Influence of Stacking on Hydrogen Bonding: Quantum Chemical Study on Pyridine−Benzene Model Complexes

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The present work focuses on the influence of aromatic stacking on the ability of an aromatic nitrogen base to accept a hydrogen bond. Substituent effects were studied at the MP2 level for 10 complexes of a substituted benzene stacked with pyridine in a parallel offset conformation. The interaction energies between each substituted benzene and pyridine were analyzed in terms of Hartree−Fock, correlation, and electrostatic contributions. It appears that the basicity of pyridine is directly related to the electrostatic interaction between the cycles. It increases with increasing electron donating character of the benzene substituents. Also, density functional theory based descriptors such as global and local hardnesses and the benzene ring polarizability are found to adequately predict the interaction energy. These findings may be important in the study of DNA/RNA chains.

Introduction

Intermolecular interaction between aromatic systems has been extensively studied during the past two decades, by both experimental[1−14] and theoretical[15−38] methods. The importance of the π/π interaction has been repeatedly stressed in many fields of chemistry and biochemistry.[39−48] The best-known example is the stacking interaction between nucleic acid bases in DNA/RNA chains which is, besides H-bonding, responsible for the stability and conformational arrangement of nucleic acids.[49−51] Indeed, aromatic stacking in biomolecules is frequently accompanied by H-bonding; however, little is known about their functional interplay.

Electrostatics-based studies on hydrated DNA base pairs show that the stacked base pairs hydrate better than the corresponding H-bonded base pairs.[52,53] Apart from the fact that more binding sites for water molecules are present in the stacked conformation, the most negative values of the molecular electrostatic potential (MEP) show up in the stacked conformations in contrast to the H-bonded ones. In recent works on substituent effect on π/π stacking, the MEP at the center of the ring was used for estimating the interaction strength between the rings[54,55] It was observed that substituted benzenes bind stronger than nonsubstituted benzenes due to both electrostatic and dispersion interactions (in the case of both electron-donating and electron-withdrawing substituents). In the study of stair motifs at protein−DNA interfaces, cooperativity was investigated for H-bonded and stacked trimers of nucleic acid bases and a charged aromatic amino acid.[56] The three-body-term contribution was found to vary from −0.4 to +7.4 kcal/mol, showing only nonadditivity, whereas cooperativity is only present for negative values of ΔE_3.

Here, we studied the interplay between aromatic stacking and hydrogen bonding using as a model system pyridine stacked in an offset parallel geometry with a benzene ring comprising an electron-withdrawing or -donating substituent. The offset parallel geometry was chosen because state-of-the art computational methods have proved it to be more stable compare to the T-shaped or the face-to-face parallel conformations.[57] We set out to gauge the influence of the stacking interaction of 10 substituted benzenes with pyridine on the basicity of pyridine at the MP2 level of theory. Interaction energy components (Hartree−Fock, electrostatic, and correlation) of the stacked dimers were considered together with the charge transfer to pyridine and the minimum of the MEP around the nitrogen of the stacked pyridine, as a measure of its hydrogen bonding capacity. Indeed, the MEP has been known for a long time[58] to be a reliable descriptor of the hydrogen bond strength: the deeper the electrostatic potential, the stronger the electrostatic interaction with water molecules and with hydrogen bond donors in general.[59−62] The polarizability, related to the London dispersion energy, and density functional theory (DFT) based reactivity descriptors such as the global and local hardnesses of the isolated substituted benzenes were used in order to assess the amplitude of the stacking interaction. This work is part of our ongoing interest in the development/use of DFT-based reactivity descriptors (conceptual DFT)[63−66] and their application to systems of biological interest.[67−74]

Theory and Computational Details

Geometry Optimization and Level of Calculation. Post Hartree−Fock methods as Møller−Plesset perturbation theory (MP)[75] and coupled cluster theory[76,77] have been tested in the past for their ability to describe the interaction energy between two benzene rings, RNA/DNA base pairs, and aromatic amino acids.[78−81] The use of the 6-31G*(0.25) basis set at the MP2 level containing one set of diffuse polarization functions with an exponent of 0.25 on second-row elements has been shown by Hobza[82] to be a good compromise between computational cost and quality. Contrary to more extended basis sets, the

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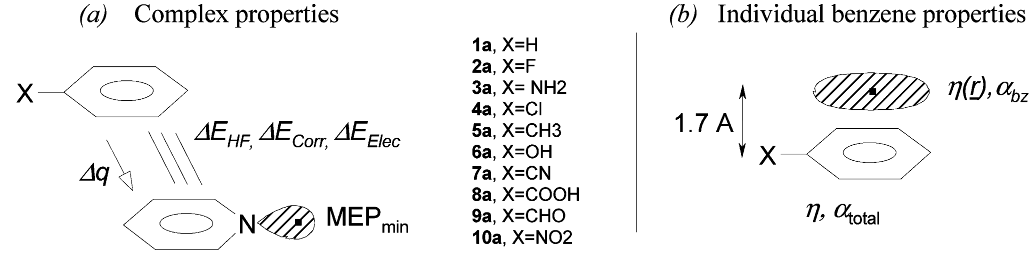

Figure 1. Calculated properties of pyridine and substituted benzenes arranged in the offset parallel conformation. (a) Complex properties: HF, correlation and electrostatic interaction energy components (ΔE_{HF}, ΔE_{corr} assumed to represent mostly the dispersion interaction energy, ΔE_{elec}), MEP minimum around the nitrogen, charge transfer Δq. (b). Properties of the individual benzenes: substituent α_{subst}, and total substituted benzene polarizabilities α_{total} (α_{bz} is calculated according to eq 3); global hardness η and local hardness $\eta(\underline{r})$ (1.7 Å above the center of the ring).

6-31G*(0.25) basis set does not overestimate too much the stacking energy compared to coupled cluster methods.

Complexes between pyridine and 10 substituted benzenes Ph−X (X = H, F, NH_2, Cl, CH_3, OH, CN, COOH, CHO, NO_2) were fully optimized at the MP2/6-31G* level of theory starting from an offset parallel conformation (Figure 1a). The isolated rings for the calculation of individual properties were optimized at the same level. Interaction energies as well as electronic properties were calculated at the MP2/6-31G*(0.25) level of theory. Corrections for basis set superposition error (BSSE) were applied using the counterpoise method.[83]

To circumvent distance dependence effects, interaction energies for each substituent case were also calculated on "fixed complexes", in which the distance as well as the orientation between the rings was kept fixed at the one obtained for the optimized benzene/pyridine complex. Substitution effects will be more pronounced on these fixed complexes because the electron-donating or -withdrawing character is not masked by geometric rearrangements.

Interaction Energy Components. The total interaction energy ΔE can be expressed as the sum of the Hartree−Fock (HF) interaction energy ΔE_{HF} and the correlation interaction energy ΔE_{corr} (Figure 1a). The HF interaction energy is roughly the sum of the electrostatic, induction, and exchange−repulsion terms; the correlation interaction energy corresponds to the dispersion energy that is assumed to be the cause of the stabilization of parallel stacked systems.[80]

The electrostatic interaction between the substituted benzenes and pyridine was calculated from a distributed multipole analysis, a "technique for describing a molecular charge distribution by using local multipoles at a number of sites within the molecule".[84] The distributed multipoles were calculated from the MP2/6-31G*(0.25) wave function at the nuclear positions up to rank 4 (hexadecapole) with GDMA version 1.3.[85] The electrostatic interaction energy between the molecules was then calculated with the ORIENT program version 3.2.[86]

Hydrogen Bonding Capacity of the Pyridine. The capability of the nitrogen atom of the stacked pyridine to accept a hydrogen bond was calculated as the minimum of the MEP around the nitrogen (Figure 1a):

$$V(\underline{r}) = \sum_{A} \frac{Z_A}{|\underline{r} - \underline{R}_A|} - \int \frac{\rho(\underline{r}')}{|\underline{r} - \underline{r}'|} \, d\underline{r}' \qquad (1)$$

where the summation runs over all the nuclei A of the system. The MEP represents the interaction energy of the system with a unit positive charge, and thus reflects mainly the hard−hard interactions between the molecules. It has been shown to adequately describe properties of chemical interest such as nucleophilicity.[87−93]

Charge transfer to pyridine was calculated as the sum of atomic Chelpg charges on the pyridine (Figure 1a).

Relation between the Stacking Energy and Polarizability, Global Hardness, and Local Hardness of the Substituted Benzenes. According to London's formula, starting from a simple model made of two spherical atoms, the dispersion interaction energy can be expressed as

$$\Delta E_{disp} = -\frac{C\alpha_1\alpha_2}{r^6} \qquad (2)$$

where α_1 and α_2 are the polarizabilities, r is the distance between the interacting partners, and C is a constant. Here we will approximate the dispersion energy by a similar expression (i.e., neglecting directional effects), where α_1 is the polarizability of pyridine and α_2 the polarizability of the substituted benzene. If α_1 is assumed constant, ΔE_{disp} is then proportional to $\alpha_2 r^{-6}$. α_2 was computed as the polarizability of the benzene ring itself in the substituted benzene (i.e., excluding the polarizability of the substituents). In each complex, the benzene substituent is located as far away as possible from the nitrogen of the pyridine (Figure 1), avoiding direct interaction with the π electrons of the pyridine. The polarizability is an additive property, at least considering its isotropic part;[94,95] hence the benzene ring polarizabilities of the 10 substituted benzenes were calculated as

$$\alpha_{bz} = \alpha_{total} - \alpha_{subst} \qquad (3)$$

α_{total} is the calculated polarizability of the substituted benzene; α_{subst} is computed as the polarizability of the radical corresponding to the substituent (e.g., $CH_3^\bullet$ in the case of toluene). The polarizabilities were obtained analytically by use of the 6-31G*(0.25) Pople basis set. Equation 2 thus becomes

$$\Delta E_{disp} = -\frac{C'\alpha_{bz}}{r^6} \qquad (4)$$

Some reactivity descriptors introduced in the framework of DFT, such as the global hardness and global softness, are related to the polarizability.[66] Indeed, Politzer was the first to put forward a relationship between the polarizability and the global softness.[96−98] Vela and Gàzquez derived an expression of the proportionality between S and α.[99] Correlations between α and S^3 on the other hand were presented by various other authors.[98,100] Hence we can write the relationship between the polarizability (α), the global softness (S), and the global hardness (η), which is equal to the inverse of S:

$$\alpha \approx S^n = \frac{1}{\eta^n} \qquad (5)$$

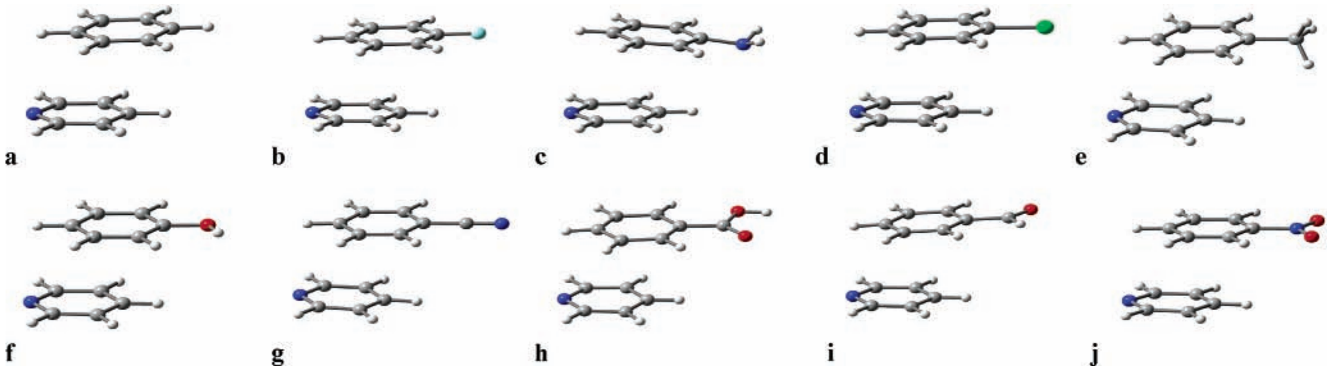

Figure 2. Ten stacked complexes of pyridine and substituted benzenes optimized in parallel offset geometry at the MP2/6-31G* level of theory. Benzene (a), fluorobenzene (b), aminobenzene (c), chlorobenzene (d), toluene (e), phenol (f), cyanobenzene (g), benzoic acid (h), benzaldehyde (i), and nitrobenzene (j).

n equals 1 or 3 depending on the proportionality used. η, the hardness, is a global property that has been sharply defined by Parr and Pearson[101] in 1983, as the second partial energy derivative with respect to the number of electrons. Considering the variation in energy when one electron is added or removed from the system and using a finite difference approximation, one gets

$$\eta = \frac{I - A}{2} \tag{6}$$

with I the vertical ionization energy and A the vertical electron affinity. For the substituted benzenes considered in this study, the calculated electron affinity values were found to be negative; hence the hardness was taken as half the ionization energy. The polarizability in eq 2 can then be approximated by the inverse of the hardness to the nth power. We obtain

$$\Delta E_{\mathrm{disp}} = -\frac{C'}{\eta^n r^6} \tag{7}$$

n equals 1 or 3 depending on the proportionality used. Both proportionalities will be tested for the ability of the global hardness to predict the dispersion interaction energy. While the polarizability of the benzene ring is used in eq 4, we consider here the global hardness as a reliable property.

In the study of cation−π systems the electrostatic potential of aromatics has been shown to provide useful guidelines in the prediction of the total interaction energy.[102,103] For a face-to-face configuration between benzene and substituted benzenes, the interaction energy increases in the series benzene, phenol, toluene, as does the electrostatic potential calculated at the center of the isolated substituted benzene ring.[55] In the context of DFT descriptors, we chose to test the local hardness $\eta(\underline{r})$ for its ability to estimate the total interaction energy between the cycles, concentrating on the cyclic moiety of the substituted benzene in analogy with eq 3. This was done to circumvent the direct dependence of the global hardness on the substituent. $\eta(\underline{r})$ mirrors the accumulation of negative charge at a defined point independently of the number of electrons of the system, and has been successfully used in the study of electrophilic attacks.[104] A word of caution has to be mentioned on the computation of the local hardness. Although a debate in the literature on the exact formulation of the local hardness is still going on, the proposal (8)[104−109] clearly received by far the most attention and will then be used here:

$$\eta(\underline{r}) = -\frac{V_{\mathrm{el}}(\underline{r})}{2N} \tag{8}$$

Here N is the number of electrons of the system, and $V_{\mathrm{el}}(\underline{r})$ is the electronic part of the electrostatic potential (eq 1). $V_{\mathrm{el}}(\underline{r})$ was evaluated at a distance of 1.7 Å above the isolated benzene rings (Figure 2b). This is about half the distance between the rings in the optimized complexes.

All calculations were carried out using the Gaussian03 package.[110]

Results and Discussion

Geometries and Interaction Energies. The structures of all optimized complexes are collected in Figure 2; the interaction energy components and distances between the centers of the cycles can be found in Table 1. For each optimized complex, the inter-ring distance is slightly smaller than for the nonsubstituted rigid benzene dimer calculated with MP2 and coupled cluster methods.[25,28,55,57] The calculated binding energies are of the same order of magnitude as the experimental binding energy of the benzene dimer: 2.4 ± 0.4 kcal/mol. In agreement with previous studies on a parallel stacked benzene dimer, dispersion appears as the major source of attraction between the rings.[80] In our optimized offset parallel geometries, we find the lowest binding energy for phenol. This is in contrast with an MP2 and CCSD study on face-to-face stacked complexes by Sinnokrot et al., where larger binding energies were observed for the benzene/phenol dimer than for the benzene dimer.[55] Note that all HF interaction energies are positive (Table 1), the electrostatic term being negative, so the sum of exchange and induction terms must be repulsive. Comparison of the MP2 interaction energies for the optimized and fixed complexes shows that for some substituents the binding energy is slightly larger in the latter case. This may be explained by the fact that the complexes were optimized with the 6-31G* basis set and the binding energies computed with the 6-31G*(0.25) basis set.

Full optimization of stacked complexes allows for structural deformations leading to a deviation from a perfect parallel arrangement of the cycles, as has been observed previously for DNA bases.[111] Nonplanarity of the amino group was noticed in complexes of nucleic acid base pairs, a structural deformation that we find here for the pyridine/aminobenzene dimer (Figure 2c). Nevertheless, Hobza and co-workers found binding energies similar to those obtained with rigid monomers.

The total and electrostatic interaction energies calculated for the fixed complexes increase nicely (in absolute value) with increasing electron-withdrawing character of the substituents. This is in agreement with a NMR study on the rotation barrier of 1,8-diarylnaphthalenes.[112,113] Electron-withdrawing substituents were found to stabilize the transition state for rotation by decreasing the repulsion between the π electrons of each ring,

TABLE 1: Properties Calculated for Isolated Substituted Benzene Molecules Ph−X and for Optimized and Fixed Complexes (See Figure 1)[a]

	optimized complexes							fixed complexes						Ph−X properties				
X	ΔE_{MP2}	ΔE_{HF}	ΔE_{corr}	ΔE_{elec}	Δq	MEP	R	ΔE_{MP2}	ΔE_{HF}	ΔE_{corr}	ΔE_{elec}	Δq	MEP	α	α_{subst}	α_{bz}	η	$\eta(\underline{r})$
NO_2	−3.79	6.89	−10.67	−0.57	0.0048	−0.0965	3.50	−3.71	6.87	−10.58	−0.51	0.0041	−0.0964	76.84	18.08	58.76	0.3923	0.0887
CN	−4.13	4.99	−9.12	−0.55	−0.0002	−0.0970	3.60	−3.63	7.06	−10.69	−0.58	−0.0015	−0.0969	74.39	14.99	59.40	0.3826	0.0927
COOH	−3.49	7.87	−11.35	−0.45	−0.0057	−0.1023	3.45	−3.53	7.27	−10.81	−0.50	−0.0054	−0.1007	78.46	18.33	60.13	0.3657	0.0939
CHO	−3.90	5.18	−9.08	−0.41	−0.0022	−0.0998	3.60	−3.39	7.44	−10.82	−0.35	−0.0061	−0.1015	64.91	9.64	55.26	0.3592	0.0970
Cl	−3.35	8.12	−11.47	−0.63	−0.0075	−0.1021	3.44	−3.48	7.27	−10.75	−0.35	−0.0074	−0.1016	71.81	10.71	61.10	0.3453	0.0966
F	−2.89	7.92	−10.81	−0.34	−0.0074	−0.1028	3.47	−2.97	7.48	−10.45	−0.26	−0.0084	−0.1028	59.45	2.41	57.04	0.3461	0.1033
H	−2.78	7.89	−10.67	−0.15	−0.0165	−0.1062	3.52	−2.78	7.89	−10.67	−0.15	−0.0165	−0.1062	58.38	0.26	58.13	0.3432	0.1062
CH_3	−3.34	5.68	−9.02	−0.02	−0.0193	−0.1067	3.64	−2.85	8.07	−10.92	−0.08	−0.0225	−0.1069	70.71	12.12	58.59	0.3305	0.1057
OH	−2.69	8.39	−11.08	−0.21	−0.0162	−0.1066	3.47	−2.90	7.70	−10.59	−0.23	−0.0155	−0.1055	63.94	5.58	58.36	0.3258	0.1050
NH_2	−3.20	7.66	−10.86	−0.51	−0.0217	−0.1116	3.48	−2.51	8.35	−10.86	0.12	−0.0380	−0.1062	66.88	9.11	57.78	0.3389	0.1130

[a] Interaction energy components, ΔE_i (kcal/mol); charge transfer to the pyridine, Δq (au); molecular electrostatic potential minimum around the pyridine nitrogen, MEP (au); distance between the rings, R (Å); total, substituent, and benzene polarizabilities, α_i (au); global and local hardness, η and $\eta(\underline{r})$ (au).

TABLE 2: Dependence of Charge Transfer to Pyridine with the Basis Set Used, Computed for the Optimized Complexes (au)

substituent	6-31G*(0.25)	6-31G*	6-31G**	6-31+G**
NO_2	0.0048	0.0040	0.0039	0.0065
CN	−0.0002	−0.0011	−0.0012	−0.0009
COOH	−0.0057	−0.0047	−0.0048	−0.0045
CHO	−0.0022	−0.0021	−0.0022	−0.0024
Cl	−0.0075	−0.0064	−0.0065	−0.0061
F	−0.0074	−0.0061	−0.0062	−0.0058
H	−0.0165	−0.0132	−0.0130	−0.0167
CH_3	−0.0193	−0.0170	−0.0169	−0.0239
OH	−0.0162	−0.0123	−0.0123	−0.0136
NH_2	−0.0217	−0.0210	−0.0209	−0.0264

whereas electron-donating groups increase the repulsion between the rings. For the optimized complexes (Table 1), this trend is clearer for electron-withdrawing groups than for electron-donating groups, as was also found in a very recent theoretical study on the influence of substituent effect in face-to-face stacked substituted benzene/benzene dimers.[55]

The correlation interaction energy, which corresponds to the dispersion energy, seems to be independent of the electron-donating/-withdrawing character of the benzene substituent. However, ΔE_{corr} shows a very good correlation with the distance between the cycles, the correlation coefficient being 0.95.

Stacking Effects on Hydrogen Bonding Capacity. The hydrogen bonding ability of the pyridine nitrogen is roughly correlated with the global hardness of the stacking substituted benzenes (Figure 3a). This trend was expected: the harder the substituted benzene, the lower the electron transfer to pyridine; the less deep the MEP minimum around the nitrogen atom will be.[114] Since the Chelpg charges show some basis set dependence, we computed the charge transfer to pyridine for different basis sets. From Table 2 the charge transfer to pyridine appears to be larger in most cases when the 6-31G*(0.25) basis set is used compared to the 6-31G* and 6-31G** basis sets; however, the substituent effect remains the same for all basis sets. The electron-withdrawing character of the NO_2 substituent in nitrobenzene turns out to be large enough to invert the electron transfer; only here electrons are pulled away from pyridine. In the case of benzonitrile (Table 1), for which the electron transfer is almost null, the MEP minimum is very close to the one calculated for the isolated pyridine at the same level of theory: −0.098 au. All in all, these findings confirm that the hydrogen bonding capacity of the nitrogen atom in pyridine depends on the electron transfer between the two rings and thus on the global hardness of the stacking compound. Furthermore, the H-bonding ability is directly related to the electrostatic part of the interaction between the rings (Figure 3b). This suggests that the effect of the stacking upon the H-bonding capacity of pyridine is monitored by the electrostatic interaction, despite its low contribution to the overall interaction energy. Indeed, the basicity of pyridine decreases with the increasing electron-withdrawing character of the benzene substituents: the deepest values of the MEP around the pyridine nitrogen are obtained for electron-donating substituents. Consistent with the scheme stated above (the more π electrons on the aryl ring, the more basic the pyridine), orbital interactions in Watson−Crick H-bonded complexes between a nitrogen lone pair donor of one base and N−H σ^* orbitals of the second acceptor base are reinforced by a small π component and constitute a large contribution to the bonding, of the same order of magnitude as the electrostatic interaction term.[115]

Local Hardness, Global Hardness, and Polarizability of the Substituted Benzene. Figure 4a shows that the polarizability

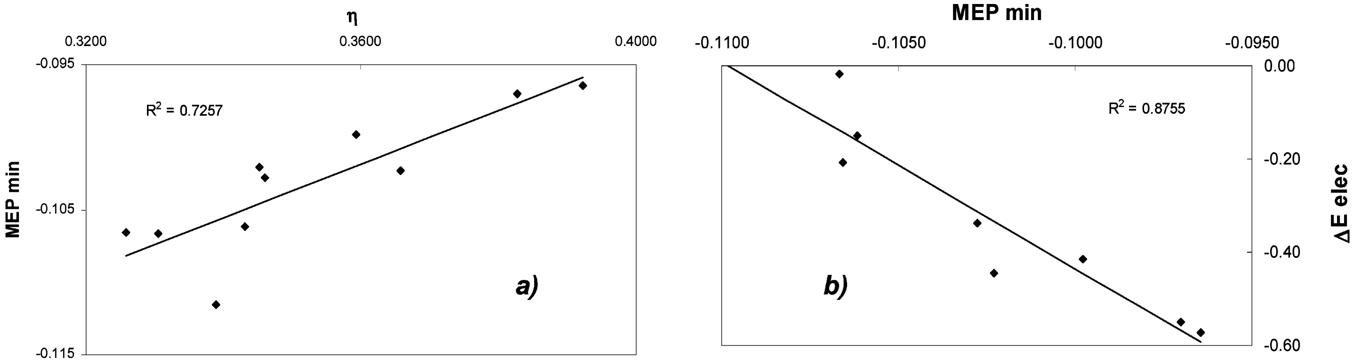

Figure 3. Interplay between complexes and individual benzene properties. (a) Molecular electrostatic potential minimum (MEP min) around the nitrogen of the stacked pyridine (au) vs global hardness (η) of the isolated substituted benzenes (au). (b) Electrostatic component of the interaction energy between pyridine and substituted benzene (ΔE_{elec} in kcal/mol) vs molecular electrostatic potential minimum (MEP min) around the nitrogen of the stacked pyridine (au). NH_2 and Cl substituents are omitted.

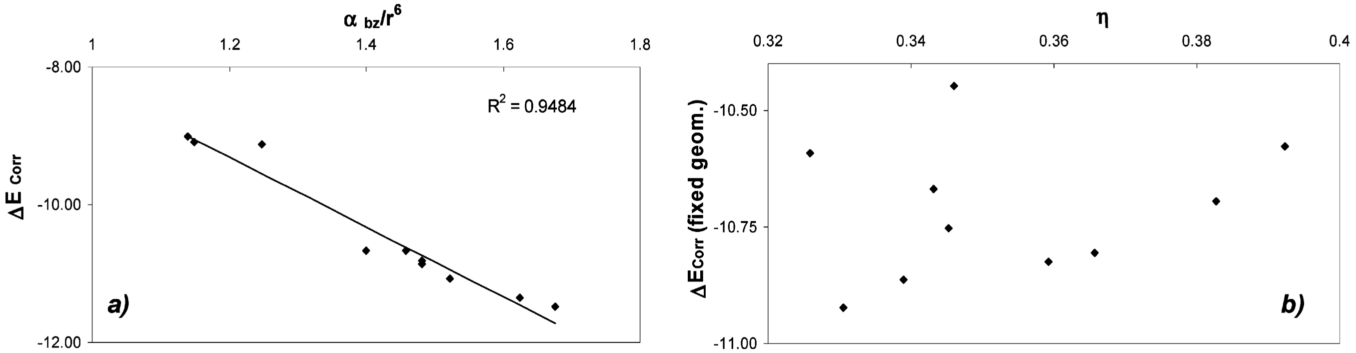

Figure 4. (a) Correlation part of the interaction energy (ΔE_{corr}) between pyridine and the substituted benzenes Ph−X (optimized structures) (kcal/mol) vs the benzene ring polarizability divided by r^6 (see eq 4) (au); (b) Correlation part of the interaction energy (ΔE_{corr}) between pyridine and the substituted benzenes Ph−X (fixed structures) (kcal/mol) vs the global hardness η of the isolated substituted benzenes (au).

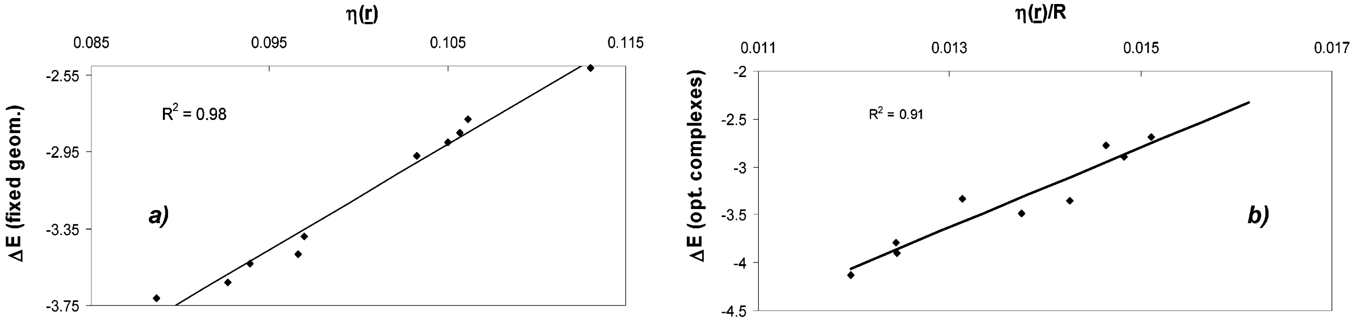

Figure 5. (a) Interaction energy (ΔE) between pyridine and the substituted benzenes Ph−X separated by a fixed distance (kcal/mol) vs local hardness $\eta(\underline{r})$. (b) Interaction energy (ΔE) between pyridine and the substituted benzenes Ph−X for the optimized complexes (kcal/mol) vs the local hardness divided by the distance between the rings $\eta(\underline{r})/R$.

of the benzene ring α_{bz} correlates well with ΔE_{corr}, as expected from eq 4. This is in agreement with a preliminary study by Sinnokrot et al.,[55] where the sequence of dispersion interaction energies for substituted benzene/benzene complexes follows that of the polarizabilities of the substituted benzenes. On the other hand, the global hardness η does not follow the correlation interaction energy (Figure 4b), which might be expected from its relation to the polarizability (cf. eq 5 and eq 7, $n = 1$). The proportionality between the dispersion interaction and $\eta^{1/3}$ has been also tested (cf. eq 7, $n = 3$); it gives in this case no better results than we observe in Figure 4b. Note that η is a property of the benzene ring and its substituent, whereas in Figure 4a only the benzene ring is considered. As α_{bz}, the local hardness $\eta(\underline{r})$ is only related to the benzene ring. In the context of hard/hard interactions (a recent critical account of the local hard and soft acids and bases principle has been published by Chattaraj),[116] $\eta(\underline{r})$ has been shown to properly describe the susceptibility toward electrophilic attack as an index of negative charge accumulation.[101] As stated above, the π/π repulsion between the cycles is a source of destabilization of the complex. It follows that a larger value of $\eta(\underline{r})$ for a particular stacking partner will increase the repulsion and lower the stabilization energy. In the present study, this trend is clear when the fixed complexes are considered (Figure 5a). In the context of electrostatic interactions, we added the distance dependency according to a simple model of charge/charge interactions. The plot of $\eta(\underline{r})/R$ vs the interaction energy calculated for the optimized complexes again yields a fair correlation with a correlation coefficient of 0.91 (Figure 5b).

Conclusion

We have studied the relation between the interaction energy of 10 substituted benzenes stacked to pyridine with the hydrogen bonding ability of the nitrogen of pyridine. The calculations show that the nitrogen atom hydrogen bonding capacity is directly related to the electrostatic interaction between the cycles and, more precisely, to the electron-donating/-withdrawing character of the substituents. Indeed, the less hard the substituted benzene, the larger the electron transfer to the pyridine and the more basic the nitrogen atom of pyridine. The correlation component of the interaction energy depends mostly on the distance between the rings. The benzene ring polarizability is a good index to predict the dispersion interaction energy. Also, DFT-based descriptors such as local hardness seem to be a good tool to predict the total interaction energy of stacked systems.

These findings will be exploited in future studies on the relation between the stacking interaction of stacked DNA bases and their capacity to accept a hydrogen bond.

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Supporting Information Available: Geometries and energies (HF and MP2/6-31G*(0.25)) of the complexes (optimized at MP2/6-31G*). This material is available free of charge via the Internet at http://pubs.acs.org.

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