The relative position of π-π interacting rings notably changes the nature of the substituent effect

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Abstract

The substituent effect in monosubstituted benzene dimers mostly follows changes on electrostatics mainly controlled by the direct interaction of the substituent and the other phenyl ring, whereas the contribution from the interacting rings is smaller. As the substituent is located further away the two contributions become of similar magnitude, so the global result is a combination of both effects. These trends are confirmed in larger systems containing a contact between phenyl rings; at closer distances the interaction of the substituent and the other ring clearly dominates over changes associated to the substituted ring, but as the substituent is located further away its contribution decreases and the contribution from the ring becomes more relevant. Care should be taken in larger systems because the observed energy change can also be affected by interactions with other regions of the molecule not directly involved in the π-π interaction.

1. Introduction

Non-covalent interactions involving aromatic species play an important role in biological systems,[1-4] and phenomena such as protein folding or DNA stabilization depend to a large extent on the contributions provided by these contacts.[4] These interactions are also relevant in materials science[5, 6] affecting, for instance, the behaviour of polycyclic aromatic hydrocarbons such as graphene flakes or ribbons as well as their aggregation and supramolecular chemistry.[7-12] This kind of interactions between aromatic systems is usually referred to as π-π interactions or π-stacking, suggesting that it is controlled by the interaction between the aromatic clouds of the interacting species, which would be placed one on top of another.[1, 2, 13] However, it has recently been suggested that these terms are confusing and do not provide an adequate description of the phenomena that actually control the interaction.[14]

These stacking interactions are usually controlled by dispersion so they can also be relevant among aliphatic species.[15-21] In fact, the interaction in the cyclohexane dimer is similar in magnitude to that of the benzene dimer, and the cyclohexane-benzene dimer is even more tightly bound than benzene or cyclohexane homodimers.[22, 23] Grimme carried out a study in which the existence of an interaction that could be attributed to π-stacking was questioned, at least when the size of the aromatic species is small.[15] Only when the aromatic species become larger a specific effect could be attributed to some sort of π-π interaction. Though the interaction in linear acene dimers and their saturated counterparts increases with increasing system size, it does so to a larger extent when aromatic species are present. This larger growing rate is primarily due to the properties of the aromatic species that result in an increase in dispersion interactions. Besides, delocalization produces a softening of the repulsive wall allowing the molecules to approach at closer distances.[18, 20, 21] This effect occurs for extended aromatic systems and is not noticeable in aromatic systems of the size of those usually found in biomolecules.

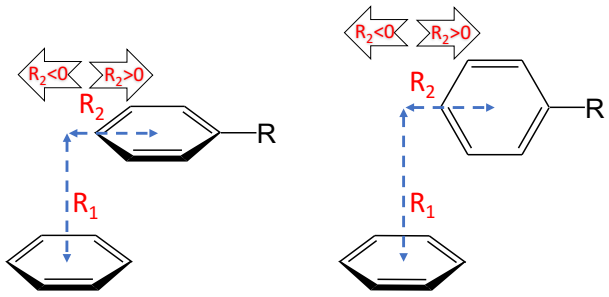
Furthermore, not only the parallel stacked orientation leads to favourable interactions between aromatic systems, and other relative orientations of the rings can provide significant stabilization. It is well-known that in benzene dimers, T-shaped structures (with one or two CH groups pointing towards the other ring) are as stable as the parallel-displaced ones.[24-31] Considering that the experimental characterization of these structures can be difficult, it has even been proposed that the term "π-π interaction" should be applied to any contact between aromatic rings whether parallel or not.[32] These and other arguments against the terms "π-stacking" or "π-π interaction" as a description of the phenomenon that occurs when aromatic species interact were collected and analysed by Martínez and Iverson,[14] proposing that the term "stacking" should only be employed as a simple descriptor of the relative orientation of the interacting species.

In any case, regardless of how we decide to name them, there are multiple cases in which the proximity between two aromatic species plays a relevant role in the characteristics of the systems. One of the great potentialities of the interactions between aromatic rings is their ability to be modulated by substitution in the rings. However, the mechanism by which substituents introduce such modulation has been the subject of debate in recent years. In the model of Hunter and Saunders (HS),[33-36] the substituent adds or removes electronic density from the aromatic ring, so the electrostatic interaction between rings is modified. By means of

these polarisation/electrostatic considerations, the HS model is able to predict the most favourable orientations for the interaction between benzene molecules, as well as the preferences in the interaction between electron-rich and electron-deficient aromatic systems. However, theoretical results show that the interaction always increases its intensity due to substitution in benzene-substituted dimers, independently of whether the substituent acts as an electron donor (ED) or as an electron withdrawing (EW) group.[37-39] Wheeler and Houk proposed a new model (WH)[40-42] that considers that the aromatic ring plays no role in changing the intensity of the interaction upon substitution, and that the entire observed effect is due to direct through-space interactions between the substituent and the other molecule. Therefore, it does not matter whether the substituent is electron-withdrawing or electron-donor, but how it interacts with the other aromatic ring. In recent years, several studies have shown that the WH model can explain a good number of observations in systems having interactions between substituted aromatic species.[40-50]

However, the simple description of substituent effects by means of direct interaction seems too simplistic in some cases. The description of the substituent effect in cation-π interactions has been improved by considering polarisation effects together with electrostatics as proposed by Bauzá et al.[51] Moreover, we have recently shown that in the interaction between cations and extended aromatic species there is a considerable part of the substituent effect that is not related to through-space interactions, but to changes in the electronic distribution of the aromatic species.[52] Also, Yourdkhani et al. have shown that in the cation-π interaction there is a contribution associated to the polarisation of the sigma skeleton.[53] The first study in which the nature of the substituent effect, and whether it follows a HS or WH picture, was directly quantified, has been presented quite recently by Parrish and Sherrill.[54] The authors, applying a methodology that allowed to naturally quantify the contributions from the substituent and the aromatic ring, studied model systems consisting in substituted benzene dimers in a fully stacked face-to-face structure. The results showed that although both effects may be present, WH is the dominant one.

Independently of the origin of the substituent effect, little attention has been paid to the role played by the relative orientation of the interacting species. Arnstein and Sherrill have shown that slipping one benzene unit along the other one clearly affects to the interaction and the substituent effect.[55] Following this idea, Riwar et al. have recently reported host-guest systems based on Rebek imide receptors designed in such a way that the relative position of two interacting rings can be controlled.[56] Thus, in one of the cases the substituent lies on top of the ring, while in the other one it is located further away from it. When the substituent group is near the ring the behaviour is not compatible with a HS picture, while this seems to be the case when located further away.



R = -NH_2, -OH, -CH_3, -H, -F, -CN, -NO_2

Figure 1. Schematic representation of the benzene dimers studied. At $R_2 = 0$ both ring centres are on top of each other.

In the present work, a study of the effect of the relative position of the rings upon the interaction in substituted aromatic rings is carried out, quantifying the contributions coming from direct interaction with the substituent and from ring polarisation. In a first step, model systems are employed consisting of parallel-stacked benzene dimers monosubstituted with a series of groups ranging from EW to ED ones; the effect of the relative position of the rings is analysed by displacing the substituted benzene parallel to the other benzene unit (Figure 1, left). Using the same set of benzene derivatives, the effect of the relative position is also studied by considering T-shaped structures (Figure 1, right). This orientation, where the substituted ring interacts with the other aromatic unit via CH groups could reveal effects associated to sigma polarisation as suggested by Yourdkhani et al.[53] Finally, after studying these model dimers, larger systems similar to those proposed by Riwar et al.[56] are considered and analysed employing the same tools in order to shed light on the role of through-space effects and ring polarisation on the global substituent effect.

2. Computational Details

The geometries of benzene and its derivatives have been obtained at the PBE0-D3BJ/def2-TZVP level.[57-59] Starting from the optimised geometry obtained for benzene, a hydrogen atom has been replaced by the substituent and then optimised by relaxing the atoms in the substituent group while keeping the rest of the atoms fixed in their positions, so all derivatives share the same geometry for the aromatic ring. Dimers formed by benzene and one of the substituted derivatives are then constructed using the two arrangements shown in Figure 1: parallel and T-shaped. The dimers have been optimised at the PBE0-D3BJ/def2-TZVP allowing two geometrical parameters to change, corresponding to the vertical displacement of the second benzene unit (R_1) and to the displacement along two *para* carbon atoms leading to slipped structures (R_2). At $R_2 = 0$ both ring centres are on top of each other, and it will be considered that R_2 is positive when the substituent moves away from the other benzene molecule and negative otherwise (see Figure 1). The interaction energies are obtained at the PBE0-D3BJ/def2-TZVP level applying the counterpoise correction.[60, 61] Also, since the main

purpose of this work is to check the effect of geometry changes upon the substituent effect, potential energy curves have been obtained by slipping the substituted molecules while keeping a constant vertical displacement (R_1 in Figure 1). As indicated in the introduction, larger complexes have also been considered in the present study.[56] In this case, the dimers have been fully optimised at the PBE0-D3BJ/def2-TZVP level.

The analysis of the interaction will be carried out by using Symmetry Adapted Perturbation Theory (SAPT) methods.[62, 63] SAPT allows the interaction energy to be obtained as a sum of contributions with physical meaning that can be identified at low orders with electrostatic, induction, exchange-repulsion and dispersion contributions. Thus, the interaction energy can be expressed as

$$\Delta E = \sum_{i=1}^{\square} \sum_{j=0}^{\square} (E_{pol}^{ij} + E_{exch}^{ij})$$

and different levels of SAPT are defined depending on how the series is truncated and which terms are included.[62, 64] The simplest SAPT level, SAPT0, is obtained by including the following terms:

$$E_{SAPT0} = E_{electr}^{10} + E_{exch}^{10} + E_{ind}^{20} + E_{exch,ind}^{20} + E_{disp}^{20} + E_{exch,disp}^{20} + \delta HF$$

with δHF being a term mostly representing induction to higher orders.[62, 64] The contributions are usually grouped as follows: $E_{ele}=E^{10}_{electr}$; $E_{rep}=E^{10}_{exch}$; $E_{ind}=E^{20}_{exch,ind} + E^{20}_{ind} + \delta HF$; $E_{dis}=E^{20}_{exch,disp} + E^{20}_{disp}$, corresponding to electrostatic, repulsion, induction and dispersion contributions to the interaction energy. In a similar way, other levels of SAPT can be defined including more terms usually related to intramonomer correlation effects. Including such terms, SAPT can provide very accurate results for interaction energies.[64] Also, the SAPT variant using DFT can provide good results with a reduced computational cost because intramonomer correlation effects are already included in the DFT description of the monomers.[65-68]

Even though the changes due to ring substitution could be ascribed to the different energy contributions provided by SAPT, the contributions from the substituent and the polarised ring cannot be split apart. In order to quantify the effect of the substituent and whether it is related to changes in the aromatic ring (HS model) or to a direct through-space interaction (WH model), the interaction has been analysed by using the Functional Group Symmetry Adapted Perturbation Theory method (F-SAPT) as proposed by Parrish and Sherrill.[69, 70] In this method, the system is split into fragments connected by linking units, and the total interaction energy is then obtained as contributions from each of the fragments and links. In the case of substituted benzene dimers, the molecule is divided into three groups corresponding to the substituent, the aromatic ring and a link.[54] With such a partitioning, the effect of the substituent is estimated by comparing the results obtained for complexes containing substituted species with a benzene dimer with an equivalent partition; that is, a hydrogen atom is considered as the substituent. To simplify the analysis, the contributions from the link have been distributed between the phenyl ring and the substituent using a 50:50 partitioning. In the case of the larger complexes, the molecules are split into more fragments as shown below, but the procedure is basically the same: fragments are defined corresponding to the

substituent and the rings, and the substituent effect is measured by comparing with the unsubstituted derivatives. Since F-SAPT calculations can only be performed at the SAPT0 level, the systems studied in this work will be analysed using the jun-cc-pVDZ basis set and corresponding auxiliary basis sets as recommended in previous work.[64] All PBE0-D3BJ calculations have been carried out with Gaussian09,[71] while SAPT calculations have been performed with the PSI4 program.[72] Molecular structures are displayed with PyMOL.[73]

Table 1. Optimised geometry (Å) and interaction energy (kcal mol^{-1}) for substituted parallel-displaced benzene dimers at the PBE0-D3BJ/def2-TZVP level. R_1 and R_2 as in Figure 1.

R	R_1	R_2	ΔE_{int}	R	R_1	R_2	ΔE_{int}
NH_2b*	3.32	-3.09	-4.81	**NH_2b***	3.51	1.74	-2.54
NH_2	3.57	-1.31	-2.55	**NH_2**	3.50	1.69	-2.78
OH	3.52	-1.64	-3.05	**OH**	3.50	1.70	-2.79
CH_3	3.51	-3.06	-3.68	**CH_3**	3.50	1.69	-2.82
H	3.50	-1.76	-2.81	**H**	3.50	1.76	-2.81
F	3.53	-1.45	-2.97	**F**	3.51	1.67	-3.00
CN	3.51	-1.45	-4.24	**CN**	3.51	1.48	-3.69
NO_2	3.47	-1.52	-4.74	**NO_2**	3.51	1.44	-3.78

* In NH_2b the hydrogen atoms of the amino group point towards the other phenyl ring.

3. Results

3.1. Bz-Bz Parallel-Displaced Dimers

3.1.1. Optimised structures

Table 1 shows the results obtained for the parallel-displaced substituted benzene dimers after partial optimisation (only R_1 and R_2 are allowed to change, see Figure 1) at the PBE0-D3BJ/def2-TZVP level. It can be observed from Table 1 that all vertical displacements (R_1) are around 3.5 Å, while there is more variety in the values of the parallel displacement (R_2), though most of them are around $\pm$1.5 Å. In any case, in most cases the interaction is more favourable in substituted systems than in the parent unsubstituted benzene dimer, especially when the substituent is over the ring ($R_2 < 0$), as already observed in previous work.[37-39, 55] In the case of the CH_3 derivative this is clearly a consequence of the formation of a C-H···π contact, as reflected in the large parallel displacement of around -3 Å needed for locating the methyl group over the centre of the phenyl ring. For aniline complexes (R =-NH_2) there are two possible orientations depending on whether the nitrogen lone pair or the hydrogen atoms point to the phenyl group, termed as NH_2 or NH_2b, respectively. The results in Table 1 show that the NH_2b orientation is significantly more favourable, also leading to the shortest R_1 value. The behaviour of this NH_2b derivative (R_1 = -3.09 Å) is like that of the CH_3 derivative because it establishes a NH···π contact. Displacing the molecule in the other direction ($R_2 > 0$) leads to somewhat less stable structures, with smaller changes relative to benzene dimer; only in the complexes with CN and NO_2 the interaction energies increases significantly, as expected for the most polarising substituents among the ones considered.

Table 2. Interaction energies and their components (kcal mol^{-1}) as obtained at the F-SAPT0/jun-cc-pVDZ level for the optimised structures (PBE0-D3BJ/def2-TZVP) of parallel-displaced substituted benzene dimers.

			$R_2<0$						$R_2>0$		
	E_{dis}	E_{rep}	E_{ele}	E_{ind}	E_{tot}		E_{dis}	E_{rep}	E_{ele}	E_{ind}	E_{tot}
NH_2b^*	-6.86	7.14	-4.04	-0.93	-4.69	**NH_2b^***	-6.66	5.84	-1.19	-0.66	-2.66
NH_2	-7.46	6.26	-0.69	-0.69	-2.58	**NH_2**	-6.80	6.04	-1.52	-0.71	-2.99
OH	-7.06	6.23	-1.49	-0.66	-2.98	**OH**	-6.65	5.94	-1.57	-0.65	-2.93
CH_3	-6.14	5.61	-2.40	-0.70	-3.62	**CH_3**	-6.80	5.98	-1.41	-0.67	-2.90
H	-6.48	5.82	-1.56	-0.65	-2.87	**H**	-6.48	5.82	-1.56	-0.65	-2.87
F	-6.75	5.95	-1.62	-0.55	-2.96	**F**	-6.56	5.87	-1.83	-0.62	-3.13
CN	-8.30	7.36	-2.89	-0.73	-4.56	**CN**	-7.09	6.30	-2.38	-0.65	-3.83
NO_2	-8.91	7.94	-3.71	-0.76	-5.43	**NO_2**	-7.15	6.36	-2.57	-0.66	-4.03

* In NH_2b the hydrogen atoms of the amino group point towards the other phenyl ring.

As commented above, the main tool for analysing the interaction in this work is SAPT.[62, 63] In previous work,[64] different levels of SAPT have been extensively tested, showing that SAPT0/jun-cc-pVDZ provides pretty good results at a low computational cost for different dimers. In fact, F-SAPT0/jun-cc-pVDZ results presented in Table 2 are very similar to those obtained at the SAPT2+(3)δMP2/aug-cc-pVTZ level (See Table S1 and Figures S1 and S2), thus confirming that its use will not affect significantly to the description of the systems studied. The results in Table 2 show, as already observed in different works,[17, 22, 28, 31] that the interaction in the slipped-parallel structure of benzene dimer is dominated by the dispersion contribution with smaller contributions from electrostatics, and the same is observed in the substituted dimers.

However, the magnitude of the changes relative to benzene dimer clearly depends on the nature of the substituent, as can be more easily observed in Figure 2. In complexes with $R_2 < 0$ the main changes are related to electrostatic and dispersion contributions. In the case of electron-withdrawing groups (F, CN, NO_2), there is a substantial increase in dispersion contribution together with a substantial increase of electrostatic stabilization (not so much in the F derivative) which are partially mitigated by an increase in repulsion energy. With electron-donor groups, there are increases in stability associated to increments in dispersion while electrostatics barely changes or even destabilizes the complex. It is worth noting the different behaviour of CH_3 and NH_2b; the formation of the XH···π contacts introduces significant increases in electrostatics. When $R_2 > 0$, changes are smaller because the substituent is further apart; however, all complexes show increases in dispersion, though these are partially cancelled out by repulsion. Only for EW groups, electrostatics are more stabilizing than in benzene dimer, leading to larger increments in stability.

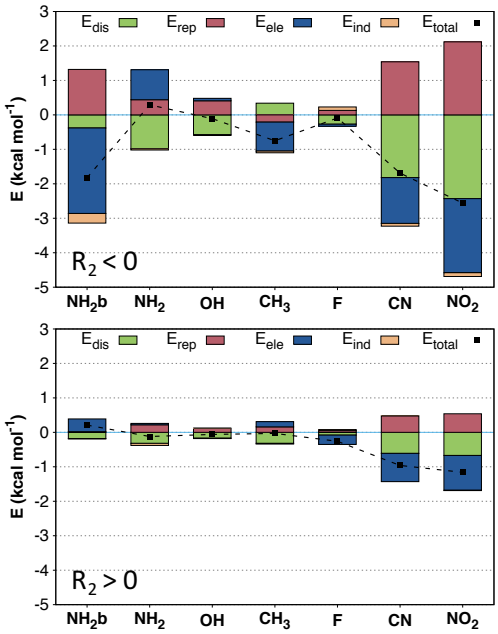


Figure 2. Energy changes and its contributions relative to benzene dimer as obtained for the optimised geometries (PBE0-D3BJ/def2-TZVP) of parallel-displaced dimers at the F-SAPT0/jun-cc-pVDZ level.

3.1.2. Parallel scans

Part of the changes discussed in the previous section could be a consequence of differences in the equilibrium geometries of the different complexes, thus blurring the effect purely originating on the substituent. Therefore, the contributions to the interaction energy have been computed at the F-SAPT0/jun-cc-pVDZ level changing the value of R_2 while keeping R_1 = 3.5 Å (the vertical displacement between rings is in most cases close to this value, see Table 1), and the substituted molecule is divided in contributions from the substituent and from the phenyl ring (C_6H_5), those coming from the linker being split 50% between the two fragments.[54]

Figure 3 summarises the results obtained for the contributions from the substituent and the phenyl ring to the global change relative to the unsubstituted benzene dimer. It becomes clear that the changes provided by the substituent (see also Figure S6) mostly come from the combination of dispersion and electrostatics. As the substituent is located closer to the phenyl ring, the contribution from dispersion increases steadily as expected considering the size of the substituents. Electrostatics shows more variation though in most cases it is the contribution determining the position of the minima. The effect of electrostatics is large in EW groups, reaching the largest value for NO_2.

On the other hand, the contributions from the phenyl group remain mostly unchanged, the larger changes in interaction energy barely reaching 1 kcal mol^{-1} (see also Figure S7). As the phenyl groups approach it is observed that in all cases repulsion decreases, independently of the nature of the substituent (ED or EW). Also, the dispersion and induction contributions barely change and remain similar to those obtained for the unsubstituted benzene dimer, while electrostatics shows more variation. There seems that the presence of the substituent alters the properties of the ring, so the electrostatic contributions become unfavourable

compared to that in benzene dimer. The effect is especially large for NO_2, where the electrostatic term becomes clearly more repulsive than in benzene dimer when the substituent is over the phenyl ring.

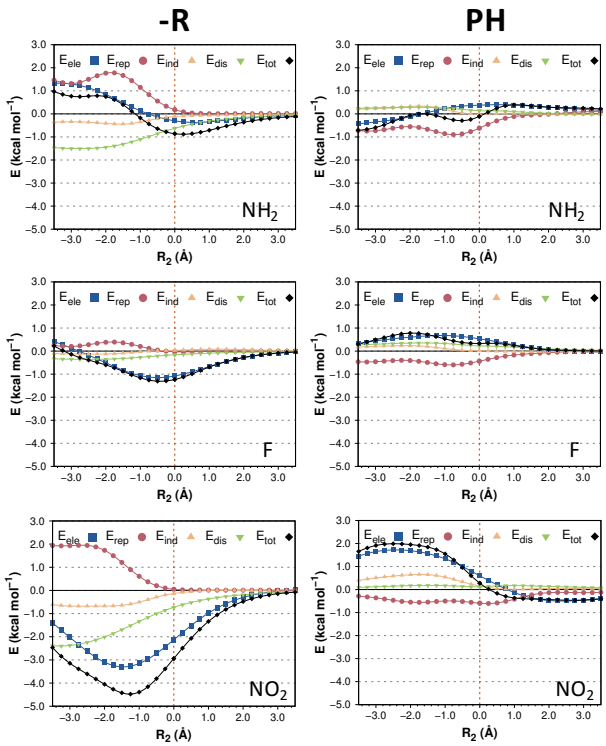


Figure 3. Contributions from the substituent (left) and the phenyl ring (right) to energy changes (relative to the benzene dimer) on the components of the interaction energy in selected parallel-displaced dimers keeping R_1 = 3.5 Å. F-SAPT0/jun-cc-pVDZ.

The results are summarised for all substituent studied in Figure 4, showing the changes on the contributions to the interaction energy at $R_2 = \pm 1.5$ Å. For $R_2 =$ -1.5 Å changes are quite complex, resulting in a mixture of contributions from dispersion and electrostatics plus an increase in repulsion. The contributions from the substituent are stabilising overall and partially cancelled by those from the ring. In most cases, the increase in stability is due to enhanced dispersion contributions with the substituent helped by an increase in electrostatics. When $R_2 = 1.5$ Å, the picture is somewhat different. Even though dispersion increases for all substituted species, the stability gain is mostly controlled by an increase in the electrostatic contribution coming from the substituent. This stabilising contribution is partially cancelled out by electrostatic destabilization from the ring, with the exception of CN and NO_2, where changes in the interaction with the ring reinforce the stability of the complexes. Thus, in all cases there are contributions from the ring and the substituent, but when the substituent is far enough from the ring its contribution decreases and contributions from the ring become of similar magnitude and have a clear impact in the final observed effect. When the substituent is close to the ring its contribution clearly dominates the energy changes, with contributions from the ring just tuning the global effect.

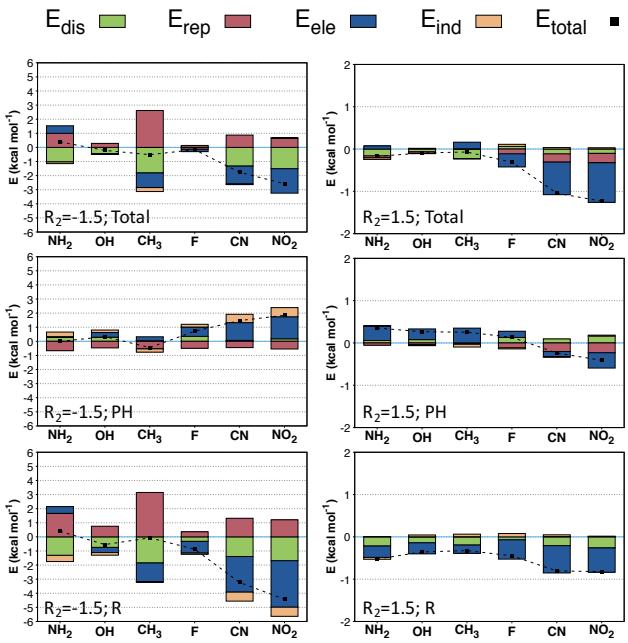


Figure 4. Total energy changes and contributions from the substituent and the ring relative to the benzene dimer at R_1 = 3.5 Å and R_2 = ±1.5 Å for parallel-displaced dimers. PH: contributions from the phenyl ring. R: contributions of the substituent. F-SAPT0/jun-cc-pVDZ.

Table 3. Optimised geometry (Å) and interaction energy (kcal mol^{-1}) for T-shaped substituted benzene dimers at the PBE0-D3BJ/def2-TZVP level.

	R_1	R_2	ΔE_{int}		R_1	R_2	ΔE_{int}
NH_2	4.78	-1.40	-3.09	**NH_2**	4.85	1.12	-2.70
OHb*	4.75	-1.46	-3.49	**OHb***	4.85	1.07	-2.88
OH	4.85	-1.06	-2.82	**OH**	4.82	1.14	-2.97
CH_3	4.80	-1.29	-3.05	**CH_3**	4.84	1.13	-2.81
H	4.84	-1.15	-2.82	**H**	4.84	1.15	-2.82
F	4.83	-1.08	-3.11	**F**	4.82	1.10	-3.18
CN	4.76	-1.12	-3.86	**CN**	4.80	1.02	-3.73
NO_2	4.79	-0.94	-3.82	**NO_2**	4.78	1.02	-3.92

* In OHb the hydrogen atom of the hydroxyl group points towards the other phenyl ring.

3.2. T-shaped dimers

Table 3 shows the results obtained for the T-shaped optimised structures allowing the distances R_1 and R_2 to change (See Figure 1). It can be observed that in these dimers there is a small variation in intermolecular distances, but in all cases the values obtained for R_1 are around 4.8 Å, while R_2 is around ±1.1 Å, with deviations in the case of NH_2, CH_3 and OHb in order to favour interactions with the ring. The interaction energy values are pretty similar to those obtained for the parallel stacked structures in Table 1. Since the substituent is located

further apart from the other phenyl ring, it is expected that the substituent effect will be weaker in these T-shaped complexes.

In a similar way to the one followed for parallel-displaced dimers, the energy surface was explored for T-shaped dimers by parallelly displacing the substituted molecule while keeping R_1 = 4.8 Å. The whole set of results is listed in Figures S11 to S16 in Supporting Information. As a summary of the observed behaviour, Figure 5 shows the different contributions to the changes in the interaction energy relative to benzene dimer, together with the contributions coming from the ring and the substituent as obtained at the F-SAPT0/jun-cc-pVDZ level.

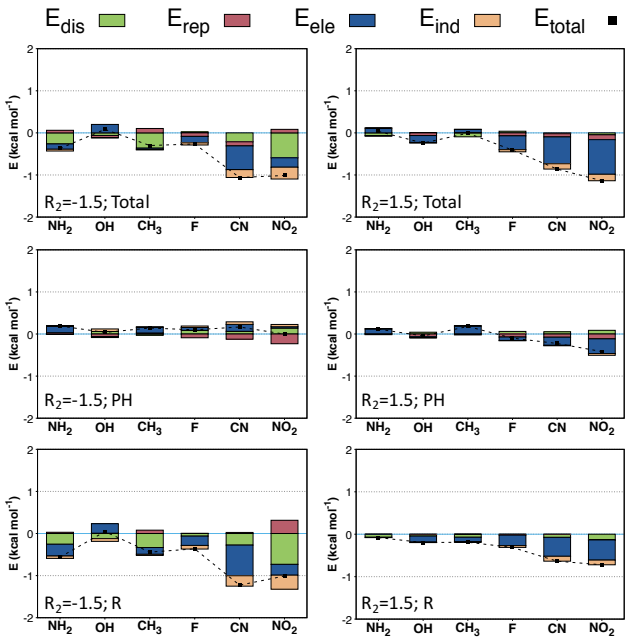
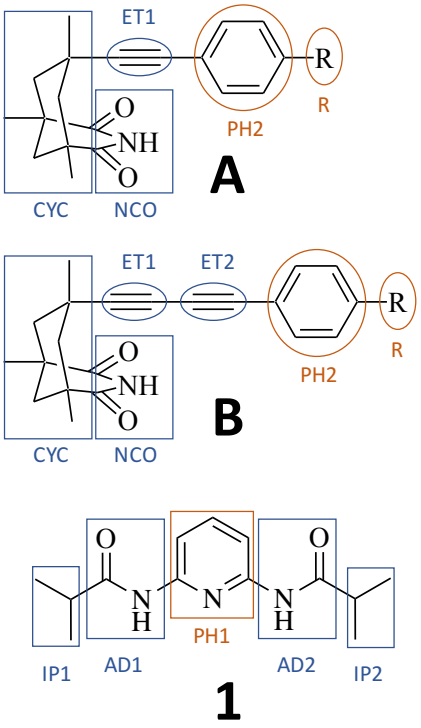


Figure 5. Total energy changes and contributions from the substituent and the ring relative to the benzene dimer at R_1 = 4.8 Å and R_2 = ±1.5 Å for T-shaped dimers. PH: contributions from the phenyl ring. R: contributions of the substituent. F-SAPT0/jun-cc-pVDZ.

When R_2 < 0 and the substituent is over the benzene molecule, changes are larger as a consequence of increased dispersion and electrostatics, mainly associated to the interaction of the substituent with the benzene molecule. The changes associated to the substituted ring are smaller and somewhat counterbalance those associated to the substituent. On the other hand, when R_2 > 0, the changes observed upon substitution are mostly electrostatic in nature, and again associated to the interaction with both the substituent and the ring.

In summary, both in parallel-displaced and T-shaped structures the substituent effect contains contributions from the direct interaction with the substituent and from changes in the polarised ring. When the substituent is close to the ring it dominates the global effect from increased dispersion and electrostatic contributions, while the role of the ring is much smaller. As the substituent is located further away from the ring the observed effect comes from similarly-sized contributions from the ring and the substituent.



R = -NH_2, -OH, -CH_3, -H, -F, -CN, -NO_2

Figure 6. Schematic representation of the species forming the dimers **1-A** and **1-B**, showing the groups on which each of the molecules is decomposed in F-SAPT0 calculations (see text).

3.3. Larger complexes

In a recent paper, Riwar et al. have pointed out the important role played by the relative arrangement between two rings upon the substituent effect.[56] Two different families of Rebek imide type receptors, (**A** and **B**, Figure 6) were taken into account,[56] leading to similar complexes with 2,6-di(isobutyramido)pyridine ligand (**1** in Figure 6), which are employed in the present work for extending the study of substituent effects to larger species. The complexes are smartly designed so the position of the rings correspond to slipped parallel stacked structures,[56] with the substituent lying over the pyridine ring of **1** in **1-A** complexes but away from it in **1-B** ones (see structures in Figure S17). Considering the results presented in previous sections, it becomes clear that even in the case of a perfect alignment of the two interacting phenyl rings, their relative position will largely affect the characteristics of the interaction.

Table 4 shows some geometric and energetic characteristics of the complexes **1-A** and **1-B** as obtained by optimisation at the PBE0-D3BJ/def2-TZVP level. Complexes with **A** have their phenyl rings located at interplane distances around 3.3 Å, a distance similar to that found in benzene dimers. The slipped distance R_2 is around -1.3 to -1.6 Å, which causes the substituent to be on top of the other phenyl ring. Therefore, in complexes **1-A** the substituent lies closer to the phenyl group and interacts directly with it. On the other hand, **B** is designed to put the substituent further away from the phenyl ring so it does not interact directly with it. As shown in Table 4, the interplane distances between phenyl rings in complexes **1-B** are around 3.5 Å,

while the slipped distances are somewhat smaller than in complexes **1-A**, with values around 1.1 Å, and thus displaced to the other side of the phenyl ring. Regarding the strength of the interaction, all complexes show similar stabilities, from -24 to -26 kcal mol^{-1}, though complexes with species **A** are slightly less favourable. The interaction is much stronger than that observed in benzene dimers because in the complexes **1-A** and **1-B** the molecules are mainly bound by a series of three hydrogen bonds (one N-H···N and two N-H···O, see Figure S17). In fact, the presence of these hydrogen bonds greatly hides the effect of the substituent upon the interaction.

Table 4. Optimised geometry (Å) and interaction energy (kcal mol^{-1}) for dimers **1-A** and **1-B** at the PBE0-D3BJ/def2-TZVP level. R_1 is the distance between ring planes; R_2 is the slipped distance between benzene rings, and R_{centre} is the distance between the centres of the ring. ΔE_{com} is the complexation energy obtained as the sum of the interaction energy (ΔE_{int}) plus the deformation energy (energy cost associated to the changes in geometry undergone by the monomers when forming the dimer).

			1-A						**1-B**		
	R_{centre}	**R_1**	**R_2**	**ΔE_{int}**	**ΔE_{com}**		**R_{centre}**	**R_1**	**R_2**	**ΔE_{int}**	**ΔE_{com}**
NH_2b^*	3.62	3.25	-1.58	-30.16	-26.45	**NH_2b^***	3.66	3.52	1.01	-30.80	-26.41
NH_2	3.58	3.30	-1.38	-29.00	-25.42	**NH_2**	3.64	3.48	1.05	-30.86	-26.45
OH	3.63	3.30	-1.51	-29.29	-25.55	**OH**	3.65	3.49	1.07	-31.10	-26.42
CH_3	3.67	3.32	-1.58	-29.00	-25.49	**CH_3**	3.67	3.52	1.04	-30.52	-26.09
H	3.70	3.34	-1.59	-27.63	-24.20	**H**	3.70	3.53	1.09	-30.24	-25.84
F	3.61	3.33	-1.39	-27.99	-24.43	**F**	3.67	3.51	1.08	-30.95	-26.29
CN	3.59	3.32	-1.36	-28.79	-24.94	**CN**	3.64	3.49	1.05	-31.60	-26.57
NO_2	3.58	3.32	-1.34	-28.53	-24.67	**NO_2**	3.65	3.49	1.06	-31.43	-26.36

* In NH_2b the hydrogen atoms of the amino group point towards the other phenyl ring.

As in benzene dimers, the effect of the substituent is more clearly seen considering the differences relative to the unsubstituted species as shown in Figure 7. It can be observed that variations in **1-A** complexes are larger than in **1-B** ones, in line with the behaviour observed in benzene dimers. Independently on whether the substituent is EW or ED, the electrostatic contribution always favours substituted species, with magnitudes similar but larger in **1-A** complexes than in **1-B** ones. The other leading contribution to the change in stability upon substitution is dispersion, especially with the larger substituents as NO_2, CN, CH_3 and NH_2. In fact, dispersion significantly contributes to the stability change even in **1-B** complexes despite the substituent being further away. **1-A** complexes exhibit larger changes in all stabilising contributions to the interaction energy due to the closer location of the substituent, but they are partially cancelled out by the accompanying increment in repulsion. Thus, the final substituent effect is quite small in all cases and always favours the substituted species unregards of the character of the substituent and independently on whether the substituent is closer to the other ring (**1-A**) or located further away (**1-B**).

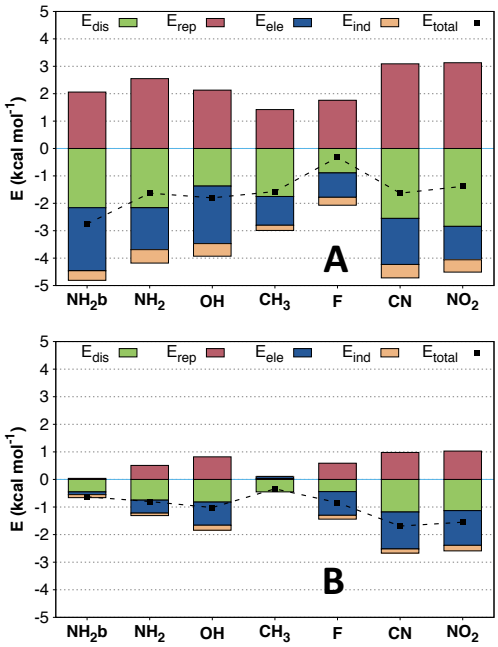


Figure 7. Energy differences in **1-A** and **1-B** relative to the unsubstituted species as obtained with F-SAPT0/jun-cc-pVDZ.

As in benzene complexes, the F-SAPT0 method allows to partition these contributions into groups allowing a more detailed analysis. As indicated in Figure 6, molecule **A** is split into five groups: phenyl ring PH2, substituent R, C-C ethynyl linker ET1, OC-NH-CO group denoted as NCO, and the cyclohexane group CYC. Molecule **B** is split the same way but now there are two C-C ethynyl linkers, ET1 and ET2. Molecule **1** is divided into 5 groups: pyridine ring PH1, the two amide groups AD1 and AD2, and the two isopropyl groups IP1 and IP2. The substituent is located on PH2 and therefore the π-π interaction between the substituted ring and the pyridine ring is characterized by the interactions between PH1 and PH2 and between PH1 and R.

Following this scheme, F-SAPT has been employed to partition the interaction into different groups and to obtain the changes relative to the unsubstituted derivatives (whole set of results in Supporting Information). Figure 8 shows the contributions to the total interaction energy and to its components coming from the defined groups in the case of the unsubstituted dimers **1-A** and **1-B**. As expected, the contacts between the phenyl ring of the pyridine and the amide groups from molecule **1** with the NCO group in molecules **A** and **B** are the main stabilising motifs in these complexes (recall that three hydrogen bonds are formed among these fragments, see Figure S17). Besides, there are favourable contributions from the interaction between the two phenyl rings and the ethynil linkers. There also are weak destabilizing contributions coming from the through-space interactions with the cyclohexane and isopropyl moieties, that mainly act as spectators. When the total interaction is decomposed into contributions, it can be observed that the electrostatic contribution mimics the results observed for total energies. In fact, the electrostatic term is the one behind the slightly repulsive interaction with the cyclohexane group. There are also large repulsive contributions that are almost cancelled out by similarly large dispersion terms, as well as larger induction contributions associated to the hydrogen bonds formed with the NCO group.

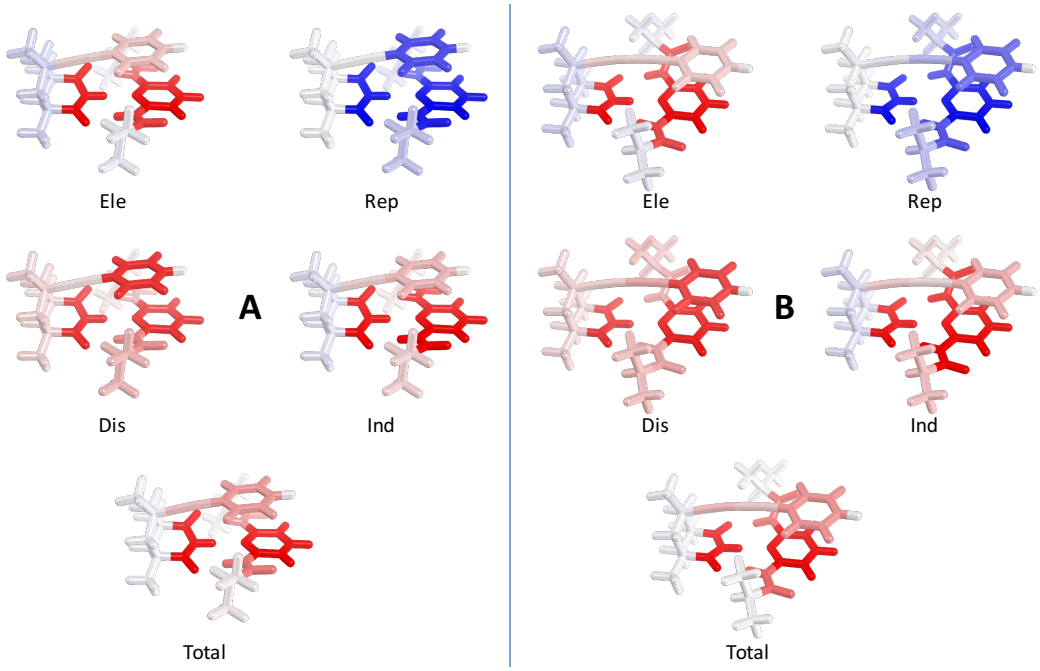


Figure 8. Contributions to the interaction energy in unsubstituted dimers **1-A** and **1-B** considering the partitioning exposed in Figure 6 using the F-SAPT0 method, coloured by the global contributions of each group. The colour scale goes from -15 kcal mol^{-1} (red) to +15 kcal mol^{-1} (blue).

Figure 9 shows the differences in total interaction energies among the groups in which the molecules have been divided (see Figure 6) relative to the unsubstituted dimers. As expected, it can be observed that in complexes **1-A** the most noticeable changes are limited to the regions around the phenyl groups and substituent. No significant variations on the interaction are observed for the bicyclic moiety CYC that acts as a supporting structure for the π-π interaction to take place properly. The small changes observed for CYC in CN and NO_2 derivatives are related to induction (see the whole set of results in Figures S19 to S25 in Supporting Information); the polarisation effect of the substituent propagates to longer distances, so the bicyclic unit is also slightly affected by the most polarising substituents. Similarly, the isopropyl groups are mere spectators, and no change is observed upon substitution. Therefore, when the substituent is included, the changes on the interaction are mostly circumscribed to the two phenyl rings and the amide groups. The interaction with the amide groups becomes more repulsive with EW groups, while it is more favourable with ED groups. The origin of these effects is the through-space electrostatic interaction between the substituent and the amide groups (see for instance the OH derivative, Figure S21). In **1-B** complexes the behaviour is similar, though weakened due to the longer distances between the substituent and the other phenyl ring. In most cases the interaction with the phenyl ring becomes more repulsive than in the unsubstituted derivative. Also, there are contributions from the linking ethynil units, now located on top of the pyridine ring of **1**.

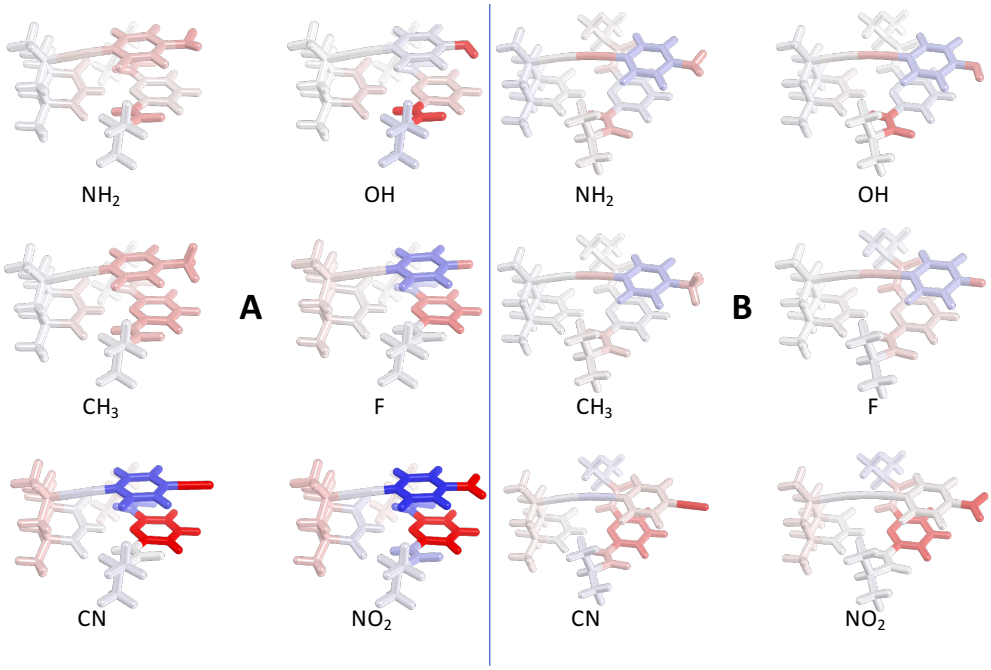


Figure 9. Contributions (relative to unsubstituted complexes) to the total interaction energy in dimers **1-A** and **1-B** considering the partitioning exposed in Figure 6 using the F-SAPT0 method, coloured by the global contributions of each group. The colour scale goes from -3 kcal mol^{-1} (red) to +3 kcal mol^{-1} (blue).

In Figure 9, the colour scale represents the sum of all pair interactions for a fragment in a molecule with all the fragments in the other one. There can be contributions coming from fragments, not directly related to the π-π interactions and the substituent effect, that can therefore hide its role and origin. However, F-SAPT0 gives information about the magnitude of the interaction and its components for each pair of fragments, so the effect directly related to the substituent and the substituted phenyl ring can be extracted from the interaction of the whole molecules. Focusing on the interactions associated to the substituent effect, they comprise the interactions of the pyridine ring of **1** (PH1) with the substituent R and the substituted phenyl ring PH2 in molecules **A** and **B**. Figure 10 shows the different contributions to the energy changes relative to the unsubstituted species that originate in interactions between the phenyl ring PH2 and substituent R with the pyridine ring PH1.

Considering the contributions coming from the interaction between the substituent (R) and the pyridine ring (PH1), there is a clear difference between complexes **1-A** and **1-B**, at least quantitatively (Figure 10, top). In **1-B** complexes the changes are all stabilising and mainly associated to the electrostatic contribution, with smaller contributions from dispersion. In dimers **1-A** the substituent is mostly on top of the pyridine ring and therefore there is a significant overlap between the substituent and the ring. Thus, EW groups exhibit a considerable increase on the interaction with the phenyl ring, with electrostatics controlling the global changes; in fact, the dominance of electrostatics also reflects in small contributions from induction with these most polarising substituents. In the case of ED groups the picture is totally different and electrostatics plays a secondary role. In all complexes, the location of the substituent onto the ring leads to moderate increases on repulsion, which are mostly

overcome by increases on dispersion, so the net effect of the substituent roughly follows electrostatics. Thus, the direct interaction between the substituent and the phenyl ring mostly follows the ED or EW character of the substituent due to changes in the direct electrostatic interaction between both moieties tuned by contributions from dispersion as the substituent comes closer to the ring.

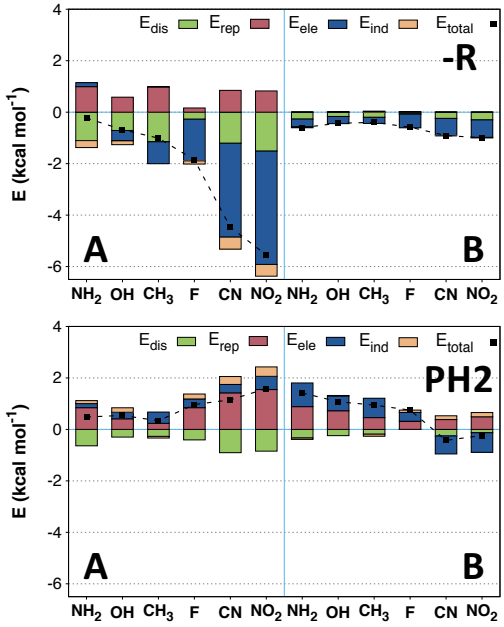


Figure 10. Contributions to the interaction energy changes relative to the unsubstituted species that originate in interactions between the phenyl ring PH2 (bottom) and R (top) in species **A** and **B** with the pyridine ring PH1 in molecule **1**. F-SAPT0/jun-cc-pVDZ.

Nevertheless, the picture is not complete until the interactions between phenyl rings are considered (Figure 10, bottom). The PH2 ring can be polarised by the substituent and therefore interact differently with PH1, as it would be the case in a HS model. Considering **1-A** complexes, the interaction between phenyl rings becomes more repulsive upon substitution, with the effect becoming larger with the larger EW character of the substituent. It can be observed that the main responsible of these changes is the repulsion contribution between rings, while dispersion becomes slightly more stabilizing upon substitution. Electrostatics also contribute to destabilize the interaction between phenyl rings, though its effect is much smaller than the one coming from changes in repulsion. In **1-B** complexes the changes are smaller, though changes in the repulsion contribution are still largely responsible of the variations on the strength of the interaction between phenyl rings (in all cases the repulsion contribution destabilizes the interaction). The only other factor significantly affecting the interaction is electrostatics, which destabilizes the interaction in most cases with the remarkable exception of the two most EW substituents. For CN and NO_2, electrostatics contribute to strengthen the interaction, so the net effect is attractive.

Consequently, the analysis of the interactions between PH1 with PH2 and R seems to indicate that the changes observed on the stability of these complexes upon substitution are

the result of a balance of different contributions, but mostly controlled by changes on electrostatics with contributions from dispersion. In **1-A** complexes the changes are dominated by the interaction with the substituent, while in **1-B** complexes there are contributions from both the substituent and the ring. Overall, the interaction energy changes as the EW character of the substituent increases, roughly following electrostatics. However, in **1-A** the effect is dominated by the substituent, while in **1-B** the net effect comes from contributions of similar magnitude from the substituent and the polarised ring.

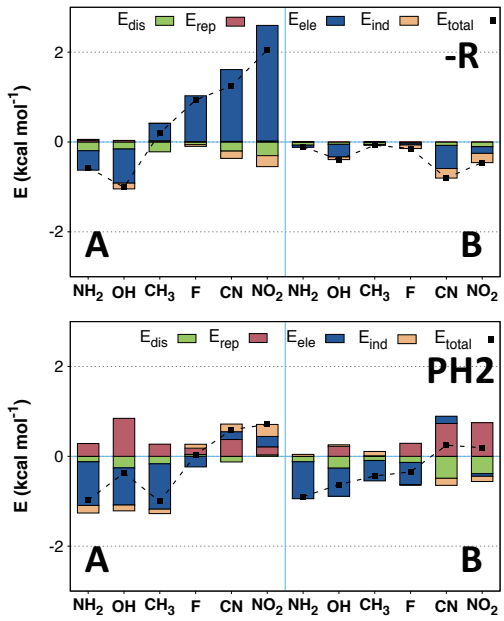


Figure 11. Contributions to the interaction energy changes relative to the unsubstituted species that originate in interactions between the phenyl ring PH2 (bottom) and R (top) in species **1-A** and **1-B** with the amide groups AD in **1** (the whole molecule except the pyridine ring; AD=IP1+AD1+IP2+AD2). F-SAPT0/jun-cc-pVDZ.

On the other hand, the total changes observed are not circumscribed to the interactions between PH2 and R with PH1. PH2 and R can also interact with other regions of **1**, thus contributing to the changes on stability. Figure 11 summarises the changes associated to interactions of PH2 and R with the sum of amide and isopropyl groups of the other molecule (AD=IP1+AM1+IP2+AM2, the rest of the molecule without the pyridine ring, see Figure 6). It can be observed that the changes on the interaction with these groups, though small, are of a magnitude similar to those observed for the interactions with the phenyl ring PH1, and therefore will have a significant impact on the final stability changes. The substituent weakly modifies the interaction with the amide groups in **1-B** complexes as a consequence of the large distance between groups (Figure 11, top). However, there is a significant electrostatic stabilisation for OH and CN, that must be related to through-space dipole-dipole interactions with the carbonyl groups. In **1-A** complexes the changes are larger and roughly follow the EW character of the group. In most cases, the interaction becomes more destabilising as the EW character of the substituent increases, reaching around 2 kcal mol^{-1} in CN and NO_2. In the case

of the interaction between the phenyl ring PH2 and the amide moieties (Figure 11, bottom), there is an electrostatic stabilisation for ED groups, while for EW ones the combined effect of electrostatics plus repulsion weakens the interaction. Thus, the observed stability changes not only depend on tuning the π-π interaction via substitution, but also on changes on the interaction strength with other groups of the interacting molecule, obscuring the effect of the substituent on the π-π interaction.

Finally, there could be interactions between PH1 and the amide groups in **1** with other regions of molecules **A** and **B** that could affect to the final global stabilities. Figure 12 shows the changes on the interaction between amide groups (AD=IP1+AD1+IP2+AD2) and PH1 with the different fragments defined in molecules **A** and **B**. It can be observed (Figure 12, top) that the interactions with PH1 are clearly dominated by changes in the interactions with the substituent (dimers **1-A**) and the phenyl group (ED groups in **1-B**). The rest of the fragments hardly contribute to the changes in interaction energy, though in **1-B** complexes there are contributions from the ethynyl linkers of similar magnitude as those obtained for the substituent. Similarly, the amide groups (Figure 12, bottom) mostly show changes in their interaction with the phenyl ring and substituent.

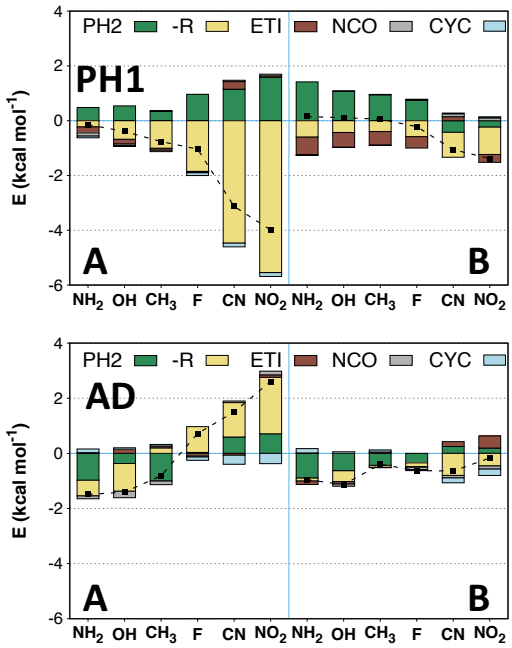


Figure 12. Contributions to the interaction energy changes relative to the unsubstituted species that originate in interactions between the phenyl ring PH1 (top) and the amide groups (bottom) in **1** with the different fragments defined in species **1-A** and **1-B**. F-SAPT0/jun-cc-pVDZ.

In summary, the changes observed upon substitution in the complexes studied are mostly related to changes in the interactions of the phenyl group PH2 and the substituent R with the pyridine ring PH1 and the amide groups, with the rest of the molecule acting mostly as spectator. Though the changes on the interaction seem to be controlled by the substituent

(and mostly by changes on the electrostatic contribution), the contributions from changes on the phenyl ring are also significant. The difference between **1-A** and **1-B** is the magnitude of the interaction with the substituent. In **1-B** the total change is the combination of similar contributions from the direct interaction of the substituent with the ring and an indirect effect produced by changes in the interaction between the two rings. In fact, the interaction between phenyl rings dominates the effect and this could be the reason for the complexes **1-B** to follow the HS picture (as the group becomes more donating, the repulsion between rings increases). In complexes **1-A** the behaviour is totally dominated by the direct interaction of the substituent with the ring, so they do seem to fit within a WH picture. However, it must be stated that the global trend is similar in both complexes as we move from EW to ED groups, though the magnitude of the changes in **1-A** is much larger than in **1-B**.

A final concern can be raised considering that the previous discussion has been performed using the optimised geometries for each dimer and in consequence part of the effects could be associated to a geometry change. In fact, increases in repulsion in EW substituents could be related to the shorter equilibrium distances between the rings. For this reason, the analysis has also been carried out using frozen geometries for the dimers. In this case, the geometry corresponds to the one obtained for the unsubstituted derivative, which is kept unchanged in the substituted dimers while the geometry of the substituent is optimised. The results of this analysis are shown in Figures S26 to S28. Even though the magnitude of the changes is smaller the general trends are like those described above. Overall, the changes on the interaction are dominated by the direct interactions with the substituent but with non-negligible contributions from the polarised ring, as well as from other regions of the interacting molecules not directly participating in the π-π contact.

4. Conclusions

The influence of the relative positions of the rings upon the substituent effect in π-π interactions has been computationally analysed by using monosubstituted benzene dimers as simplified models, but also considering larger systems showing distance-dependence of the substituent effect. The changes observed in the stability of the complexes have been analysed using F-SAPT0, providing not only information about the nature of the interaction and its controlling factors, but also allowing to quantify the contributions coming from different regions of the interacting species.

In parallel-displaced benzene dimers the results indicate that, as expected, the changes relative to the benzene dimer become larger as the substituent comes closer to the benzene ring. Though the interaction is dominated by dispersion, there seems that the effect of the substituent mostly follows the trends observed for the electrostatic contribution. The results indicate that the energy change is dominated by the direct interaction between the substituent and the other phenyl ring. When the substituent is close to the phenyl ring, the contribution from the substituent mainly comes from electrostatics and dispersion, and it is larger than the changes observed in the interaction between phenyl rings (which usually opposes the contribution from the substituent). On the other hand, when the substituent is

located further away from the ring the contributions coming from the ring and the substituent are similar in magnitude. A similar behaviour is observed in T-shaped benzene dimers.

When considering larger systems, the substituent effects are quite small in magnitude and partially hidden due to other interactions present in the complex. Nevertheless, the F-SAPT0 partitioning allows isolating the contributions from the rings and the substituent. Considering just the two phenyl rings and the substituent, the picture is similar to that observed in model benzene dimers; that is, the substituent dominates at short distances, while the contribution from the polarised ring can be the dominant one when the substituent is located further away from the ring. Caution must be taken when interpreting energy changes upon substitution in larger systems because changes on the interaction between the substituent and parts of the molecule other than the phenyl ring can change the stability of the complexes. Thus, the observed effect can be a consequence of the substituent effect upon the π-π interaction or not.

Overall, the results indicate that both ring polarisation and through-space interaction with the ring are present and contributing to the total substituent effect. The outcome of these two contributions depends on the relative position of the interacting rings; electrostatic interaction with the substituent dominates when the substituent is located near the phenyl ring, while its contribution becomes smaller and of similar magnitude as the one coming from the polarised ring as the substituent is located further away.

Acknowledgments

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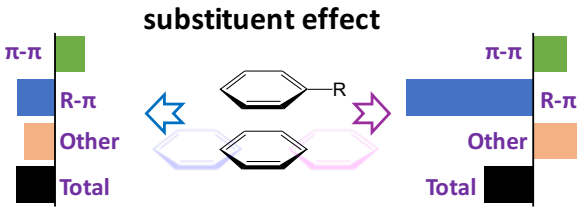

The nature of the substituent effect depends markedly on the relative position of the interacting rings. Contributions not directly related to the π-π interaction can affect significantly to the observed value.