JOURNAL OF PHYSICAL ORGANIC CHEMISTRY
J. Phys. Org. Chem. 2005; **18:** 491–497
Published online 1 February 2005 in Wiley InterScience (www.interscience.wiley.com). DOI: 10.1002/poc.901

Chiral recognition in phosphinic acid dimers

Óscar Picazo,[1] Ibon Alkorta,[1]* Jose Elguero,[1] Otilia Mó[2] and Manuel Yáñez[2]

[1]Instituto de Química Médica (CSIC), Juan de la Cierva 3, E-28006 Madrid, Spain
[2]Departamento de Química, C-9, Universidad Autónoma de Madrid, Cantoblanco, E-28049 Madrid, Spain

Received 1 October 2004; revised 3 December 2004; accepted 8 December 2004

ABSTRACT: A theoretical study of chiral recognition in the minimum and proton transfer transition state structures of 15 pairs of chiral phosphinic acid dimers was carried out using DFT and MP2 methods, up to the MP2/6–311++G(3df,2p) level. The proton transfer proceeds via a concerted pathway in all cases studied. Even though these complexes show high interaction energies, of the order of 120 kJ mol^{-1}, and short interatomic HB distances, our results show small energy differences between the homochiral (*RR* or *SS*) and the heterochiral dimers (*RS* or *SR*) both in the equilibrium configuration and in the proton transfer transition state owing to the disposition of the nonoxygen substituents of the phosphorus atom as proved with additional model complexes. Copyright © 2005 John Wiley & Sons, Ltd.

KEYWORDS: phosphinic acids; *ab initio* calculations; hydrogen bond; chiral discrimination; proton transfer

INTRODUCTION

The forces that determine molecular structures can be classified into covalent, metallic and noncovalent, which, with some overlapping, correspond to strong, medium and weak or to organic, coordination and supramolecular chemistry. All have the same importance for chemistry and for life, but the weaker they are, the more difficult they are to study and characterize.

Concerning non-covalent interactions, it is important to consider, in addition to their strength, the fact that there are two possibilities: either the groups that interact are complementary (the most common case) or identical. Identical groups that show attractive effects are found only in van der Waals interactions (possible also for different groups). A metallic center can bring together two identical ligands such as two phosphines, two cyclopentadienyls or two benzenes. One of the most important of the weak interactions, the hydrogen bond (HB), always occurs between two complementary groups (Scheme 1).

This assertion needs to be clarified. For instance, two or more water molecules are associated through HBs. However the two molecules are different: one acts as an HB donor (HBD, —O) and the other as an HB acceptor (HBA, ⊃—, Scheme 2). The same happens to all HBs between identical molecules.

When two neutral molecules, a charged and a neutral molecule or two molecules of opposite charge approach each other, a bimolecular equilibrium structure is formed. If both molecules are chiral (this is the most common case but it is not a necessary condition),[1] two supramolecular complexes that differ in energy can be formed, the *RR*(*SS*) and the *RS*(*SR*) forms. This phenomenon is called chiral recognition; the name becomes self-recognition if the two molecules are identical. The recognition could involve three, two or one interaction. From simple parity considerations, if three centered HBs are excluded, self-recognition using HBs is only possible in the case of two interactions (see Scheme 3, complex 2b). One interaction needs identical groups (⊢, complex 1a) and three interactions need one (complex 3b) or three identical groups (a rather improbable situation unless metallic centers are involved).

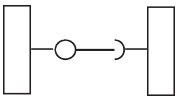
Bifurcated (three-centered) HBs[2] destroy the 1:1 parity and three interactions between two identical molecules are possible (Scheme 4).

We need now to discuss the famous three-point attachment (TPA) model of Easson and Stedman of 1933.[3,4] This model applies clearly to the case of complementary groups belonging to two different molecules (Scheme 5), for instance to drug receptor interaction or to chiral chromatography.

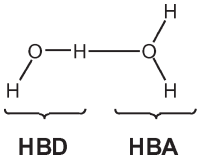
The rule was later restated by Pirkle and House as 'chiral recognition requires a minimum of three simultaneous interactions, with at least one of these interactions to be stereochemically dependent'.[5] There has been controversy about the minimum requirements for chiral recognition.[6–8] Further insights into TPA were provided by the work of Copeland[9] and Lebrilla and co-workers.[10]

However, this model does not apply to self-recognition. As we have discussed previously, self-recognition usually

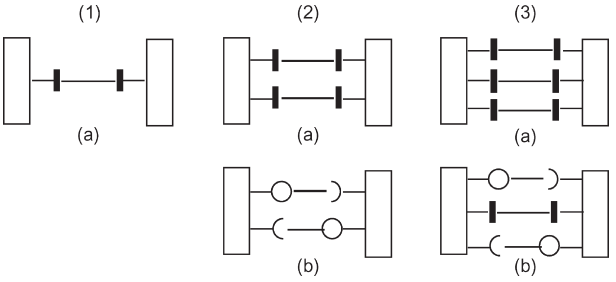
**Correspondence to:* I. Alkorta, Instituto de Química Médica (CSIC), Juan de la Cierva 3, E-28006 Madrid, Spain.
E-mail: ibon@iqm.csic.es
Contract/grant sponsor: Ministerio de Ciencia y Tecnología; *Contract/grant numbers*: BQU-2003-01251, BQU-2003-00289.



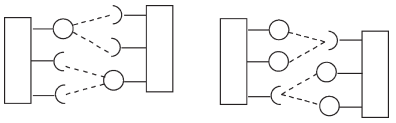
Scheme 1



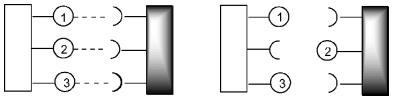
Scheme 2



Scheme 3. Bimolecular complexes between identical molecules



Scheme 4. Bimolecular complexes involving three-centered hydrogen bonds



Scheme 5. Two examples of the TPA model

occurs through mechanism 2b (Scheme 3) when hydrogen bonds (HBs) mediated the interaction. We have in progress a research program aimed at the study and comprehension of chiral self-recognition between enantiomers mediated by HBs. We have used monomers that have both a hydrogen-bond donor (HBD) and a hydrogen-bond acceptor (HBA) site, that is, in the dimer the two monomers are linked by two HBs, e.g. hydrogen peroxide,[11] α-amino alcohols,[12] sulfoxides[13] and pyrrolo[2,3-*c*]pyrroles.[14]

We have now turned our attention to phosphinic acid (PA) derivatives, for two reasons. One is that they are commercial chiral phosphinic acids (they become prochiral in solution owing to prototropic tautomerism involving the P═O and the P—O—H groups). The second and most important reason is that the phosphinic acid dimer represents one of the strongest neutral hydrogen-bonded dimers described in the literature. The IR spectrum in gas phase of dimethylphosphinic acid published by Denisov and co-workers[15] showed the existence of the characteristic *ABC* structure of the ν(OH) band, only compatible with the presence of two very strong HBs within the dimer. The experimental value of the dimerization enthalpy for the dimethylphosphinic acid ($100\,\mathrm{kJ\,mol^{-1}}$) has been reproduced using DFT calculations with large basis sets.[16] Theoretically, the possibility of obtaining spontaneous proton transfer (autoionization) in some PA heterodimers has been demonstrated.[17]

The tetrahedral nature of the phosphorus atom in the PA derivatives opens up the possibility of obtaining chiral compounds as in the case of the phosphinic amides or the PA derivatives, recently described.[18] In 1977, Harger analyzed the chiral recognition in phosphinic amides,[19] and more recently Paladini *et al*. studied the enantiodiscrimination of metallic complexes of α-aminophosphonic acids using mass spectrometric techniques.[20]

Several other experimental studies have addressed the chiral recognition through HB interactions. Thus, gas-phase complexations of 2-butanol[21] and glycidol[22] dimers have been carried out and the dimers, trimers and tetramers of lactate have been characterized using FTIR spectroscopy.[23] In addition to our work cited above,[11–14] other workers have provided examples of chiral recognition. For instance, the diastereomeric interaction between a chiral system with the two enantiomeric forms of another molecule has been calculated for simple ether derivatives of oxirane and hydrogen peroxide.[24] The solvent effect on chiral discrimination has been studied in dimers of hydrogen peroxide and its methyl derivative.[25] The interaction of 2-naphthyl-1-ethanol with chiral and non-chiral alcohols has been studied experimental and theoretically.[26]

In the present work, the chiral recognition of a chiral PA derivative by itself (homochiral dimer, *RR* or *SS*, true self-recognition) or by its enantiomer (heterochiral dimer, *RS* or *SR*, pseudo self-recognition) through an HB complex was investigated using DFT and *ab initio* methods. In addition, the proton transfer processes for all the dimers considered previously have been studied.

METHODS

The geometries and energies of the monomers and dimers were obtained using the Gaussian 98 package.[27] Initially, the geometries were optimized using the B3LYP/6–31+G(d,p) method.[28,29] The minimum and transition state nature of the structures was verified by frequency calculation at the same computational level. A further optimization was carried out at the MP2/6–311+G(d,p) level.[30,31] Finally, the MP2/6–311++G(3df,2p) energies were evaluated on the MP2/6–311+G(d,p) geometries (abbreviated as MP2/G2). The energies were corrected

from the inherent Basis Set Superposition Error (BSSE) using the full counterpoise method[32] as defined by

$$\mathrm{BSSE(AB)} = E(\mathrm{A})_{\mathrm{A}} - E(\mathrm{A})_{\mathrm{AB}} + E(\mathrm{B})_{\mathrm{B}} - E(\mathrm{B})_{\mathrm{AB}} \quad (1)$$

where $E(\mathrm{A})_{\mathrm{AB}}$ represents the energy calculated for monomer A using its geometry in the complex and the complete set of basis functions used to describe the dimer and $E(\mathrm{A})_{\mathrm{A}}$ is the energy for monomer A using its geometry in the complex and its basis set.

RESULTS AND DISCUSSION

The chirality of the phosphinic acids relies on the presence of two non-identical substituents on the phosphorus atom and the position of the hydrogen bond to one of the two oxygens linked to the phosphorus. The gas-phase intramolecular proton transfer (Fig. 1), which could lead to the racemization of some of the molecules studied here, presents very high activation barriers ($>140\,\mathrm{kJ\,mol^{-1}}$) as shown in Table 1. The three methods considered here provide similar results. Systematically, the lower barriers are those evaluated at the MP2/6–311++G(3df,2p)//MP2/6–311+G** level, followed by the B3LYP/6–31+G** estimates. Larger barriers are obtained at the MP2/6–311+G** level, but the differences observed are never greater than $11\,\mathrm{kJ\,mol^{-1}}$, which represents 7% of the total value.

The height of the barrier increases with the electron-withdrawing capacity of the substituents. If one of the substituents is fixed, the following trend can be observed in the activation barriers as a function of the other substituent: tBu < Me < Br < Cl < F, CF_3. Further, the barriers are larger for the fluorine-substituted series than for the unsubstituted compounds, the barriers for the methylated derivatives being the smallest.

A schematic representation of the phosphinic acid dimers is shown in Fig. 2. The proton transfer TS structures correspond to a concerted process with a higher symmetry than the corresponding minima. In addition, the proton transfer produces an inversion of the chirality of the phosphinic acids molecules; thus, an *RR* dimer after the proton transfer generates an *SS* dimer whereas the *RS* dimer is connected with the *SR* dimer.

The interaction energies and concerted proton transfer barriers of the 15 pairs of dimers studied here are given in

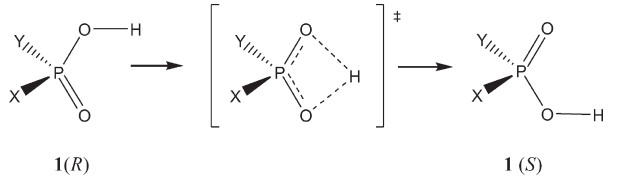


Figure 1. Schematic representation of the proton transfer process in the isolated phosphinic acid monomers

Table 1. Calculated intramolecular TS barriers ($\mathrm{kJ\,mol^{-1}}$) in the gas phase

X	Y	B3LYP/ 6–31+G**	MP2/ 6–311+G**	MP2/G2
F	H	159.64	165.60	156.05
Cl	H	156.18	161.57	150.43
Br	H	155.28	161.19	150.56
CH_3	H	146.06	151.21	142.73
CF_3	H	159.22	165.04	155.91
$C(CH_3)_3$	H	141.98	147.62	139.10
F	CH_3	154.47	160.71	151.02
Cl	CH_3	151.87	157.10	147.00
Br	CH_3	150.98	156.66	147.07
CF_3	CH_3	153.71	159.00	151.05
$C(CH_3)_3$	CH_3	137.47	142.67	134.99
Cl	F	163.77	168.85	159.95
Br	F	161.58	166.92	158.59
CF_3	F	166.53	172.94	164.25
$C(CH_3)_3$	F	150.25	157.32	147.55

Table 2. The values obtained show interaction energies between −93 and $-106\,\mathrm{kJ\,mol^{-1}}$ at the highest computational level considered here [MP2/6–311++G(3df,2p)//MP2/6–311+G**], that have been used as reference values. The B3LYP/6–31+G** results systematically underestimate those results, the average difference being $8\,\mathrm{kJ\,mol^{-1}}$. The interaction energies obtained at the MP2/6–311+G** level of theory are very similar to those calculated with the larger basis set, the largest absolute deviation being $2\,\mathrm{kJ\,mol^{-1}}$, but when the BSSE correction is taken into account the difference increases to an average of $15\,\mathrm{kJ\,mol^{-1}}$.

The barriers obtained (between 14 and $20\,\mathrm{kJ\,mol^{-1}}$) indicate the ease of the proton transfer process (Table 2). In addition, the inclusion of ZPE corrections obtained using harmonic frequencies[8] leads to negative TS barriers, an indication that this is, in practice, an almost barrierless process as in the case of low barrier hydrogen bonds (LBHB).[33] The comparison of the different methods provides a picture radically different to that obtained from the energies of the minima. In this case, the B3LYP/6–311+G** calculation yields similar values to those at the MP2 level with the large basis set, underestimating those by $2.2\,\mathrm{kJ\,mol^{-1}}$ on average. These results are in accord with previous reports that have shown that DFT calculations underestimate TS barriers.[34] In contrast, the MP2/6–311+G** values are systematically larger than the reference values in the a range 4.0–7.8 $\mathrm{kJ\,mol^{-1}}$ and an average of $5.7\,\mathrm{kJ\,mol^{-}}$ for the cases studied here.

Some of the geometric parameters of the complexes studied are given in Table 3. The strength of the interaction is reflected in short H···O distances (1.59 Å on average) and in elongation of the covalent O—H bond (0.04 Å) with respect to the corresponding value in the isolated monomers. The effect of the substituents on the HB seems to be small owing to the narrow range of values

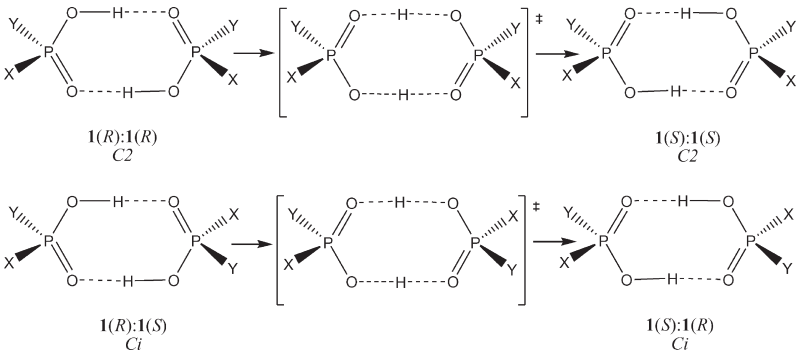


Figure 2. Schematic representation of the homochiral and heterochiral dimers and proton transfer processes

Table 2. Calculated corrected interaction energies and TS barriers (kJ mol^{-1}) for the chiral phosphinic acid dimers

			Minima			TS		
X	Y	Chirality	B3LYP	MP2	MP2/G2	B3LYP	MP2	MP2/G2
F	H	*RR*	−90.25	−80.78	−95.61	14.60	24.26	17.34
F	H	*RS*	−90.80	−81.28	−95.44	14.51	24.10	17.01
Cl	H	*RR*	−87.37	−79.07	−95.73	15.99	25.78	18.25
Cl	H	*RS*	−88.44	−79.97	−95.79	15.67	24.70	17.29
Br	H	*RR*	−85.29	−78.52	−95.51	16.49	26.61	19.11
Br	H	*RS*	−87.45	−79.24	−95.14	15.67	25.55	17.75
CH_3	H	*RR*	−94.99	−86.27	−100.62	16.70	24.84	19.73
CH_3	H	*RS*	−96.48	−86.90	−100.90	15.48	23.28	17.77
CF_3	H	*RR*	−88.45	−79.17	−95.24	15.30	25.75	18.59
CF_3	H	*RS*	−89.27	−79.47	−95.42	14.81	23.89	18.04
$C(CH_3)_3$	H	*RR*	−95.06	−88.43	−102.65	15.19	20.22	15.80
$C(CH_3)_3$	H	*RS*	−95.95	−88.70	−102.56	13.84	20.06	16.07
F	CH_3	*RR*	−93.22	−84.60	−98.60	14.08	22.03	16.50
F	CH_3	*RS*	−94.13	−85.31	−98.91	13.80	21.73	16.36
Cl	CH_3	*RR*	−90.41	−83.67	−99.50	15.12	22.45	17.33
Cl	CH_3	*RS*	−91.99	−85.12	−99.66	14.64	21.78	16.22
Br	CH_3	*RR*	−88.06	−83.79	−99.67	15.31	22.88	17.76
Br	CH_3	*RS*	−90.74	−84.82	−99.53	14.34	22.11	16.51
CF_3	CH_3	*RR*	−91.83	−84.44	−105.86	14.32	22.14	16.97
CF_3	CH_3	*RS*	−93.68	−85.78	−106.53	13.52	20.59	16.39
$C(CH_3)_3$	CH_3	*RR*	−94.24	−89.27	−104.68	13.58	17.73	13.34
$C(CH_3)_3$	CH_3	*RS*	−95.15	−90.01	−105.28	14.18	20.45	16.30
Cl	F	*RR*	−86.29	−80.16	−93.90	16.08	24.16	18.24
Cl	F	*RS*	−86.31	−79.91	−93.61	16.12	24.43	18.21
Br	F	*RR*	−83.87	−78.43	−93.35	17.43	25.34	18.66
Br	F	*RS*	−84.98	−78.56	−93.13	16.87	25.49	18.58
CF_3	F	*RR*	−86.70	−79.10	−93.23	14.78	22.61	17.83
CF_3	F	*RS*	−86.87	−79.09	−93.03	14.48	22.51	17.29
$C(CH_3)_3$	F	*RR*	−94.07	−85.57	−101.47	13.58	19.37	15.01
$C(CH_3)_3$	F	*RS*	−94.84	−86.11	−101.88	12.89	19.15	14.82

obtained for the different geometric parameters of the HB (0.07 and 0.01 Å in the O···H and O—H distances, respectively).

In the TS structures, compression of the systems is observed, which facilitates the proton transfer, as compared with the minima. Thus the interatomic O···O distance changes on average from 2.58 Å in the minima to 2.38 Å in the TS. In addition, it is observed that the OHO angle shows a value of 177° on average for the TSs, whereas for the minima this average is 169°, in agreement with the general rule that states that shorter HBs are in general more linear.[35] As discussed previously for the minima, distances obtained for the geometric parameters of the HB vary in a very narrow range (0.006 Å for the O···H distance).

The chiral discrimination values, obtained as the difference between the homo-and the heterochiral structures (minima or TS), are given in Table 4. In the case of the

Table 3. Geometrical parameters (Å, °) of the phosphinic acid dimers and the TS structures

			Minima				TS		
X	Y	Chirality	O···H	OH	O···O	O···HO	O···H	O···O	O···HO
F	H	*RR*	1.593	1.001	2.584	169.8	1.192	2.383	176.6
F	H	*RS*	1.596	1.001	2.586	169.2	1.192	2.383	176.4
Cl	H	*RR*	1.616	0.999	2.598	166.4	1.194	2.385	175.3
Cl	H	*RS*	1.608	1.001	2.591	166.1	1.194	2.386	175.0
Br	H	*RR*	1.620	1.000	2.601	166.1	1.195	2.387	175.1
Br	H	*RS*	1.615	1.000	2.595	165.3	1.195	2.388	174.9
CH_3	H	*RR*	1.597	1.001	2.589	169.5	1.192	2.384	177.8
CH_3	H	*RS*	1.589	1.003	2.583	169.7	1.194	2.388	176.8
CF_3	H	*RR*	1.615	1.000	2.599	167.0	1.194	2.386	176.0
CF_3	H	*RS*	1.605	1.002	2.591	167.1	1.195	2.387	175.3
$C(CH_3)_3$	H	*RR*	1.571	1.006	2.572	172.0	1.191	2.382	178.4
$C(CH_3)_3$	H	*RS*	1.569	1.006	2.570	172.5	1.193	2.386	178.2
F	CH_3	*RR*	1.578	1.004	2.576	171.8	1.192	2.384	177.3
F	CH_3	*RS*	1.576	1.004	2.574	171.2	1.193	2.385	177.2
Cl	CH_3	*RR*	1.586	1.004	2.580	169.5	1.194	2.387	176.5
Cl	CH_3	*RS*	1.583	1.004	2.575	168.6	1.194	2.386	176.3
Br	CH_3	*RR*	1.590	1.004	2.584	169.7	1.195	2.388	176.4
Br	CH_3	*RS*	1.588	1.004	2.579	168.4	1.195	2.388	176.3
CF_3	CH_3	*RR*	1.582	1.005	2.578	170.4	1.193	2.386	177.0
CF_3	CH_3	*RS*	1.573	1.007	2.570	170.0	1.195	2.388	176.2
$C(CH_3)_3$	CH_3	*RR*	1.563	1.008	2.571	169.9	1.191	2.383	179.5
$C(CH_3)_3$	CH_3	*RS*	1.569	1.006	2.570	172.5	1.194	2.387	178.2
Cl	F	*RR*	1.583	1.000	2.574	170.0	1.189	2.379	178.1
Cl	F	*RS*	1.589	1.000	2.577	168.7	1.189	2.379	175.0
Br	F	*RR*	1.604	0.999	2.590	168.4	1.190	2.380	178.3
Br	F	*RS*	1.604	0.999	2.589	168.0	1.190	2.380	178.0
CF_3	F	*RR*	1.583	1.002	2.575	170.0	1.191	2.381	177.0
CF_3	F	*RS*	1.580	1.003	2.573	170.1	1.191	2.381	177.2
$C(CH_3)_3$	F	*RR*	1.558	1.007	2.561	173.5	1.192	2.383	177.5
$C(CH_3)_3$	F	*RS*	1.553	1.008	2.557	173.5	1.192	2.383	178.5

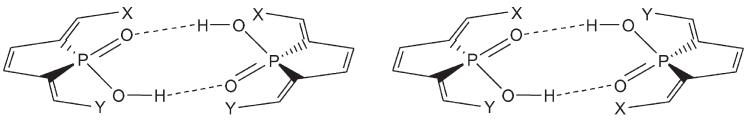
Table 4. Chiral discrimination in the phosphinic acid dimers (kJ mol^{-1})[a]

		Minima			TS		
X	Y	B3LYP	MP2	MP2/G2	B3LYP	MP2	MP2/G2
F	H	−0.54	−0.50	0.16	−0.66	−0.99	−0.13
Cl	H	−1.07	−0.90	−0.07	−1.52	−1.16	−0.82
Br	H	−2.16	−0.72	0.37	−0.48	−1.54	−0.87
CH_3	H	−1.49	−0.63	−0.28	−2.78	−2.88	−2.52
CF_3	H	−0.82	−0.30	−0.18	−1.33	−0.99	0.22
$C(CH_3)_3$	H	−0.88	−0.27	0.09	−2.15	−0.16	0.29
F	CH_3	−0.92	−0.71	−0.31	−1.16	−1.52	−0.58
Cl	CH_3	−1.58	−1.44	−0.16	−2.00	−0.81	−0.93
Br	CH_3	−2.67	−1.02	0.14	−0.94	−1.43	−0.99
CF_3	CH_3	−1.85	−1.34	−0.67	−2.61	−2.69	−1.22
$C(CH_3)_3$	CH_3	−0.91	−0.75	−0.60	−0.24	1.70	1.77
Cl	F	−0.01	0.26	0.29	−0.13	0.03	−0.11
Br	F	−1.10	−0.13	0.22	−0.72	−0.42	0.00
CF_3	F	−0.17	0.01	0.20	−0.56	−0.32	−0.38
$C(CH_3)_3$	F	−0.77	−0.54	−0.41	−1.44	−1.25	−0.88

[a] The homochiral dimer is used as reference in all cases.

minima, the BSSE corrections were considered and it was found to be specially important in the bromine derivatives at the B3LYP/6–31+G** level, where this correction accounts for a change of as much as 2.7 kJ mol^{-1} in the energy gap between the homo and the heterochiral complexes.

The comparison of the corrected relative energies of the minima shows that in all cases the B3LYP/6–31+G**



2(*R*):**2**(*R*) **2**(*R*):**2**(*S*)

Figure 3. New dimers designed to increase the interaction between the non-oxygen substituents of the phosphorus atom

Table 5. Calculated corrected interaction energies, chiral discrimination (kJ mol^{-1}) and HB geometric characteristics (Å, °) for the dimers of **2** calculated at the B3LYP/6–31+G** level

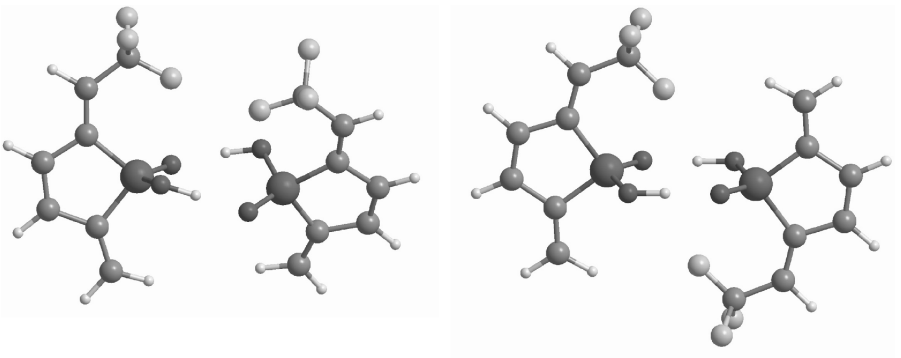
X	Y	Chirality	E_I	Chiral discrimination	O···H	OH···O
F	H	*RR*	−87.68		1.549	175.9
F	H	*RS*	−90.44	−2.76	1.545	176.3
Cl	H	*RR*	−85.96		1.555	174.7
Cl	H	*RS*	−87.21	−1.25	1.543	177.0
Br	H	*RR*	−82.72		1.555	175.0
Br	H	*RS*	−82.02	0.70	1.545	176.2
CH_3	H	*RR*	−88.12		1.580	172.3
CH_3	H	*RS*	−87.67	0.45	1.586	173.3
CF_3	H	*RR*	−77.38		1.567	172.4
CF_3	H	*RS*	−86.56	−9.19	1.533	177.0
$C(CH_3)_3$	H	*RR*	−85.41		1.593	172.1
$C(CH_3)_3$	H	*RS*	−86.67	−1.26	1.596	174.3

approach favors systematically the heterochiral complexes. Similar findings, with the only exception of the (F, Cl) and the (F, CF_3) derivatives are observed when the MP2/6–311+G** approach is used. Conversely, for almost half of the complexes studied (7 out of 15), the MP2/G2 approach predicts the homochiral complexes to be the most stable. In summary, the B3LYP calculations correspond in all cases to a preference for the heterochiral complexes; two homochiral complexes are preferred at the MP2/6–311+G** level and seven at the MP2/G2 level.

The analysis of the MP2/G2 data shows that the replacement of the hydrogen by a methyl group as a substituent of the phosphorus atom favors the corresponding heterochiral complex, with the only exception of the bromine derivative. Fluorine substitution has a less systematic effect and only for three out of the five complexes are the heterochiral complexes favored. In any case, for the complexes studied at the MP2/G2 level, the chiral recognition in the minima is small, ranging from −0.67 to 0.37 kJ mol^{-1}.

In the TS (Table 4), the compression of the O···O distance associated with the proton transfer increases, in general, the chiral discrimination in the heterochiral cases at all the computational levels. These results agree with previous reports of chiral proton transfer.[14] The largest chiral discrimination, at the three computational levels considered here, corresponds to the monomethylated derivative ($X = CH_3$, $Y = H$) with an energy value of −2.52 kJ mol^{-1} at the MP2/G2 level. Only in one case is the homochiral TS favored [$X = C(CH_3)_3$, $Y = CH_3$] with a relative energy of 1.77 kJ mol^{-1}.

The small chiral discrimination found in the dimers studied could be associated with the tetrahedral disposition of the phosphorus atom that keeps far apart the non-oxygen substituents, reducing the possibility of interaction between them, in both the homo- and the heterochiral complexes and, subsequently, diminishing the energy differences. A way to check this hypothesis is to build a molecular scaffold that locates the substituents in closer proximity within the dimers (Fig. 3).



RR *RS*

Figure 4. Optimized geometries of the homo- and heterochiral X/Y = CF_3/H dimers calculated at the B3LYP/6–31+G** level

The calculated interaction energies and the chiral discrimination of the dimers of **2** are reported in Table 5. Several of the characteristics of these dimers are similar to those of the dimers of **1**, such as the interaction energy and geometric characteristic of the HB formed. However, in the case of **2**, several of the complexes show large chiral discriminations, especially in the case of the $X/Y = CF_3/H$ dimers, where the heterochiral complex is $9.2\,kJ\,mol^{-1}$ more stable than the homochiral complex (Fig. 4).

CONCLUSIONS

The interaction energies in the dimers are very large whereas the barriers for the proton transfer process have very small TS, which in practice disappear when ZPE corrections using harmonic frequencies are included.

Even though these complexes show large interaction energies and short interatomic HB distances, the chiral discrimination values are very dependent on the position of the non-oxygen substituents. Hence only scaffolds that orient the substituent in the same region of the space within the dimer are able to provide significant chiral discrimination.

To have a clear self-recognition between molecules through HBs, two conditions are necessary: strong HBs and proximity of the substituents (i.e. weak forces between substituents, such as steric hindrance, dipole–dipole, hydrophobic, electrostatic and dispersive interactions). However, the relative weight of these two conditions cannot be easily established *a priori*. Our study shows that phosphinic acids amply satisfy the first condition but not the second. These results together with those reported in our previous work[11–14] lead to the inescapable conclusion that proximity is more important than strength.

The HB distance contraction characteristic of the TSs[14] increases the discrimination. This is related to the fact that kinetic resolutions have more chances of succeeding than equilibrium-based procedures.

It has been proved again that chiral self-recognition does not need three points; two, and maybe one, are sufficient. The interaction between two chiral entities is diastereomeric independently of the number, 1–3, of the attachments. It is hoped that this proposal will initiate an extensive re-examination of chiral recognition.

Acknowledgements

This work was carried out with financial support from the Ministerio de Ciencia y Tecnología (Projects Nos BQU-2003-01251 and BQU-2003-00289). Thanks are due to the CTI (CSIC) and CESGA for allocation of computer time.

REFERENCES

1. Mateos-Timoneda MA, Crego-Calama M, Reinhoudt DN. *Chem. Soc. Rev.* 2004; **33**: 363–372.
2. Rozas I, Alkorta I, Elguero J. *J. Phys. Chem. A* 1998; **102**: 9925–9932.
3. Easson L, Stedman E. *Biochem. J*. 1933; **27**: 1257–1266.
4. Ogston AG. *Nature* 1948; **163**: 963.
5. Pirkle WH, House DW. *J. Org. Chem*. 1979; **44**: 1957–1960.
6. Davankov VA. *Chirality* 1997; **9**: 99–102.
7. Booth TD, Wahnon D, Wainer IW. *Chirality* 1997; **9**: 96–98.
8. Pirkle WH. *Chirality* 1997; **9**: 103.
9. Copeland RA. *Enzymes: A Practical Introduction to Structure, Mechanisms and Data Analysis* (2nd edn). J Wiley: New York, 2000; 149–150.
10. Ramirez J, Ahn S, Grigorean G, Lebrilla CB. *J. Am. Chem. Soc.* 2000; **122**: 6884–6890; Ahn S, Ramirez J, Grigorean G, Lebrilla CB. *J. Am. Soc. Mass Spectrom*. 2001; **12**: 276–287; Grigorean G, Lebrilla CB. *Anal. Chem*. 2001; **73**: 1684; Lebrilla CB. *Acc. Chem. Res*. 2001; **34**: 653–661.
11. Alkorta I, Elguero J. *J. Chem. Phys*. 2002; **117**: 6463–6467.
12. Alkorta I, Elguero J. *J. Am. Chem. Soc*. 2002; **124**: 1488–1493.
13. Alkorta I, Picazo O, Elguero J. *Tetrahedron: Asymmetry* 2004; **15**: 1391–1399.
14. Picazo O, Alkorta I, Elguero J. *J. Org. Chem*. 2003; **68**: 7486–7489.
15. Denisov GS, Tokhadze KG. *Dokl. Phys. Chem*. 1994; **337**: 117–119; Tokhadze KG, Denisov GS, Wierzejewska M, Drozd M. *J. Mol. Struct*. 1997; **404**: 55–62.
16. González L, Mó O, Yáñez M, Elguero J. *J. Chem. Phys*. 1998; **109**: 2685–2693.
17. Mó O, Yáñez M, González L, Elguero J. *Phys. Chem. Phys*. 2001; 456–467.
18. Guillen F, Rivard M, Toffano M, Legros JY, Daran JC, Fiaud JC. *Tetrahedron* 2002; **58**: 5896–5904.
19. Harger MJP, *J. Chem. Soc., Perkin Trans. 2* 1977; 1882–1887.
20. Paladini A, Calcagni C, Di Palma T, Speranza M, Lagana A, Fago G, Filippi A, Satta M, Giardini Guidoni A. *Chirality* 2001; **13**: 707–711.
21. King AK, Howard BJ. *Chem. Phys. Lett*. 2001; **348**: 343–349.
22. Borho N, Haber T, Suhm MA. *Phys. Chem. Chem. Phys*. 2001; **3**: 1945–1948.
23. Borho N, Suhm MA. *Org. Biomol. Chem*. 2003; **1**: 4351–4358.
24. Portmann S, Inauen A, Lüthi HP, Leutwyler S. *J. Chem. Phys*. 2000; **113**: 9577–9585.
25. Du DM, Fu AP, Zhou ZY. *Chem. Phys. Lett.* 2004; **392**: 162–167.
26. Al Rabaa A, Le Barbu K, Lahmani F, Zehnacker-Rentien A. *J. Phys. Chem. A* 1997**; 101**: 3273–3278; Le Barbu K, Brenner V, Millie P, Lahmani F, Zehnacker-Rentien A. *J. Phys. Chem. A* 1998; **102**: 128–137; Le Barbu K, Lahmani F, Zehnacker-Rentien A. *J. Phys. Chem. A* 2002; **106**: 6271–6278.
27. Frisch MJ, Trucks GW, Schlegel HB, Scuseria GE, Robb MA, Cheeseman JR, Zakrzewski VG, Montgomery JA, Stratmann RE, Burant JC, Dapprich S, Millam JM, Daniels AD, Kudin KN, Strain MC, Farkas O, Tomasi J, Barone V, Cossi M, Cammi R, Mennucci B, Pomelli C, Adamo C, Clifford S, Ochterski J, Petersson GA, Ayala PY, Cui Q, Morokuma K, Malick DK, Rabuck AD, Raghavachari K, Foresman JB, Cioslowski J, Ortiz JV, Stefanov BB, Liu G, Liashenko A, Piskorz P, Komaromi I, Gomperts R, Martin RL, Fox DJ, Keith T, Al-Laham MA, Peng CY, Nanayakkara A, González C, Challacombe M, Gill PMW, Johnson BG, Chen W, Wong MW, Andrés JL, Head-Gordon M, Replogle ES, Pople JA. *Gaussian 98*. Gaussian: Pittsburgh, PA, 1998.
28. Becke AD. *J. Chem. Phys*., 1993; **98**: 5648–5652; Lee C, Yang W, Parr RG. *Phys. Rev. B* 1988; **37**: 785–789.
29. Hariharan PA, Pople JA. *Theor. Chim. Acta* 1973; **28**: 213–222.
30. Møller C, Plesset MS. *Phys. Rev.* 1934; **46**: 618–622.
31. Frisch MJ, Pople JA, Krishnam R, Binkley JS. *J. Chem. Phys*. 1984; **80**: 3265–3269.
32. Boys SF, Bernardi F. *Mol. Phys*. 1970; **19**: 553–566.
33. Perrin CL, Nielson JB. *Annu. Rev. Phys. Chem.* 1997; **48:** 511–544.
34. Bach RD, Glukhovtsev MN, Gonzalez C, Marquez M, Estévez CM, Baboul AG, Schlegel HB. *J. Phys. Chem. A* 1997; **101**: 6092–6100; Durant JL. *Chem. Phys. Lett.* 1996; **256**: 595–602.
35. Jeffrey GA, Saenger W. *Hydrogen Bonding in Biological Structures*. Springer: Berlin, 1991.