Solvent effect on halogen bonding: The case of the I···O interaction

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ABSTRACT

The solvent effect on the I···O halogen bonding in complexes of iodobenzene derivatives with formaldehyde has been investigated by systematically varying the substituents on the iodobenzene ring. Calculations have been performed at MP2 and DFT levels of theory, using the aug-cc-pVDZ basis set and the pseudopotential for iodine. Within the DFT approach, a series of the most widely used exchange-correlation functionals have been considered, comprising PBE, PBE0, B3LYP, BH&HLYP, M06-2X and M06-HF. Results obtained in diethylether and in water using the conductor-like polarizable continuum model (CPCM) have been compared with in vacuo results. Though halogen bonding distances were found to systematically shorten when moving from vacuo to diethylether and then to water, the associated interaction energies showed a decrease in absolute value, indicating that solvent has a destabilizing effect on this interaction. By comparison with MP2 results, all the considered functionals, B3LYP excepted, have been found adequate to describe halogen bonding. As far as the interaction energies are concerned, the best performance was obtained with the M06-HF functional in vacuo and the PBE functional in solution. The geometrical parameters characterizing halogen bonds were better reproduced by the M06-2X functional.

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1. Introduction

Halogen bonding is an interaction between a halogen atom and an acceptor group (behaving as a Lewis base), whose strength grows up with the dimensions of the halogen (F ≪ Cl < Br < I) [1–5]. As such it shares many physical properties with the most known hydrogen bond where the hydrogen replaces the halogen atom. Halogen bonding has received in the last decade an increasing attention as a tool to direct intermolecular recognition processes with applications in several fields ranging from crystal engineering [6] to the development of new materials such as organic semiconductors and superconductors [7–9], liquid crystals and materials with non linear optical properties [10].

Recently there has also been a growing attention of the importance of halogen bond in biochemistry and medicinal chemistry. The evidence that halogen bonds can compete with hydrogen bonds in stabilizing DNA junctions using brominated uracil [11] was one of the first items drawing the attention of halogen bond in the biochemistry community. In addition many currently used drugs are halogen-substituted, as the introduction of a halogen atom is a widely used technique in medicinal chemistry to increase the half-life of the drug and to facilitate the membrane permeability in order to reach the biological target. Moreover, it was recently shown [12] that the introduction of a halogen atom can be used as well to increase the binding affinity of a drug, permitting to obtain an increase of almost two order of magnitude in its activity by substitution of an hydrogen with a iodine atom.

At the same time, attention was also drawn on halogen bonding in solution phase, for example in anion recognition processes [13–15]. Up to now, however, there are only few theoretical investigations of the solvent effect on the halogen bond properties [16–18].

But why an electronegative halogen atom can favourably interact with an acceptor atom behaving as a Lewis base? A simple interpretation has been given by Politzer et al. [19,20], using an argument based on the behaviour of the electrostatic potential around the halogen atoms. The electrostatic potential around an isolated halogen atom (as for any other atom) is of course always positive at any distance from the nucleus, and this can be pictorially seen as the predominance of the concentrated nuclear charge over the dispersed electron cloud. The valence electronic structure of a halogen atom bonded to another atom (lets consider along the z-axis) can be represented as $s^2 p_x^2 p_y^2 p_z^1$ and so there is a depletion of electronic charge along the z-axis (with respect to a 5/3 mean population of p electrons in each direction for the isolated

atom). The electronic depletion along the bond axis is compensated by an increase of the electronic charge in the directions perpendicular to the bond axis. This electronic arrangement results in a strong anisotropy of the electrostatic potential around a covalently bonded halogen atom. In particular a region of positive electrostatic potential, called σ-hole, arises on the halogen in the region outwards the covalent bond, while a crown of negative electrostatic potential is localized around the direction of the D—X bond. The presence of the σ-hole explains the interaction of a halogen atom with a Lewis base located along the extension of the D—X bond. The anisotropy of the electrostatic potential and the existence of the σ-hole have been confirmed by quantum mechanical calculations on different systems, and Politzer was also able to show a positive correlation between the value of the electrostatic potential on the sigma hole and the force of the interaction [19–21].

The size of the σ-hole was found to depend on the electron withdrawing capabilities of the D group and on the nature of halogen atoms. In particular, the σ-hole is more pronounced for the iodine atom, owing to its larger polarizability, decreases for bromine and chlorine atoms, and then disappears for the fluorine atom, except in the presence of strongly electronegative D groups. This ordering is in agreement with the above mentioned scale of halogen bond interactions.

We observe that the anisotropy of the electrostatic potential, which can be adequately described by Quantum Mechanical (QM) methods, cannot be described by traditional force fields which are based on a set of atom centered charges. This is a serious problem in the modelling of proteins interacting with halogenated ligands. In fact, the large number of atoms involved in such systems prohibits the use of QM approaches and makes Quantum Mechanics/Molecular Mechanics (QM/MM) hybrid methods the obliged choice. Suitable modifications of traditional force fields have been however very recently proposed to overcome this problem [22].

In order to deepen our knowledge on the geometrical and energetic features of halogen bonding, we report here the results of a theoretical study of the solvation effects on this interaction. Calculations have been performed on dimers constituted by iodobenzene derivatives with formaldehyde in two solvents (diethylether and water). In the present study, the results of previous investigations on halogen bonding in solution [16–18] are complemented by taking into consideration different substitution schemes on the iodobenzene ring, in order to systematically modulate the force of the halogen bond, from weak to moderate interaction. The choice of formaldehyde is due to the fact that a survey [23] of protein–halogenated ligand complexes has evidenced the frequent occurrence of halogen bonding with oxygen atoms of a peptidic bond. In the present study, we focused our attention on iodine-based halogen bonds because they are characterized by the stronger interaction energies, allowing to better elucidate the variations observed when moving from vacuo to solvent. Finally, as from a biological point of view the interactions are established in water or within a protein, we have chosen as solvents water and diethylether, whose dielectric constant has a value near to that existing at the interior of a protein.

Calculations have been carried out at both the MP2 level, in order to adequately describe the electronic correlation effects, and the DFT level using different density functionals, in order to evaluate their capacity to reproduce the effects of the solvents in the description of the halogen bond.
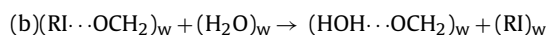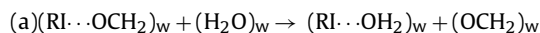
2. Computational details

All ab initio calculations reported in this work were carried out using the Gaussian '09 program [24]. Full geometry optimization were performed by the ab-initio second order Moller–Plesset perturbation (MP2) method [25] and density functional theory (DFT) using some of the most widely used functionals, where different percentages of Hartree–Fock (HF) exchange are combined with the generalized gradient approximation (GGA) expression. In particular we have considered the following functionals: (i) PBE, i.e., the GGA-corrected functional of Perdew et al. [26] which is the only non-hybrid functional we have considered; (ii) PBE0 (also known as PBE1PBE), which mixes the PBE pure GGA functional with 25% of HF exchange [27]; (iii) B3LYP and (iv) BH&HLYP, where correlation is provided by the LYP expression [28] and the exchange part is a mixture of the Becke exchange functional [29] with 20% and 50% of HF exchange, respectively. The BH&HLYP functional, in particular, has been shown to qualitatively reproduce the PES of MP2 calculations for several instances of π-stacking interactions [30,31]. (v) M06-2X [32] and (vi) M06-HF [33,34], two hybrid meta-GGA functionals, which depend also on local spin kinetic energy density besides depending on the gradient of the local spin densities, characterized by 54% and 100% of HF exchange, respectively. The latter functionals have been explicitly suggested for the study of noncovalent interactions [32].

The aug-cc-pVDZ-PP basis set [35], which uses pseudopotential to describe the inner core orbitals, was used for iodine, whereas for all other atoms the aug-cc-pVDZ basis set [36] was adopted. These basis set have already shown to be of good quality to describe various halogen-bonded systems [21,37,38]. All the minimum geometries were confirmed by verifying that all vibrational frequencies at the MP2 level are real.

Solvent effects have been taken into account using the conductor-like polarizable continuum model, CPCM [39], considering as solvents water and diethylether. In particular the latter was chosen to mimic a dielectric medium which can be typically found at the interior of a protein. The validity of the continuum model for the present calculations was checked by including, as preliminary test, the possibility of explicit interactions of the halogenated molecules with solvent molecules. Such preliminary check was obviously limited to water, because diethylether was considered as solvent only as an expedient to mimic the interior of a protein. Explicit interactions with diethylether molecules would be therefore unphysical in principle.

We have considered the possibility that explicit water molecules in solution could preferentially interact with the iodobenzene derivatives RI and/or with formaldehyde, giving rise to halogen- and/or hydrogen-bonded dimers, respectively, more stable than the RI$\cdots$formaldehyde pair. To this aim, we have evaluated the energy variations associated with the two 'reactions':

$$(a)(RI\cdots OCH_2)_w + (H_2O)_w \rightarrow (RI\cdots OH_2)_w + (OCH_2)_w$$

$$(b)(RI\cdots OCH_2)_w + (H_2O)_w \rightarrow (HOH\cdots OCH_2)_w + (RI)_w$$

where the subscript w indicates that calculations were performed in water through the CPCM approach. We have found that, in the case of pentafluoroiodobenzene, which gives rise to the stronger halogen bond interaction here examined, both reactions are characterized by positive values of ΔE at MP2/aug-cc-pVDZ level (0.67 and 0.48 kcal/mol for (a) and (b), respectively), indicating that interaction between RI and formaldehyde is preferred over those of both RI and formaldehyde with water. In the case of 3,5-difluoroiodobenzene, giving rise to an intermediate interaction, ΔE increases for the first reaction but becomes slightly negative for the second one ($\Delta E = 0.75$ and -0.56 kcal/mol, respectively), indicating that, globally, the RI$\cdots$OCH$_2$ complex is still favoured. Only in case of weak interaction, the ΔE values for (a) and (b)

Table 1
Interaction energies (kcal/mol) of the dimers with formaldehyde optimized in vacuo at MP2 and DFT level.[a]

		MP2		PBE		PBE0		B3LYP		BH&HLYP		M06-2X		M06-HF	
		ΔE	ΔE_{CP}	ΔE	ΔE_{CP}	ΔE	ΔE_{CP}	ΔE	ΔE_{CP}	ΔE	ΔE_{CP}	ΔE	ΔE_{CP}	ΔE	ΔE_{CP}
1	p-Amino-iodobenzene	−3.97	−2.25	−2.17	−1.82	−2.05	−1.69	−1.33	−0.99	−1.73	−1.38	−3.15	−2.79	−2.48	−2.06
2	Iodobenzene	−4.07	−2.34	−2.33	−2.01	−2.19	−1.81	−1.49	−1.17	−1.89	−1.56	−3.25	−2.92	−2.58	−2.17
3	o-Amino-iodobenzene	−4.29	−2.54	−2.36	−2.07	−2.25	−1.93	−1.52	−1.23	−1.95	−1.63	−3.36	−3.01	−2.71	−2.31
4	p-Chloro-iodobenzene	−4.31	−2.57	−2.64	−2.28	−2.48	−2.12	−1.78	−1.44	−2.18	−1.83	−3.53	−3.17	−2.82	−2.42
5	m-Chloro-iodobenzene	−4.35	−2.62	−2.69	−2.35	−2.48	−2.18	−1.78	−1.49	−2.20	−1.89	−3.59	−3.23	−2.86	−2.45
6	3,5-Difluoro-iodobenzene	−4.57	−2.82	−2.97	−2.62	−2.78	−2.43	−2.10	−1.77	−2.52	−2.17	−3.81	−3.45	−3.16	−2.76
7	p-Cyano-iodobenzene	−4.55	−2.83	−3.03	−2.68	−2.81	−2.45	−2.15	−1.81	−2.53	−2.16	−3.76	−3.40	−3.09	−2.69
8	3,4,5-Trifluoro-iodobenzene	−4.74	−2.98	−3.15	−2.79	−2.90	−2.55	−2.29	−1.94	−2.67	−2.31	−3.90	−3.56	−3.27	−2.84
9	3,5-Dicyano-iodobenzene	−5.23	−3.48	−3.79	−3.42	−3.58	−3.20	−2.86	−2.51	−3.29	−2.93	−4.49	−4.13	−3.77	−3.36
10	Pentafluoroiodobenzene	−5.81	−3.93	−4.35	−3.94	−4.04	−3.62	−3.36	−2.97	−3.78	−3.36	−5.10	−4.68	−4.58	−4.12
	MAE				0.24		0.44		1.10		0.71		0.60		0.16

[a] In the last row, the mean absolute error with respect to MP2 calculations is reported.

becomes comparable in magnitude (for iodobenzene they are 0.81 and −0.92 kcal/mol, respectively), and solvation of formaldehyde can compete with the formation of the halogen-bonded RI···OCH₂ complex. We can then conclude that the approximation of considering the solvent as a continuum can be considered as acceptable for the present study, taking into account that, for the weaker interactions here examined, we have get the limit of validity of the model.

The interaction energy ΔE was computed as the difference between the energy of the dimer and the sum of the energies of the monomers at the geometry assumed in the dimer. In order to take into account the basis set superpostion error (BSSE), the values of interaction energy obtained in vacuo were corrected with the Boys and Bernardi procedure [40], to give the counterpoise corrected interaction energies ΔE_{CP}. The BSSE correction term evaluated in vacuo was also used to correct the interaction energies evaluated in solvent calculations as reported in [16].

3. Results and discussion

3.1. Gas-phase calculations

Calculations have been performed on a series of halogen-bonded complexes of variously substituted iodobenzene with formaldehyde. The different substitution schemes on iodobenzene were used as a simple way to modulate the strength of the interaction with formaldehyde, which has been chosen as a simple model of the peptidic bond in proteins according to the work by Riley and Merz [16].

The halogen bond interaction energies of the complexes optimized in vacuo at different theoretical levels are listed in Table 1. In Fig. 1, we report the electrostatic potential computed on an isosurface of electron density of 0.001 au, according to the Bader's suggestion [41], for a selected subset of iodobenzene derivatives studied in this work, that is, p-amino-iodobenzene (top), m-chloro-iodobenzene (middle) and pentafluoro-iodobenzene (bottom). From this figure, it is well evident the anisotropy of the electrostatic potential around the halogen atom, responsible for the formation of halogen bonding. In particular, we note the presence of the positive electrostatic region, the so-called σ-hole, located in the direction of the D—X bond, which allows an interaction with a Lewis basis, represented in this case by one lone pair of the oxygen of the formaldehyde molecule. Moreover, from Fig. 1 it can be qualitatively observed that the introduction of electron-withdrawing groups on iodobenzene increases the extension of the sigma hole on the iodine atom. This corresponds to increasing (i.e., more negative) interaction energies, from −2.25 to −2.57 and then

to −3.93 kcal/mol (MP2 values corrected for BSSE) on going from p-amino- to m-chloro- and pentafluoro-iodobenzene.

In general, we observe from Table 1 that the interaction energies depend on the nature, number and position of the substituent(s) on the ring: stronger halogen bonds are in fact observed with increasing the strength of the electron-withdrawing groups (compare e.g. p-chloro-iodobenzene with p-cyano-iodobenzene, $\Delta E_{CP} = -2.57$ and −2.83 kcal/mol, respectively, at MP2 level), the number of substituents (compare e.g. 3,5-difluoro- with 3,4,5-trifluoro and pentafluoro-iodobenzene, $\Delta E_{CP} = -2.82$, −2.98 and −3.93 kcal/mol, respectively), and with changing the position of the substituents (compare e.g. p-amino- with o-amino-iodobenzene, $\Delta E_{CP} = -2.25$ and −2.54 kcal/mol, respectively). Such dependencies, as already qualitatively observed in Fig. 1, are ascribable to the different anisotropy of the electrostatic potential around the iodine atom, and in particular on the nature of the σ-hole, as originated by the different substitution schemes on the ring.

By comparing the different methods of computation, we note from Table 1 that, taking the MP2 results as a reference, the interaction energies computed at DFT level are in all cases underestimated, with the only remarkable exception of the M06-2X functional. Moreover, the M06-HF and PBE functionals appear to better reproduce the MP2 results, while B3LYP provides the worst results. The mean absolute errors (MAE) in the CP corrected interactions energies, i.e., the mean absolute deviations from the MP2 values, are in fact 0.16, 0.24 and 1.10 kcal/mol for the three functionals, respectively. It is to be noted that introduction of 25% of HF exchange in the PBE functional, giving rise to PBE0, implies an increase of MAE from 0.24 to 0.44 kcal/mol. On the other hand, increasing the percentage of HF exchange from 20% to 50% (in B3LYP and BH&HLYP, respectively) and from 54% to 100% (in M06-2X and M06-HF, respectively) makes the MAE to decrease from 1.10 to 0.71 kcal/mol and from 0.60 to 0.16 kcal/mol, respectively. In all cases, anyway, the examined functionals appear to adequately model the subtle variations in the interaction energies as due to the different substitutions on the iodobenzene ring. ΔE and ΔE_{CP} values computed at DFT level are in fact always increasing on going from complexes **1** to **10**, as obtained by MP2 calculations, excepted for a swapping of complexes **6** and **7** given by both M06 functionals.

In Table 2, the geometrical parameters of the halogen bonds in the different dimers optimized in vacuo are reported. We observe that in all cases the I···O distances are well below the sum of the van der Waals radii of iodine and oxygen [42], amounting to 3.50 Å, and, in the case of MP2 calculations, they decrease or are comparable with increasing the strength of the interaction. DFT approaches, on the other hand, provide some significant exceptions to such trend.
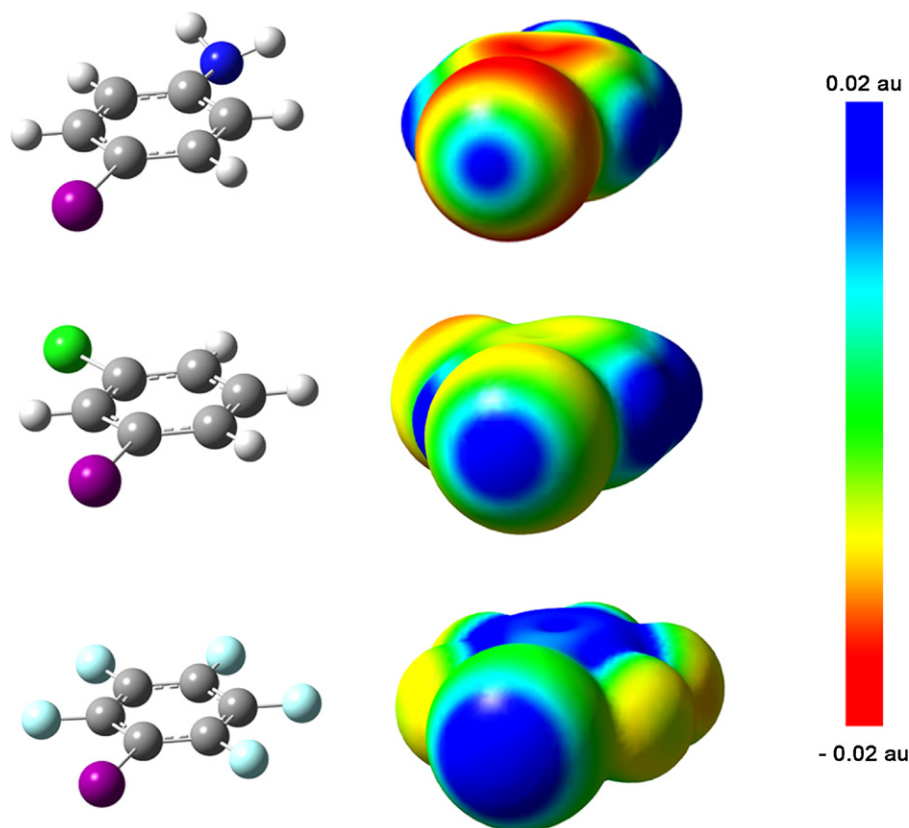
Fig. 1. Electrostatic potential mapped onto the surface of electron density (0.001 electrons/Bohr^3) for p-amino-iodobenzene, m-chloro-iodobenzene and pentafluoroiodobenzene: the extension of the σ-hole increases with the introduction of electron withdrawing groups on the benzene ring.

In particular, the I⋯O distance is predicted by all functional (except for PBE) to decrease on going from dimer **2** to **3**, though the interaction energy increases in this direction. Taking again the MP2 results as a reference, the better results are given by the M06-2X and M06-HF functionals (MAE are 0.010 and 0.013 Å, respectively), while the worst agreement is provided once again by B3LYP (0.101 Å). The angles C—I⋯O are always close to linearity and the deviations with respect to 180° tend to reduce with increasing the halogen bond strength at all levels of theory used. The MP2 angles are reproduced by the different DFT methods with a similar accuracy degree, MAE values ranging from 0.8° (M06-2X) to 1.9° (M06-HF). Finally, we observe a slight, though not systematic, shortening of the C—I bond length with increasing the strength of halogen bonding, which is reproduced by all computation methods. In this case the better agreement with MP2 is provided by M06-2X (MAE is 0.001 Å), while PBE and B3LYP give the greater deviations (MAE is 0.025 Å in both cases).

3.2. Solvent calculations

Owing to the importance of the electrostatic contribution in halogen bonding, it is to be expected that solvent would have a non-negligible influence on the physical chemical properties of this interaction. To describe such solvation effects, we have used the CPCM model, where the solvent is treated as a uniform medium characterized by its dielectric constant. All the systems have been reoptimized in two solvents, namely diethylether, whose dielectric constant $\varepsilon = 4.24$ is very close to the value existing at the interior of a protein [43], and water ($\varepsilon = 78.36$).

The interaction energies and the geometrical parameters of the optimized structures obtained using the CPCM model are reported in Tables 3 and 4, respectively, for calculations in diethylether, and in Tables 5 and 6, respectively, for calculations in water. It appears that the solvent has two main effects on halogen bonding. From the energetic point of view, the solvent systematically reduces the strength of the interaction, and the reduction is more pronounced with the increase of the dielectric constant. Moreover, the strength order observed in vacuo remains substantially unaltered when moving to solvent (at MP2 level, only complexes **6** and **7** exchange their position). The better agreement with CPCM MP2 calculations is provided by the PBE functional, which provides a MAE of 0.11 and 0.13 kcal/mol in diethylether and in water, respectively. Similar to what observed for vacuum calculations, introduction of HF exchange in PBE makes the agreement worse (MAE becomes 0.14 and 0.26 kcal/mol in diethylether and in water, respectively, using PBE0), while the increase of the percentage of HF exchange (from B3LYP to BH&HLYP and from M06-2X to M06-HF) systematically improves the agreement with MP2.

From the geometrical point of view, on the other hand, the presence of the solvent implies a systematic decrease in the I⋯O distances at all theoretical levels, as previously reported for other halogen bonded dimers [18]. Moreover, we observe an increase (towards 180°) of the C—I⋯O angles on going from vacuo to diethylether and then to water, leading to halogen bonds very close to the linear arrangement. The mean reductions of the I⋯O distances and the mean increases of the C—I⋯O angles from vacuo to diethylether are 0.017 Å and 3.5° for MP2 calculations. The corresponding variations from vacuo to water amount 0.021 Å and 4.7°. Interestingly, the reduction in the distances and the greater tendency to linearity observed when going from vacuo to solvent are then not correlated to an increase of the strength of the interaction, as could be naively expected. In other words, for

Table 2
Geometrical parameters of the dimers with formaldehyde optimized in vacuo at MP2 and DFT level.[a]

	Distance I···O (Å)							Angle C-I···O (°)							Distance C-I (Å)						
	MP2	PBE	PBE0	B3LYP	BH&HLYP	M06-2X	M06-HF	MP2	PBE	PBE0	B3LYP	BH&HLYP	M06-2X	M06-HF	MP2	PBE	PBE0	B3LYP	BH&HLYP	M06-2X	M06-HF
1	3.131	3.146	3.206	3.296	3.249	3.122	3.156	169.6	167.9	167.8	168.2	168.8	168.7	165.3	2.107	2.132	2.109	2.133	2.110	2.108	2.096
2	3.114	3.165	3.162	3.220	3.197	3.102	3.123	170.2	169.4	169.2	172.6	171.4	169.4	167.8	2.109	2.134	2.110	2.134	2.112	2.110	2.096
3	3.114	3.103	3.185	3.254	3.219	3.112	3.138	169.7	169.3	168.4	170.3	170.0	168.6	166.0	2.111	2.139	2.114	2.140	2.116	2.112	2.098
4	3.083	3.085	3.122	3.179	3.162	3.076	3.079	171.0	170.5	170.4	173.4	172.6	170.0	170.3	2.106	2.131	2.107	2.131	2.109	2.107	2.092
5	3.079	3.046	3.108	3.180	3.155	3.070	3.067	171.0	173.3	171.5	173.2	172.7	170.6	169.8	2.107	2.132	2.109	2.132	2.110	2.107	2.094
6	3.054	3.049	3.067	3.141	3.118	3.049	3.048	171.6	173.6	173.3	173.8	173.7	168.7	169.5	2.105	2.129	2.106	2.129	2.107	2.106	2.089
7	3.056	3.031	3.065	3.144	3.119	3.043	3.051	171.9	173.8	174.4	174.0	174.8	172.4	170.1	2.104	2.127	2.105	2.128	2.106	2.104	2.091
8	3.037	2.984	3.048	3.122	3.100	3.029	3.012	172.1	173.8	174.1	174.1	174.5	172.3	173.9	2.104	2.129	2.106	2.128	2.106	2.104	2.087
9	2.994	2.922	3.000	3.077	3.059	2.975	2.987	173.5	174.5	174.5	175.0	175.2	173.8	173.7	2.103	2.128	2.104	2.127	2.105	2.104	2.086
10	2.946	3.146	2.944	3.006	2.998	2.935	2.934	173.2	174.4	174.0	174.6	174.2	173.1	172.1	2.090	2.116	2.093	2.116	2.095	2.092	2.070
		0.047	0.030	0.101	0.077	0.010	0.013		1.4	1.3	1.8	1.6	0.8	1.9		0.025	0.002	0.025	0.003	0.001	0.015

[a] In the last row, the mean absolute error with respect to MP2 calculations is reported.

Table 3
Interaction energies (kcal/mol) of the dimers with formaldehyde optimized in diethylether at MP2 and DFT level.[a]

		MP2		PBE		PBE0		B3LYP		BHandHLYP		M06-2X		M06-HF	
		ΔE	ΔE_{CP}	ΔE	ΔE_{CP}	ΔE	ΔE_{CP}	ΔE	ΔE_{CP}	ΔE	ΔE_{CP}	ΔE	ΔE_{CP}	ΔE	ΔE_{CP}
1	p-Amino-iodobenzene	−3.33	−1.61	−1.73	−1.38	−1.91	−1.55	−0.83	−0.49	−1.16	−0.81	−2.49	−2.13	−1.43	−1.01
2	Iodobenzene	−3.42	−1.69	−1.91	−1.59	−1.69	−1.31	−0.98	−0.66	−1.31	−0.98	−2.60	−2.27	−1.83	−1.42
3	o-Amino-iodobenzene	−3.57	−1.82	−1.92	−1.63	−2.02	−1.70	−1.00	−0.71	−1.34	−1.02	−2.61	−2.26	−1.71	−1.31
4	p-Chloro-iodobenzene	−3.61	−1.87	−2.15	−1.79	−2.31	−1.95	−1.19	−0.85	−1.52	−1.17	−2.88	−2.52	−1.78	−1.38
5	m-Chloro-iodobenzene	−3.64	−1.91	−2.29	−1.95	−2.02	−1.72	−1.31	−1.02	−1.63	−1.32	−2.90	−2.54	−1.90	−1.49
6	3,5-Difluoro-iodobenzene	−3.83	−2.08	−2.45	−2.10	−2.48	−2.13	−1.45	−1.12	−1.79	−1.44	−3.06	−2.70	−2.32	−1.91
7	p-Cyano-iodobenzene	−3.75	−2.03	−2.42	−2.07	−2.38	−2.02	−1.42	−1.08	−1.77	−1.40	−3.06	−2.70	−1.94	−1.55
8	3,4,5-Trifluoro-iodobenzene	−3.96	−2.20	−2.59	−2.23	−2.32	−1.97	−1.58	−1.23	−1.94	−1.58	−3.23	−2.89	−2.47	−2.05
9	3,5-Dicyano-iodobenzene	−4.26	−2.51	−3.00	−2.63	−2.99	−2.61	−1.90	−1.55	−2.22	−1.86	−3.52	−3.16	−2.49	−2.08
10	Pentafluoroiodobenzene	−4.97	−3.09	−3.75	−3.34	−3.28	−2.86	−2.57	−2.18	−2.86	−2.44	−4.24	−3.82	−3.53	−3.07
	MAE				0.11		0.14		0.99		0.68		0.62		0.36

[a] In the last row, the mean absolute error with respect to MP2 calculations is reported.

Table 4
Geometrical parameters of the of the dimers with formaldehyde optimized in diethylether at MP2 and DFT level.[a]

	Distance I···O (Å)							Angle C—I···O (°)							Distance C—I (Å)						
	MP2	PBE	PBE0	B3LYP	BH&HLYP	M06-2X	M06-HF	MP2	PBE	PBE0	B3LYP	BH&HLYP	M06-2X	M06-HF	MP2	PBE	PBE0	B3LYP	BH&HLYP	M06-2X	M06-HF
1	3.111	3.133	3.154	3.252	3.214	3.109	3.148	174.0	175.9	175.9	176.6	176.4	173.1	171.4	2.110	2.136	2.112	2.137	2.114	2.111	2.098
2	3.097	3.105	3.126	3.220	3.188	3.109	3.130	174.0	175.9	175.9	176.6	176.5	170.8	170.5	2.111	2.138	2.114	2.138	2.115	2.114	2.102
3	3.090	3.116	3.137	3.232	3.196	3.095	3.126	173.9	175.5	175.5	175.8	176.0	172.8	171.4	2.112	2.142	2.116	2.142	2.118	2.114	2.100
4	3.069	3.066	3.091	3.177	3.152	3.066	3.085	174.6	176.1	176.3	176.7	176.7	173.7	172.5	2.108	2.134	2.110	2.134	2.111	2.109	2.095
5	3.062	3.053	3.078	3.160	3.140	3.046	3.076	174.5	177.3	177.0	178.2	177.8	173.6	173.3	2.109	2.136	2.111	2.135	2.112	2.111	2.095
6	3.037	3.026	3.050	3.126	3.111	3.012	3.032	174.9	176.2	176.2	177.0	177.1	175.5	175.3	2.106	2.132	2.108	2.131	2.108	2.107	2.090
7	3.049	3.034	3.056	3.142	3.119	3.017	3.052	175.0	176.2	176.4	177.0	177.2	175.6	174.2	2.106	2.129	2.107	2.130	2.108	2.107	2.093
8	3.021	3.007	3.032	3.111	3.093	2.998	3.016	175.1	176.2	176.0	177.0	176.9	175.5	175.3	2.106	2.131	2.107	2.130	2.108	2.107	2.089
9	2.987	2.966	2.991	3.070	3.058	2.975	2.987	176.0	176.5	176.7	177.8	178.0	175.6	174.3	2.104	2.130	2.106	2.129	2.107	2.105	2.089
10	2.916	2.878	2.910	2.964	2.969	2.923	2.926	176.6	177.4	177.4	179.9	178.6	175.5	174.6	2.092	2.120	2.096	2.118	2.096	2.093	2.071
		0.017	0.020	0.102	0.080	0.014	0.016		1.5	1.5	2.4	2.3	1.0	1.7		0.026	0.002	0.027	0.004	0.001	0.012

[a] In the last row, the mean absolute error with respect to MP2 calculations is reported.

Table 5
Interaction energies (kcal/mol) of the dimers with formaldehyde optimized in water at MP2 and DFT level.[a]

		MP2		PBE		PBE0		B3LYP		BH&HLYP		M06-2X		M06-HF	
		ΔE	ΔE_{CP}	ΔE	ΔE_{CP}	ΔE	ΔE_{CP}	ΔE	ΔE_{CP}	ΔE	ΔE_{CP}	ΔE	ΔE_{CP}	ΔE	ΔE_{CP}
1	p-Amino-iodobenzene	−3.14	−1.42	−1.62	−1.27	−1.40	−1.04	−0.70	−0.36	−1.02	−0.67	−2.32	−1.96	−1.25	−0.83
2	Iodobenzene	−3.22	−1.49	−1.79	−1.48	−1.54	−1.16	−0.83	−0.51	−1.14	−0.81	−2.42	−2.09	−1.64	−1.23
3	o-Amino-iodobenzene	−3.33	−1.58	−1.76	−1.46	−1.52	−1.20	−0.81	−0.52	−1.13	−0.81	−2.38	−2.03	−1.48	−1.08
4	p-Chloro-iodobenzene	−3.39	−1.65	−1.99	−1.63	−1.72	−1.36	−1.00	−0.66	−1.31	−0.96	−2.67	−2.31	−1.56	−1.16
5	m-Chloro-iodobenzene	−3.42	−1.69	−2.13	−1.80	−1.80	−1.50	−1.11	−0.82	−1.41	−1.10	−2.69	−2.33	−1.68	−1.27
6	3,5-dIfluoro-iodobenzene	−3.59	−1.84	−2.27	−1.92	−1.96	−1.61	−1.23	−0.89	−1.54	−1.19	−2.84	−2.48	−2.08	−1.67
7	p-Cyano-iodobenzene	−3.48	−1.76	−2.25	−1.89	−1.94	−1.58	−1.20	−0.86	−1.51	−1.14	−2.82	−2.46	−1.71	−1.31
8	3,4,5-Trifluoro-iodobenzene	−3.70	−1.94	−2.39	−2.03	−2.10	−1.75	−1.33	−0.99	−1.68	−1.32	−3.00	−2.66	−2.23	−1.80
9	3,5-Dicyano-iodobenzene	−3.92	−2.17	−2.75	−2.38	−2.32	−1.94	−1.59	−1.24	−1.83	−1.47	−3.17	−2.81	−2.36	−1.95
10	Pentafluoroiodobenzene	−4.68	−2.81	−3.60	−3.20	−3.04	−2.62	−2.30	−1.91	−2.55	−2.13	−3.94	−3.52	−3.20	−2.74
	MAE			0.13		0.26		0.96		0.67		0.63		0.33	

[a] In the last row, the mean absolute error with respect to MP2 calculations is reported.

a same halogen bond distance and angle, a much weaker interaction should be expected in solvent with respect to the gas phase.

The decrease of the I···O distances in solvent with respect to vacuum is always accompanied by a slight increase of the C—I bond lengths. The relationships between the variations of the I···O and the C—I distances has been already observed for hydrogen bonded systems [44], for which it has been interpreted as a nonadditivity/polarization effect in PCM calculations [17]. It has also been reported that the distance I···O in the dimer iodobenzene/water is further reduced if one or two explicit water molecules, hydrogen-bonded to the water molecule acting as halogen bond acceptor, are added to the dimer [18]. This further confirms the solvent effect on the halogen bonding geometry.

By analyzing the geometrical parameters obtained with DFT calculations in solution, the better agreement with MP2 is given by the M06-2X functional (MAE for I···O, C—I···O and C—I are 0.014 and 0.012 Å, 1.0 and 2.2°, and 0.001 Å in diethylether and water, respectively), while the worst agreement is provided by B3LYP (the corresponding MAE are 0.102 and 0.104 Å, 2.4 and 2.2°, and 0.027 and 0.026 Å in diethylether and water, respectively). We also observe that, while the PBE and M06-2X functionals appear superior to the other ones in reproducing absolute values of energy or geometrical parameters in solution, their variations are well reproduced by all functionals, B3LYP included, evidently for a cancellation of errors.

In Fig. 2(top) we report a plot of the strength of halogen bonding against the maximum value assumed by the electrostatic potential, computed at the MP2 level, on the isosurface of electron density (0.001 au) in the region of the σ-hole, denoted as $V_{S,max}$. Results obtained in vacuo, diethylether and water are reported (Fig. 2 left, centre and right, respectively). In all cases, it is evident a negative correlation, according to results already reported by Politzer for a series of halogen bonded dimers [19–21], including in particular brominated benzenes and pyrimidines [45], indicating explicitly that a more pronounced σ-hole determines a stronger halogen bond. This is also confirmed by the I···O distances (Fig. 2, bottom), which tend as well to decrease with increasing of $V_{S,max}$. The presence of the solvent gives rise to a shifting of the curves towards lower interaction energies and shorter I···O distances. The same behaviour is obtained at the DFT level for all functionals.

The previous considerations have been made by considering the variations of the electrostatic potential on the 0.001 au isosurface of electron density. It can be interesting also to analyze how the electrostatic potential changes moving away from this isosurface. In Fig. 3, we report some positive contour lines of the electrostatic potential superimposed with the 0.001 au contour line of the electron density, on the plane of the phenyl group of two compounds, namely p-amino-iodobenzene and pentafluorobenzene, in vacuo (Fig. 3a and b) and in water (Fig. 3c and d). From both vacuum and solvent results, it is well evident the different extension of the protuberance in the C—I region outside the space delimited by the 0.001 au electron density isosurface: it is quite limited for p-amino-iodobenzene, which gives rise to the weaker halogen-bonded dimer (Fig. 3a and c), while increases considerably along the C—I bond for pentafluorobenzene, which is associated to the stronger interaction (Fig. 3b and d). Clearly, the extension of such protuberance is strictly connected to the extension of the σ-hole. Such representation makes however more evident why larger σ-holes give rise not only to stronger interactions, but also to C—I···O angles closer to linearity. Stronger halogen bond donors are in fact able to 'capture' Lewis basis at longer distances with respect to weaker donors, making more favourable the linear approach between the interacting species.
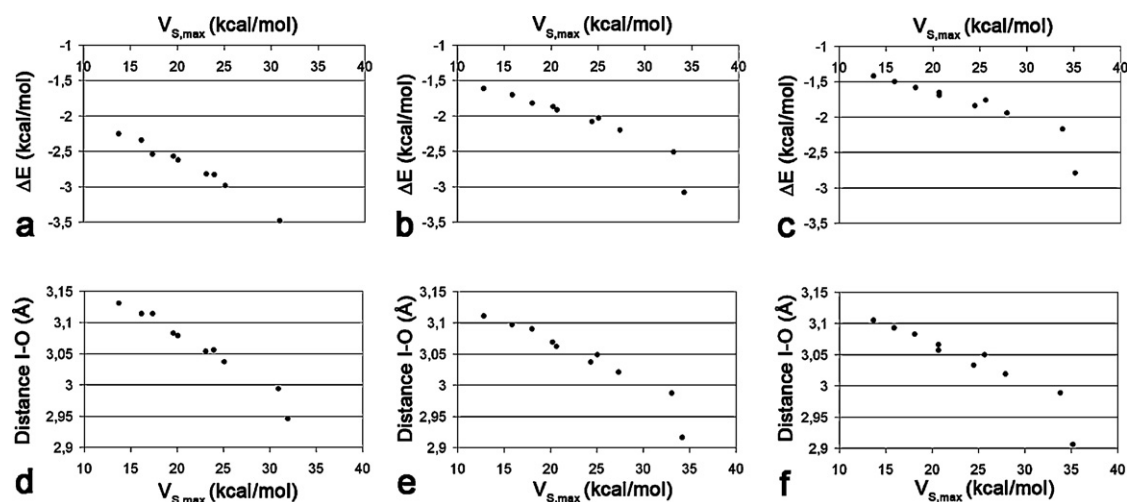
Table 6
Geometrical parameters of the dimers with formaldehyde optimized in water at MP2 and DFT level.[a]

	Distance I···O (Å)							Angle C—I···O (°)							Distance C—I (Å)						
	MP2	PBE	PBE0	B3LYP	BH&HLYP	M06-2X	M06-HF	MP2	PBE	PBE0	B3LYP	BH&HLYP	M06-2X	M06-HF	MP2	PBE	PBE0	B3LYP	BH&HLYP	M06-2X	M06-HF
1	3.105	3.132	3.154	3.261	3.219	3.107	3.147	175.6	177.1	177.4	178.1	177.9	174.5	173.4	2.111	2.138	2.114	2.138	2.115	2.112	2.100
2	3.093	3.101	3.126	3.223	3.191	3.089	3.130	175.4	177.0	177.2	178.0	178.0	174.7	172.2	2.112	2.140	2.115	2.139	2.116	2.113	2.103
3	3.083	3.111	3.134	3.232	3.198	3.092	3.121	175.5	174.7	176.6	177.2	177.4	173.9	173.7	2.113	2.143	2.117	2.143	2.119	2.115	2.101
4	3.066	3.063	3.090	3.182	3.154	3.063	3.087	175.8	177.1	177.3	177.8	178.0	175.0	174.2	2.109	2.135	2.111	2.135	2.112	2.110	2.096
5	3.057	3.045	3.075	3.157	3.140	3.046	3.079	175.9	178.0	178.5	179.3	178.9	174.7	174.7	2.110	2.137	2.112	2.136	2.113	2.112	2.096
6	3.033	3.019	3.047	3.127	3.111	3.014	3.036	176.1	177.1	177.3	178.1	178.3	176.4	176.3	2.107	2.133	2.109	2.131	2.109	2.108	2.091
7	3.050	3.028	3.056	3.140	3.122	3.019	3.061	176.1	176.8	177.1	177.7	177.7	176.1	174.9	2.107	2.130	2.107	2.131	2.109	2.108	2.094
8	3.019	3.001	3.028	3.107	3.092	2.998	3.020	176.2	177.2	176.7	178.2	177.7	176.0	175.8	2.106	2.132	2.108	2.130	2.108	2.107	2.089
9	2.989	2.962	2.992	3.062	3.064	2.978	3.003	176.7	177.2	177.4	179.8	178.9	176.3	176.3	2.104	2.130	2.106	2.129	2.107	2.105	2.088
10	2.906	2.852	2.896	2.949	2.959	2.918	2.924	177.7	179.7	178.9	178.7	179.9	176.3	175.6	2.093	2.122	2.097	2.119	2.097	2.093	2.071
		0.021	0.022	0.104	0.085	0.012	0.021		1.3	1.3	2.2	2.2	0.8	1.4		0.027	0.002	0.026	0.003	0.001	0.014

[a] In the last row, the mean absolute error with respect to MP2 calculations is reported.

Fig. 2. Plots of the I···O distance and interaction energy ΔE versus $V_{S,max}$, the maximum value assumed by the electrostatic potential on the isosurface of electron density (0.001 au) in the region of the sigma hole, calculated in vacuo (a and d), diethylether (b and e) and water (c and f) at MP2 level.
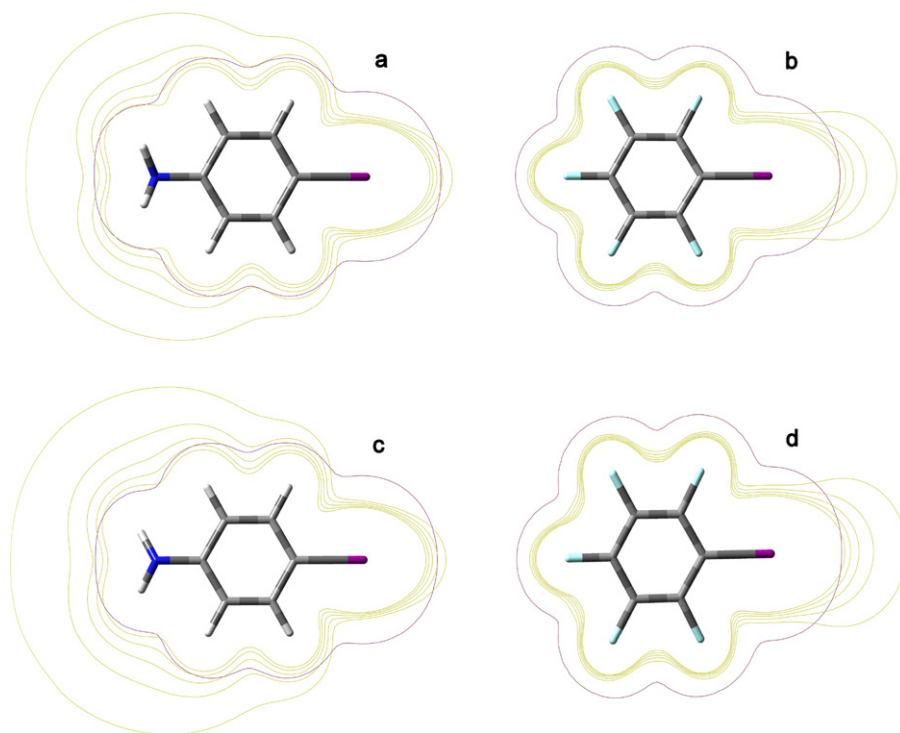

Fig. 3. Positive contour lines (from 0.01 to 0.05 au) of the electrostatic potential superimposed with the 0.001 au contour line of the electron density, on the plane of the phenyl group of *p*-amino-iodobenzene and pentafluorobenzene, in vacuo (a and b) and in water (c and d).

4. Conclusions

The results of MP2 and DFT calculations performed with the aug-cc-pVDZ basis set on a series of I···O halogen-bonded complexes of iodobenzene derivatives with formaldehyde in vacuo and in solution are here reported. Within the DFT approach, some of the most widely used functionals have been considered, in order to single out the best ones in reproducing the MP2 results.

Different substitution schemes on iodobenzene were used in order to systematically modulate the strength of halogen bond from weak to moderate interaction. The effect of two solvents, i.e., diethylether and water, on the energetical and geometrical aspects of the interaction, have been investigated by comparison with results obtained in vacuo. In particular, diethylether has been chosen owing to its dielectric constant, whose value is close to that existing at the interior of a protein. The interaction energy was found to depend on nature, number and position of the substituent(s) on the iodobenzene ring, and a correlation with the maximum value assumed by the electrostatic potential on the isosurface of electron density (0.001 au) in the region of the σ-hole was found in both vacuo and solvent, at all levels of theory. The shape of the electrostatic potential allows as well to explain the correlation existing between strength and linearity of halogen bonding.

We found that solvent acts in a systematic way on both geometry and strength of halogen bonding: it implies, from one side, a shortening of the I···O distance and a greater tendency to linearity of the C—I···O angle, and, from the other side, a decrease of the interaction energy. Such effects were found to increase with the

polarity of the solvent. Though halogen bonding appears then to be destabilized in solvent with respect to the gas phase, it plays anyway a fundamental role in biological systems, in synergy or even in competition with hydrogen bond. For example, a recent study of the importance of halogen bonding in novel inhibitors of human Cathepsin L has shown that it was possible to increase the activity of a ligand of almost two orders of magnitude, by substitution of a hydrogen with an iodine atom [12].

From a technical point of view, our study points to the conclusion that, taking the MP2 results as a reference, all the considered functionals have been found adequate to describe halogen bonding, with the only exception of B3LYP, which underestimates the interaction energies and overestimates the I$\cdots$O distances by about 1 kcal/mol and 0.1 Å, respectively, on average. The interaction energies have been reproduced with the highest accuracy by the M06-HF and the PBE functionals in vacuo and in solution, respectively (MAE below 0.16 kcal/mol), while the geometry of halogen bond was better described by the M06-2X functional in both vacuo and solution (MAE below 0.014 Å). Within each class of examined functionals, the effect on the interaction energy of introducing different percentages of Hartree–Fock (HF) exchange has been analyzed. On going from PBE to PBE0, implying a variation from 0% to 25% of HF exchange, MAE increases. On the other hand, in B3LYP and BH&HLYP, where the percentage of HF exchange varies from 20% to 50%, and in M06-2X and M06-HF, where it varies from 54% to 100%, MAE decreases. These trends are observed both in vacuo and in solution.

Acknowledgements

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