.03	−9.83	1.04
H/CF_3	R/R C-1	−11.53	−9.95	1.45
H/CF_3	R/R B-1	−12.18	−10.73	0.67
H/CF_3	R/R B-2	−8.87	−7.38	4.02
H/CF_3	R/S C-2	−12.83	−11.40	0.00
H/CF_3	R/S C-3	−11.15	−9.48	1.92
H/CF_3	R/S B-3	−12.08	−10.50	0.90
F/CH_3	R/R C-1	−11.62	−10.27	1.73
F/CH_3	R/R B-1	−9.53	−8.24	3.76
F/CH_3	R/R B-2	−11.79	−10.40	1.60
F/CH_3	R/S C-2	−10.14	−8.88	3.12
F/CH_3	R/S C-3	−13.40	−12.00	0.00
F/CH_3	R/S B-3	−12.24	−10.83	1.17
CF_3/CH_3	R/R C-1	−11.00	−9.43	0.20
CF_3/CH_3	R/R B-1	−10.44	−9.07	0.56
CF_3/CH_3	R/R B-2	−8.75	−7.21	2.42
CF_3/CH_3	R/S C-2	−11.74	−10.30	−0.67
CF_3/CH_3	R/S C-3	−11.31	−9.63	0.00
CF_3/CH_3	R/S B-3	−10.69	−9.24	0.39

energies E_{I+BSSE} can be evaluated for each complex:

$$E_I = E_{AB} - E^{A}{}_{A} - E^{B}{}_{B}$$

$$BSSE = (E^{AB}{}_{A'} - E^{A}{}_{A'}) + (E^{AB}{}_{B'} - E^{A}{}_{B'})$$

$$E_{I+BSSE} = E_I + BSSE$$

where $E^{A}A$ represents the energy of the minimum geometry of the isolated molecule A calculated with its basis set and $E^{AB}{}_{A'}$ corresponds to the calculated energy of molecule A with its geometry in the AB complex using the basis function of the complex AB.

To characterize the intermolecular HB and other contacts, an analysis of the electron density has been carried using the atoms in molecules (AIM) methodology[22] and the AIMPAC programs.[23]

Table 2. Hydrogen Bond Distance (Å) and Angle (deg) of the Calculated Dimers at the B3LYP/6-311++G** Level[a]

substituents X/Y	chirality and confign	H···N distance	O–H···N angle
H/H	C	1.881	174.7
H/H	B	1.900	177.7
F/F	C	1.831	177.0
F/F	B	1.840	175.2
CH_3/CH_3	C	1.918	175.5
CH_3/CH_3	B	1.916	166.9
CF_3/CF_3	C	1.877	176.9
CF_3/CF_3	B	1.944	160.8
F/H	R/R C-1	1.863/1.882	177.8/178.6
F/H	R/R B-1	1.890	176.1
F/H	R/R B-2	1.880	173.9
F/H	R/S C-2	1.882	174.7
F/H	R/S C-3	1.866	175.8
F/H	R/S B-3	1.860/1.886	177.1/174.4
H/CH_3	R/R C-1	1.906/1.899	172.9/178.1
H/CH_3	R/R B-1	1.892	178.9
H/CH_3	R/R B-2	1.965	167.9
H/CH_3	R/S C-2	1.878	176.6
H/CH_3	R/S C-3	1.931	175.7
H/CH_3	R/S B-3	1.913/1.917	176.1/175.6
H/CF_3	R/R C-1	1.892/1.862	176.1/173.1
H/CF_3	R/R B-1	1.871	176.4
H/CF_3	R/R B-2	1.949	162.9
H/CF_3	R/S C-2	1.852	172.9
H/CF_3	R/S C-3	1.895	179.0
H/CF_3	R/S B-3	1.875/1.903	174.5/171.7
F/CH_3	R/R C-1	1.854/1.881	175.3/177.2
F/CH_3	R/R B-1	1.894	174.9
F/CH_3	R/R B-2	1.869	172.7
F/CH_3	R/S C-2	1.889	177.1
F/CH_3	R/S C-3	1.853	175.9
F/CH_3	R/S B-3	1.860/1.894	176.6/174.5
CF_3/CH_3	R/R C-1	1.906/1.880	177.3/175.8
CF_3/CH_3	R/R B-1	1.918	169.1
CF_3/CH_3	R/R B-2	1.957	160.7
CF_3/CH_3	R/S C-2	1.890	174.5
CF_3/CH_3	R/S C-3	1.897	177.1
CF_3/CH_3	R/S B-3	1.939/1.931	164.2/164.6

[a] One parameter is given for the symmetric dimers, and two are given for the nonsymmetric ones.

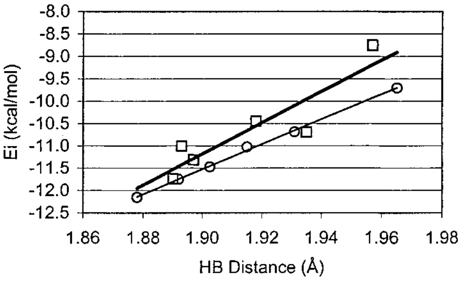

Figure 4. Interaction energy vs average HB distance for the dimers of X/Y = H/CH_3 (circles) and CF_3/CH_3 (squares). The corresponding linear relationships represented show correlation coefficients of 0.999 and 0.91, respectively. For the rest of the cases the correlation coefficients are 0.93, 0.97, and 0.93 for X/Y = H/F, H/CF_3, and F/CH_3, respectively.

An estimation of the solvation energy has been taken into account by using the PCM method[24] on the optimized geometry in gas phase. This method considered three electrostatic components (unpolarized solute−solvent, polarized solute−solvent, and the solute polarization) and the cavitation, dispersion, and repulsion components of the solvation process for different solvents. In this case, the water as solvent has been considered due to its biological importance.

Results and Discussion

Only configurations with two OH···N hydrogen bonds between the interacting monomers have been considered since they should be more favorable than the ones with only one HB. In the case of the nonchiral monomers, the complexes can adopt two configurations shown in Figure 3 (pseudoboat, B, and pseudochair, C). For the chiral monomers, initially, 12 configurations can be proposed. Half of them are mirror images of

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Table 3. Electron Properties, Electron Density ρ, and Laplacian $\nabla^2\rho$ (au) of the HB and Additional Intermolecular Contacts

		HB		additional contacts[a]			
substituents X/Y	chirality and confign	ρ	$\nabla^2\rho$	ρ	$\nabla^2\rho$	atoms involved	contact distance
H/H	C	0.036	0.091				
H/H	B	0.035	0.089				
F/F	C	0.040	0.094				
F/F	B	0.039	0.093	0.002	0.010	F···F	3.520
CH_3/CH_3	C	0.034	0.086				
CH_3/CH_3	B	0.030	0.082	0.005	0.014	$CH_3 \cdots H_3C$	2.287
CF_3/CF_3	C	0.036	0.090				
CF_3/CF_3	B	0.031	0.083	0.008	0.037	$CF_3 \cdots F_3C$	2.781
F/H	R/R C-1	0.038/0.036	0.091/0.090				
F/H	R/R B-1	0.035	0.089				
F/H	R/R B-2	0.036	0.089				
F/H	R/S C-2	0.036	0.090				
F/H	R/S C-3	0.037	0.091				
F/H	R/S B-3	0.038/0.036	0.091/0.090	0.003	0.012	H···F	3.060
H/CH_3	R/R C-1	0.034/0.035	0.088/0.089				
H/CH_3	R/R B-1	0.036	0.089				
H/CH_3	R/R B-2	0.030	0.081	0.005	0.013	$CH_3 \cdots H_3C$	2.340
H/CH_3	R/S C-2	0.037	0.091				
H/CH_3	R/S C-3	0.033	0.085				
H/CH_3	R/S B-3	0.034/0.034	0.087/0.086	0.004	0.011	$H \cdots H_3C$	2.550
H/CF_3	R/R C-1	0.035/0.038	0.089/0.092				
H/CF_3	R/R B-1	0.037	0.091				
H/CF_3	R/R B-2	0.030	0.083	0.007	0.033	$CF_3 \cdots F_3C$	2.830
H/CF_3	R/S C-2	0.039	0.094				
H/CF_3	R/S C-3	0.035	0.088	0.005	0.023	$NH \cdots F_3C$	2.710
H/CF_3	R/S B-3	0.037/0.034	0.090/0.088	0.007	0.026	$H \cdots F_3C$	2.560
F/CH_3	R/R C-1	0.038/0.036	0.092/0.090				
F/CH_3	R/R B-1	0.035	0.089	0.003	0.010	$CH_3 \cdots H_3C$	2.520
F/CH_3	R/R B-2	0.037	0.091				
F/CH_3	R/S C-2	0.035	0.090				
F/CH_3	R/S C-3	0.038	0.092				
F/CH_3	R/S B-3	0.038/0.035	0.091/0.089	0.007	0.026	$CH_3 \cdots F$	2.510
CF_3/CH_3	R/R C-1	0.034/0.036	0.088/0.090	0.006	0.025	$CF_3 \cdots HN$	2.710
CF_3/CH_3	R/R B-1	0.033	0.086	0.006	0.015	$CH_3 \cdots H_3C$	2.240
CF_3/CH_3	R/R B-2	0.030	0.082	0.007	0.035	$CF_3 \cdots F_3C$	2.810
CF_3/CH_3	R/S C-2	0.036	0.089				
CF_3/CH_3	R/S C-3	0.035	0.088	0.006	0.025	$CF_3 \cdots HN$	2.660
CF_3/CH_3	R/S B-3	0.031/0.032	0.085/0.084	0.008	0.030	$CF_3 \cdots H_3C$	2.400

[a] The atoms involved in the interaction and its distance (Å) are indicated.

the other half. Only one set of unique configurations will be considered since the mirror images have the same energy and geometric parameters (the dihedral angles show the same value but opposite sign). The six unique configurations studied for each dimer, which correspond to three homochiral dimers (*RR* or *SS*) and three heterochiral ones (*RS* or *SR*), can be grouped in three chairs, C1−3, and three boats, B1−3.

The calculated total and interaction energies of the monomers and the complexes at the B3LYP/6-311++G** are gathered in Table 1. A selection of the geometric parameters of the optimized dimers calculated at the B3LYP/6-311++G** are gathered in Table 2.

The interaction energy of the calculated dimers ranges between −9 and −14 kcal/mol, which is reduced slightly by the inclusion of the BSSE between −7 and −12 kcal/mol. If the contribution of each HB can be considered independent, the results indicate that the average isolated HB strength is approximately 6 kcal/mol, which corresponds to a HB of medium strength similar to that of the water dimer (5.3 kcal/mol). The effect of the BSSE correction is not very important in this case due to the usage of a large basis set in conjunction with a density functional theoretical (DFT) method. It represents between 10 and 20% of the interaction energy. In addition, the BSSE differences found for each set of calculated dimers are very small (the larger one is 0.3 kcal/mol).

The HB distances (H···N distance) range between 1.83 and 1.97 Å and the HB angles are very close to linear, except in a few cases, which corresponds to the less favorable minima, where the HB angles reach values close to 160°. The sensitivity of the HB toward the relative energy of these systems is such that for all cases the shortest HBs correspond to the configuration with the lowest energy. Moreover, acceptable linear correlation can be found between these two parameters for each series of complexes (in all cases the correlation coefficient is larger than 0.9). In Figure 4, the correlations with the best and worse correlation coefficients are represented. In general, those systems with few additional contacts are the ones with the best correlations.

In the complexes of the nonchiral monomers, the chair configuration, C, is more stable than the boat one, B, by a small difference. These energetic differences increases as the size of the X group does (0.55, 0.90, 1.02, and 2.34 kcal/mol for H, F, CH_3, and CF_3, respectively). A repulsive interaction of the substituent in axial disposition in the boat configuration is observed in the more bulky cases ($X = CH_3$ and CF_3). The geometries of the HB are distorted by the effect of these interactions: in the bulkiest case ($X = CF_3$) the HB distance increased 0.07 Å and the HB angle varied by 16° when comparing the chair and boat configurations. The energetic preference of the equatorial disposition is in agreement with a

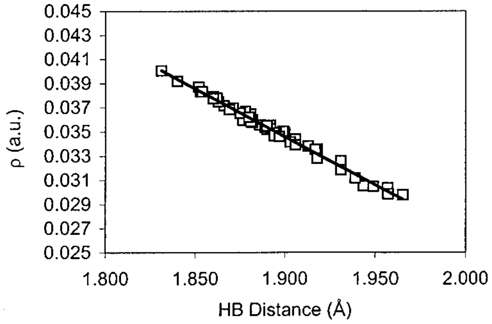

Figure 5. Linear correlation between the HB distance *d* and the electron density in the BCP ρ. The fitted equation is $\rho = 0.19 - 0.08\ d$, $r = 0.994$.

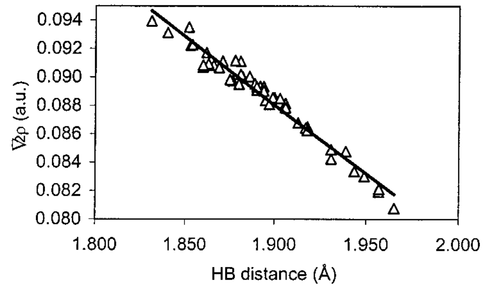

Figure 6. Linear correlation between the HB distance *d* and the Laplacian of the electron density in the BCP $\nabla^2\rho$. The fitted equation is $\nabla^2\rho = 0.27 - 0.10\ d$, $r = 0.98$.

recent report that showed similarities in the conformational behaviors of covalent and HB systems.[25]

For the chiral systems, the most favorable energetic dimers obtained in all cases correspond to a heterochiral (*RS*) one in a chair configuration and the worse one is a homochiral (*RR*) one in a boat configuration. The maximum diference between these two extreme configurations is 4 kcal/mol. Surprisingly, if the homochiral dimers are considered alone, the more stable configuration corresponds to another boat, except for X/Y = CH_3/CF_3, where the chair configuration is the most stable. Chemically, the preference of the heterochiral complex indicates that, for a racemic mixture or a mixture slightly enriched in one of the chiral forms, no separation in the gas phase will be possible without the participation of other external chiral system.

The AIM methodology allows study of noncovalent interactions as HB and van der Waals contacts. While it has been used as a standard tool for the study of HBs, its application to treat other weak interactions is rather scarce. In the present case, we have used it to detect additional contact between the monomers that can indicate stabilizing or destabilizing interactions. On a equilibrium structure all the forces are compensated, and thus all the bond critical points (BCP) found indicate stabilizing contacts. However, some of these contacts can have destabilizing effects in other parts of the molecule. In the present study, several BCPs between F···F and H···H pairs are observed; while they are approximately at the van der Waals distance (i.e., they are slightly stabilizing), they perturb the HB, weakening it (Table 3). The observed values of the electron density of these intermolecular interactions are very small (less than 0.01 au), as usual for van der Waals complexes.[26] In addition, if the van der Waals radii defined by Bondi[27] are considered (1.20 and 1.47 Å for H and F, respectively), there are several cases with contacts slightly smaller than the sum of the corresponding radii. In general, in the present study, and due to the characteristic of the molecules selected, additional BCPs destabilize the complex.

Table 4. Free Energy of Solvation ΔG_{solv} and Electrostatic and Nonelectrostatic Components (kcal/mol) Calculated with the PCM Model at the B3LYP/6-311++G** Level

substituents X/Y	chirality and confign	ΔG_{solv}	electrostatic	nonelectrostatic[a]	E_{rel} (incl solv)
H/H	C	−11.75	−13.74	1.99	2.62
H/H	B	−14.92	−16.86	1.94	0.00
F/F	C	−13.19	−17.59	4.40	0.00
F/F	B	−13.31	−17.57	4.26	0.78
CH_3/CH_3	C	−8.64	−12.84	4.20	0.00
CH_3/CH_3	B	−7.42	−11.45	4.03	2.24
CF_3/CF_3	C	−2.36	−13.27	10.91	0.00
CF_3/CF_3	B	−4.16	−14.76	10.60	0.54
F/H	R/R C-1	−19.65	−23.17	3.52	0.77
F/H	R/R B-1	−14.17	−17.52	3.35	7.66
F/H	R/R B-2	−19.24	−22.93	3.69	1.08
F/H	R/S C-2	−19.17	−22.51	3.34	2.32
F/H	R/S C-3	−18.85	−22.67	3.82	0.00
F/H	R/S B-3	−18.64	−22.04	3.40	1.27
H/CH_3	R/R C-1	−15.65	−19.13	3.48	0.00
H/CH_3	R/R B-1	−10.21	−13.39	3.18	5.16
H/CH_3	R/R B-2	−11.37	−15.35	3.98	6.05
H/CH_3	R/S C-2	−7.51	−10.53	3.02	7.45
H/CH_3	R/S C-3	−13.77	−17.67	3.90	2.66
H/CH_3	R/S B-3	−12.95	−16.20	3.25	3.14
H/CF_3	R/R C-1	−17.64	−24.43	6.79	0.95
H/CF_3	R/R B-1	−17.93	−24.22	6.29	0.00
H/CF_3	R/R B-2	−17.56	−24.53	6.97	3.68
H/CF_3	R/S C-2	−14.75	−20.87	6.12	2.53
H/CF_3	R/S C-3	−16.93	−24.02	7.09	2.03
H/CF_3	R/S B-3	−14.06	−20.50	6.44	3.97
F/CH_3	R/R C-1	−11.86	−16.14	4.28	1.33
F/CH_3	R/R B-1	−12.51	−16.94	4.43	2.77
F/CH_3	R/R B-2	−13.02	−17.09	4.07	0.00
F/CH_3	R/S C-2	−12.96	−17.46	4.50	1.71
F/CH_3	R/S C-3	−10.44	−14.56	4.12	0.97
F/CH_3	R/S B-3	−11.46	−15.73	4.27	1.10
CF_3/CH_3	R/R C-1	−6.57	−14.15	7.58	2.70
CF_3/CH_3	R/R B-1	−8.26	−15.62	7.36	1.57
CF_3/CH_3	R/R B-2	−7.88	−15.20	7.32	3.64
CF_3/CH_3	R/S C-2	−8.54	−16.05	7.51	0.00
CF_3/CH_3	R/S C-3	−5.73	−13.44	7.71	3.23
CF_3/CH_3	R/S B-3	−6.67	−14.06	7.39	2.91

[a] The nonelectrostatic term includes the cavitation, dispersion, and repulsion energies.

Regarding the values of the electron density and the Laplacian at the HB critical points, they range between 0.03 and 0.04 au for the electron density and 0.08−0.095 au for the Laplacian. These values are typical of standard HBs (the calculated values for the water dimer obtained at the same computational level are 0.025 and 0.093 au for a HB distance of 1.934 Å). As shown previously, a relationship between the values of these two parameters and the HB distance can be obtained (Figures 5 and 6). In this case and due to the small ranges of the properties, a linear fit can be found with an excellent correlation coefficient. When the range studied is larger, the relationship found is between the logarithm of the property (electron density and Laplacian) vs the HB distance.[28−30]

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Another critical point generated by the interaction of the two monomers corresponds to the ring critical point generated by the two HBs and the covalent bonds. The electron density of these critical points is approximately 0.006 au, and its Laplacian 0.025 au is an indication of the large size of the ring formed (six covalent bond plus two HBs).

The estimation of the ΔG_{solv} in water calculated with the PCM method is gathered in Table 4. The values range from −4 kcal/mol for the dimer of $X = Y = CF_3$ to −19 for X/Y = F/H. The decomposition of the ΔG_{solv} in electronic and nonelectronic terms shows that the latter values are very similar for all the complexes in each dimer set, since they depend on its volume and this is very similar for all of them. Thus, the electronic terms are the ones that generate the solvation differences. An analysis of the values obtained for the solvation shows that, for the nonchiral dimers, the largest ΔG_{solv} corresponds in three cases to the pseudoboat disposition (X = H, F, CF_3) and in one case to the chair configuration (X = CH_3). For the complexes obtained with the chiral monomers, the most favorable ΔG_{solv} is associated, in all cases, with an *RR* structure except for X/Y = CH_3/CF_3.

The inclusion of the solvation effect produces important changes in the relative energy of the dimers. Thus, in three of the cases studied (X/Y = H/CH_3, H/CF_3, F/CH_3), the inclusion of the solvation energy yields that one of the homochiral configurations became the most stable, in contrast with the gas-phase results.

Conclusion

The dimers of a series of nonchiral and chiral α-amino alcohols have been studied by means of DFT (B3LYP/6-311++G**) calculations. Six configurations with two HBs for each case have been considered, three in a chair configuration and another three in a boat one. The energetic results indicate that in the gas phase and in all cases studied, the most stable dimer corresponds to a heterochiral one. A linear correlation has been found in all cases between the interaction energy and the average HB distance. The AIM methodology has been used to analyze the intermolecular contact in the dimers. Bond critical points have been found between moieties that are interacting and weakened the HB interaction. The electronic properties of the HB critical points (electron density and Laplacian) have been shown to linearly correlate with the HB distance. Finally, the free energy of solvation in water has been estimated using the PCM. In several of the cases studied, a homochiral configuration became the most stable. These results indicate the importance of the media in the homochiral and heterochiral recognition.

The variation of the relative energy between homochiral and heterochiral complexes as a function of the environment could be directly related to the diferent mechanisms proposed for the enantioselective separations in racemic mixtures.[31] These processes together with the natural generation of small enantiomeric exceses by magnetic fields,[32] polarized light, or adsorption in chiral phases of crystals[33] could lead to a scenario similar to the one carried out in nature to select the first building blocks that derived in the actual molecules with unique chirality (L-amino acids and D-sugars).

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Supporting Information Available: Tables with absolute energies and Cartesian coordinates of the calculated geometry of all the monomers and dimers (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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